A molecular genetics perspective on the heritability of human behavior and group differences

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Preface

What is this about?

When ordinary people talk to geneticists, the questions they often most want to have answered are: “*How much does genetics matter for behavior?*” and “*Is race real?*”. These will sometimes fold together to form a third question: “*Are racial differences in behavior and outcomes explained by genetics?*”. Contrary to popular belief, all three questions have been heavily debated for decades within the fields of quantitative, population, and behavioral genetics. In many cases these questions are unanswerable or ill-posed, but the field has expanded great effort into understanding why they are unanswerable, what one can expect from theory, and what is answerable with data. Millions of individuals have been genotyped to answer questions like “how much of your educational attainment is in your genes?” or “how do the effects of genetic variants differ across populations?”. However, many of these discussions happen behind journal paywalls or in single sentence news quotes and do not filter down in a coherent way to the general public. **The goal of this document is to distill the recent findings from molecular studies of behavioral traits and group differences in a way that is both comprehensive and broadly understandable.** In the end, my hope is that the lay reader has the tools and general understanding to seek out accurate answers to the complicated questions in genetics. For readers with expertise in genetics, my hope is that this document will tie together concepts that still typically reside in individual papers and supplementary notes into a bigger whole and identify important limitations and open questions.

Why a molecular perspective?

Molecular data (i.e. directly measured genetic variation) provides opportunities to use the subtle variations between individuals and groups to better distinguish correlation from causation. When we know who has which genetic variant we can: look at unrelated individuals that are unlikely to directly share environments and ask if subtle differences in their genetic variability relate to their

phenotype; look at siblings and quantify if subtle differences in the *specific* alleles they share relate to their outcomes; use genetic data from students who experienced some intervention – say, staying in school for an extra year – and ask if subtle genetic differences in them or their families influenced the effectiveness of the intervention; etc and so on. Having tools to distinguish *correlations* (patterns that we tend to observe in the world) from *causes* (factors that influence changes in the world) is critical to understanding how our world and society works and has been greatly enabled by molecular studies (R. C. Lewontin 2006).

Molecular genetics is also simply becoming a bigger part of life. Ordinary people are often experiencing genetics through commercial services quantifying cancer risk genes, polygenic scores, and genetic ancestry. There is a need for context and clarity on what these molecular tools can and cannot tell us.

A word on not being an easy mark

Large-scale genetic studies present a genuine opportunity to expand our understanding of the world. But they also involve the use of complicated statistical techniques, large datasets that often can't be manually inspected, and opaque quantities. Naturally, this has created space for scammers and bigots who can exploit the complexity of data. Just as it is important to distinguish correlations from causes, it is important not to be an easy mark for con artists. Spend some time discussing these questions out in the world and you will run into several common trends: (a) misrepresentation of what is being estimated: not defining (or defining imprecisely) the quantities of interest; (b) misrepresentation of causal versus correlational studies, and particularly a preference for broad claims from correlative studies over precise claims from causal studies; (c) the gish gallop: jumping from topic to topic or study to study rather than attempting to reach an understanding (often making use of [a] and [b] along the way). This document will thus strive to (a) provide precise definitions, (b) distinguish correlation/causation, and (c) present findings comprehensively. In later sections, some time will also be spent discussing common scams and misconceptions.

A word on basic moral principles

There is no question as to the moral dignity and respect for all individuals. It is wrong to treat people differently simply because they belong to a certain race/ethnicity, sex/gender/sexual orientation, national origin, or religion. It is wrong to allow harm to people for factors they have little or no control over. A fundamental principle of our society is that individuals have a right to be treated as individuals and this principle does not hinge on parameters of heritability, group variance, or group mean.

Genetic findings often still take on a moral valence with respect to how one should *feel* about unfairness in the world and how much can be done to change it. And let's be honest: many people just want to use genetics as an excuse to see the current (or prior) state of society as "the way things are meant to be" or to be cruel to others. As heritability is a descriptive, non-causal,

mathematical abstraction (see below) it provides no insights on moral questions. Anyone using genetics to argue against moral dignity or claim that genetics tells us how things “should be” is taking you for an easy mark.

A word about myself

Who am I?

- I received a PhD in Computer Science from Columbia, where my research focused on population genetics; specifically much of my PhD work involved developing algorithms for efficiently finding Identical-By-Descent (IBD) segments in large populations.
- I was then a postdoc in Biostatistics / Genetic Epidemiology at the Harvard School of Public Health, where my research involved heritability, Genome-Wide Association Studies (GWAS), and integration of molecular/regulatory data to identify disease mechanisms.
- I am now an Associate Professor at Harvard Medical School and the principal investigator for a lab focused primarily on cancer and disease genetics.
- I remain interested in heritability and behavioral genetics approaches as tools that can probe the biases and confounders that influence how we use genetics to intervene on disease.
- If that sort of thing is important, I’ve led and contributed to the development of a variety of statistical methods that were published in fancy journals or got a lot of citations (ex: this, this, this, this, and this).

Some of my implicit biases:

- Nearly every geneticist benefits personally when the contribution of genetics is high and the environment is low. There is a common assumption that geneticists somehow profit from spreading a “blank slate agenda”, but the reality is that our job is often about making predictions from genetic variation, and when heritability is high that makes our job easier. High heritability means we find associations with smaller studies, our statistical instruments have more power, we can argue that our role is fundamental to understanding disease, and we get more grant money. The endogenous pressure in the field is to emphasize high heritability and the “special” nature of genetics and to prioritize genetic confounding over other sources of confounding.
- Because of my background and ongoing work, I’m generally predisposed to favor molecular genetics models, particularly those focusing on common variation. Because of my experiences interacting with human beings I’m also predisposed to be skeptical of genetic determinism or primacy. Though the goal here is to summarize and think through findings with some amount of consensus, I will sometimes stray into speculation and try to indicate those instances with a 🔥.

Concepts

1.0 | Summary

- **Heritability is a mathematical abstraction that assigns discrete labels to correlated components of trait variance**. Because correlated variance can be partitioned in a multitude of ways, there is no “true” measure of heritability in the population. All heritability estimators are defined with respect to specific assumptions on genetic and environmental variance.
- **A concise definition of additive heritability is the fraction of trait *variation* that can be predicted from a linear combination of measured genetic *features* in a specific environmental context.** This definition is neither causal (genetic features can predict a trait by capturing environmental or other correlations) nor is it prospective (genetic variants predictive in one context may no longer be predictive in another context).
- **As heritability is typically a ratio of two variance terms it alone cannot identify: differences in the genetic or environmental trait mean; compensatory shifts in the genetic and environmental trait variance; the presence/absence of gene-environment interactions; genetic or environmental heterogeneity.** Heritability is thus completely uninformative of trait “architecture” or causal mechanisms.
- **Heritability is neither an upper or lower bound on trait malleability.** There are many examples of high heritability traits shifting substantially over time through environmental changes (e.g. eyesight) and, on the other hand, low heritability genetic variation pointing to biological mechanisms with large effects when intervened on directly (e.g. cholesterol medication).
- **Cultural forces will influence apparent heritability and association of genetic variants**. The same genetic variance in the same environmental context can have different predictive accuracy (and thus heritability) under different cultural structures: particularly in the context of assortative mating.

1.1 | Heritability

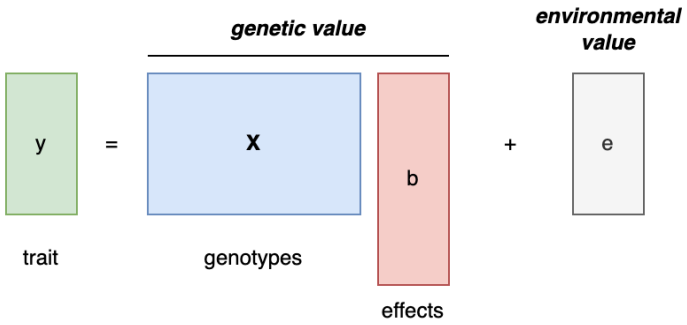
The definition of heritability has been discussed and debated for decades, often starting from assumptions on genetic causality, independence of environments, and selective breeding and then working backwards to caveats and limitations in real populations (Stoltenberg 1997). In plants, cattle, or dogs (where the terminology originated) assumptions about environments and selective breeding may be reasonable or directly testable and modifiable. In humans, the genetics/environment dichotomy does not hold and so a causal definition is either erroneous from the start or unusably vague. Here, I will instead define heritability in purely correlative/predictive terms and then work forwards to the very limited set of causal conclusions we can draw from it.

What it measures

Let's start simple and build up. Consider a continuous trait [y] that varies in a given population and a single genetic variant [x]: the "heritability" of that variant is the magnitude of its association with the trait, or the squared correlation between [x] and [y]. Run a large genetic study, correlate [x] and [y], square the correlation (and adjust for noise), and you have the heritability of that trait attributable to that variant – that's it! Note that we've made no assumptions about *how* [x] associates with [y]: it could be causally impacting the trait in the individual or non-causally correlated with some environment that influenced their trait (or a technical artifact for that matter): all heritability quantifies is the magnitude of the correlation.

For "complex" traits, where many genetic mutations are associated, each with some positive or negative "effect size", the *genetic value* of that trait in an individual is the sum of all the increasing/decreasing effects they carry. If we then think of the total trait as a simple sum of the genetic value and an independent *environmental value*, the additive heritability is the ratio of the variance of the genetic value over the total variance. When heritability is 0, that means the variance of the trait cannot be assigned to any of the genetic value, and when heritability is 1 that means the variance of the trait can be assigned to all of the genetic value. I'm using the terms "can/cannot be assigned" because we've made the simplifying assumption that the genetic and environmental terms are independent. **In the real world, genetics and environment are obviously not independent "components" but correlated and interacting processes; every estimator of heritability implicitly or explicitly makes a choice about how to assign the correlated variance**. Since an oracle will not tell us which assignment is correct, heritability (and related terms like "genetic values") is thus always an abstraction of complex underlying processes (more on this later).

Mathematically, that additive model looks like this:



Heritability is Var(Xb)/Var(y) or equivalently the squared correlation between the genetic value and the trait [Cor(Xb,y)^2], where [Xb] is also the best additive genetic predictor of [y]. This is perhaps the most direct definition of heritability: **how much of [y] *could* have been predicted from a weighted sum of [X]**. This definition is specific to the population in which it is being estimated *and* to the genetic variation that goes into estimating it.

Finally, a bit of jargon: heritability from the additive model is also often called "narrow sense" heritability, in contrast to "broad-sense" heritability which also includes the contribution of non-additive (e.g. dominance) and interaction effects. At the molecular level, the distinction between additive and non-additive terms is somewhat arbitrary, since one can include non-additive combinations of genetic material in [**X**] (for example, [**X**] could be defined to contain all pairs of [$x_i * x_j$] mutation products and thus also estimate the association of two-way interactions or all [x_i^2] terms to estimate dominance).

What it doesn't measure

Heritability is not a *causal* parameter. Because genotypes precede phenotypes and (generally) cannot be influenced by phenotypes, heritability is often implicitly treated as being *causal* when it is not. As a simple example, if you have two variants ([x_C] and [x_{NC}]) that are perfectly correlated in the population and [x_C] influences the trait while the [x_{NC}] doesn't (i.e. it is a "tag"), the heritability from [x_{NC}] alone will be the same as the heritability from [x_C] alone (and will be the same as the heritability from [x_C,x_{NC}] together). This is important because if we intervene on [x_{NC}] we will not actually influence the trait. Disentangling causality gets more complicated if, for example, genetic variants in a study participant are correlated with genetic variants in their parents, who also influenced their trait through the environment: now this variation is completely non-causal in the participant and, in fact, should point us to interventions on the parenting environment rather than on a genetic mechanism.

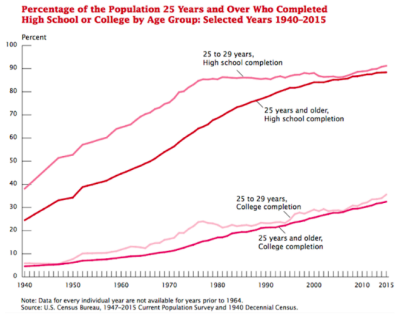
The fact that heritability *feels* intuitively causal but is merely a correlation makes it ripe for misinformation. Where ordinarily it would be nonsensical to argue that just because we see that two populations have different rates of college attainment we therefore know what *causes* the difference; a bullshit artist can invoke the "high heritability of education" (perhaps even rattle off a few twin study estimates to the decimal point) and claim confidently that the cause must be "bad genes", cloaked in the appearance of scientific rigor. This has created a cottage industry of "noticers", who loudly "notice" that certain demographics are associated with certain outcomes

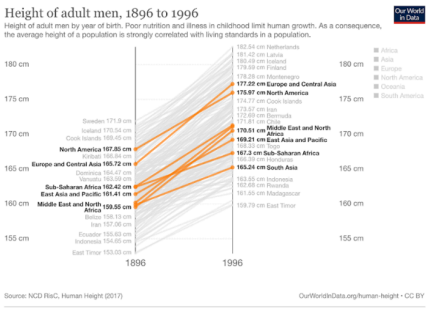
and either explicitly or implicitly argue that, since those outcomes are heritable, these correlations must also be causal and deterministic. Causal inference is hard but "noticing" is easy, and so noticers can stay busy spotting meaningless correlations, hoping that you will be convinced by the sheer volume of their observations.

Heritability does not tell us anything about the *malleability* of a trait (i.e. whether the trait can be intervened on or modified). Even when all of the assumptions are met and the estimates are unbiased, heritability is just a quantification of the association of genetics and environment with the trait; changing the environment can make the genetics irrelevant or changing the genetics could make the environment irrelevant. Consider the classic example of eyesight: highly heritable but easily malleable through the use of glasses (high heritability, high malleability). Are glasses a "large" environmental variance that's compensating for high heritability? The question is clearly nonsensical: variance is a mathematical concept and the mathematical variance of glasses-wearing trivially depends on how many people have them. But this is the kind of logic one gets into when thinking that heritability is a surrogate for malleability. For an example in the opposite direction, consider the case of the gene *PCSK9*: a tiny number of individuals carry rare loss-of-function mutations in *PCSK9* that dramatically reduce their bad cholesterol, but because most people carry a normal functioning version of *PCSK9*, these variants do not "explain" much of the population variance in bad cholesterol (i.e. contribute much to heritability). However, when drugs that inhibit *PCSK9* are administered to the general population they have a highly significant effect on the trait mean (low heritability, high malleability).

Other historical examples include the rapid change in human height over the past 100 years or the rapid growth in educational attainment in the US. Height has changed rankings across continental groups, almost certainly brought on by improved nutrition. Even though it is a highly heritable trait (by nearly any estimate), mean height has shifted by ~2 standard deviations in just five generations (insufficient time for any evolution to have occurred). But ask most people and they will tell you height is *just the way it is* because of genetics. Significant increases in height have even been observed within western countries in the past several generations (Fredriks et al. 2000). Likewise, there has been rapid growth in educational attainment in the US. The number of college graduates has doubled from 1980 to today (notably, the former would be the time a typical contemporary biobank participant was of college-age). Are these changes driven by low heritability? Almost certainly not, heritability is merely a *retrospective* measure and does not tell us about the *prospective* impact of changing the environment.

Substantial changes in educational attainment in the US and height globally/nationally.
(left) Changes in the percentage of the US population who have completed high-school or college over time; (middle) Changes in adult male height over a century; (right) changes in height in The Netherlands from 1955 to 1997, attributed to improved nutrition, health, and hygiene.





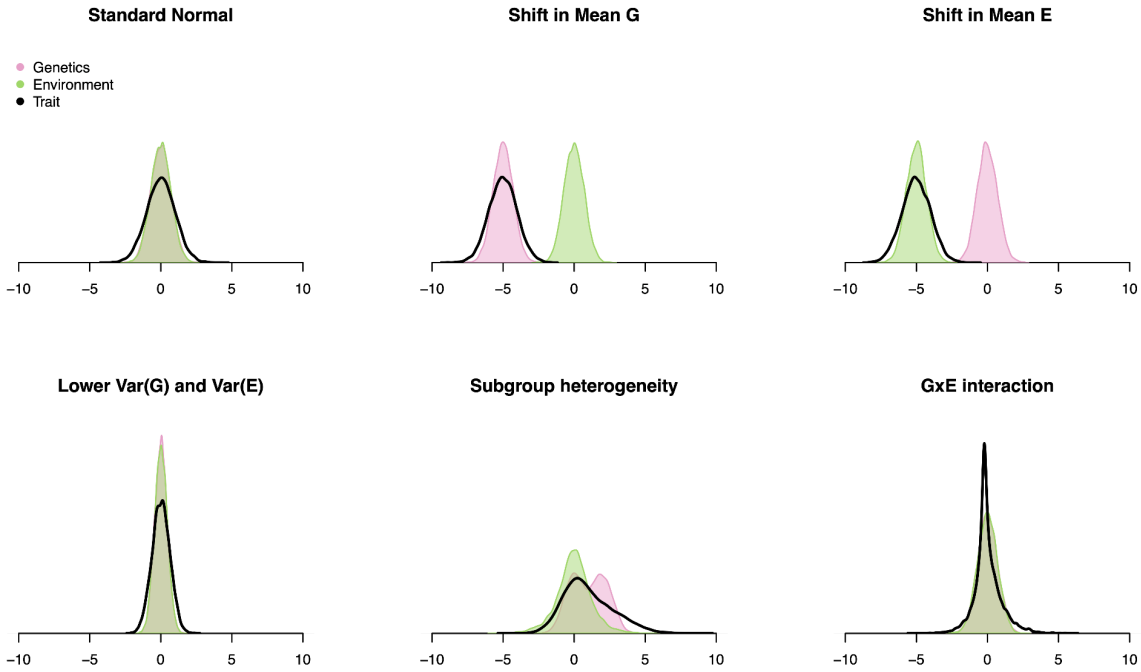
Heritability does not tell us anything about a population mean/average, because it operates on variance. For example, if everyone in a given population suddenly grew exactly 5 inches, the heritability of height would stay the same because only the population mean (and not the variance) will have changed. In fact, it is quite common in heritability analyses to center and scale the trait and regress out nuisance covariates so that the heritability estimate loses any "real world" scale entirely.

Heritability does not tell us anything about the total variance of the trait, because it is just a proportion of the total variance. Imagine a future where a drug eradicates some disease, except for a small number of people who cannot tolerate the drug because of a pathogenic mutation. In this society, the heritability of the disease is now 100% – all disease cases are caused by a genetic mutation – but the variance of the disease is very low. In contrast, most adults have two eyes except for those who experience an environmental trauma – the variance is low and the heritability is low. So the notions of heritability, mean, and variance are distinct.

To illustrate these points, let's look at very different traits that produce the same heritability (i.e. the correlation of the genetic component and the total trait is 50% in the population). It's trivial to see that shifts in mean have no effect on the heritability estimate and neither do compensatory shifts in variance (i.e. when both genetic variance and trait variance are shrunk). One can additionally construct more complex scenarios with subgroup heterogeneity or Gene-Environment interaction that produce equivalent heritability estimates by simply fiddling with various variance terms. **In short, heritability tells us how much of the trait *could have been predicted* from the genetics in the population we studied, with no guarantees on causality, malleability, or trait architecture.**

Six very different traits with equivalent heritabilities.

The distribution of the genetic value (pink), environmental value (green), and total trait (black) is shown for: (a) A trait with 50% genetic variance and 50% environmental variance; (b) A trait where the genetic value has been shifted by five standard deviations; (c) A trait where the environmental value has been shifted by five standard deviations; (d) A trait with 25% genetic variance and 25% environmental variance; (e) A trait with two subpopulations, one of which has a genetic value shifted by two standard deviations and environmental variance increased by five-fold; (f) A trait with 50% genetic variance, 5% environmental variance and 45% gene-environment interaction variance. In all six instances, the squared correlation between the genetic value and the phenotype is 0.5



Heritability and liability for dichotomous traits

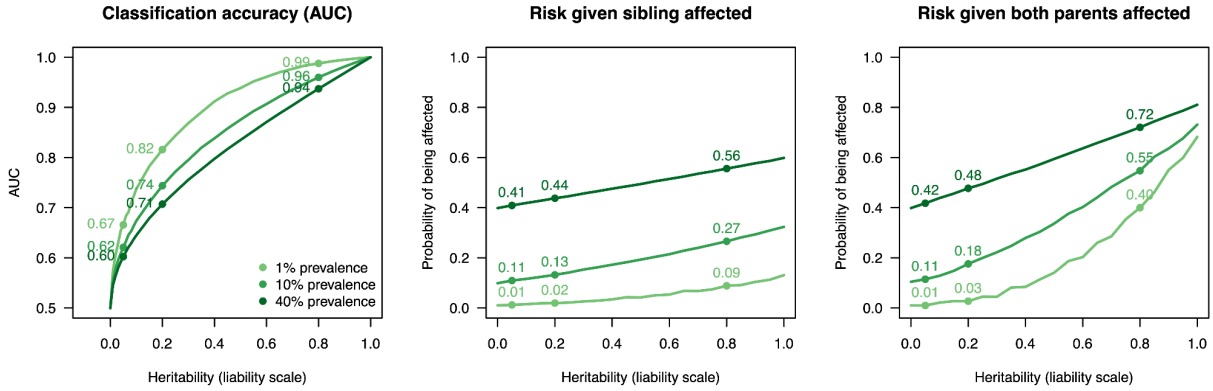
Up to this point we've considered heritability for continuous traits, where [Xb] ads up to a numerical value (e.g. height). For dichotomous (aka case/control) traits, this formulation is modified slightly so that [y] is an underlying normally distributed *liability*, and individuals who exceed a threshold of liability are affected/cases while the rest are controls. In other words, a transformation is applied to [y] to turn the top x% into cases, where x is the disease prevalence. This is the *liability threshold* model and it is the primary statistical model for working with dichotomous traits.

The figure below shows various consequences of this transformation as a function of h2g and disease prevalence. There are several details to notice. First, the amount of genetic variation within families is surprisingly high: even for a trait with heritability of 100% and a prevalence of 40%, the risk for an individual increases to just ~60% if they have an affected relative or 80% with two affected parents. This means that even for a completely heritable trait, there will be many families in which both parents are cases and the child is not. Second, individual risk depends on both the heritability and the prevalence. So for a trait with heritability of 100% and a prevalence of 1%, the risk for an individual with an affected sibling is still just ~15% – this is much higher than the population prevalence but still much lower than heritability alone might imply. Third, classification accuracy (defined as Area Under the Curve for a binary predictor based on the genetic value) is highly non-linear with respect to the heritability especially for low prevalence traits. It is thus difficult to think intuitively about how heritability translates into the ability to distinguish cases from controls.

Aspects of the liability threshold model.

*(**left**) Classification accuracy, (**middle**) the probability that an individual is an affected case given their*

*sibling is a case, (**right**) the risk that an individual is an affected case given both their parents are cases. In each plot, the results are shown for three levels of prevalence and points are indicated for representative heritabilities: 5% (roughly the h2g of educational attainment), 20% (roughly the h2g of hypertension and other biomarker traits), 80% (roughly the twin h2 of height and other highly heritable traits).*



A word on “missing” heritability

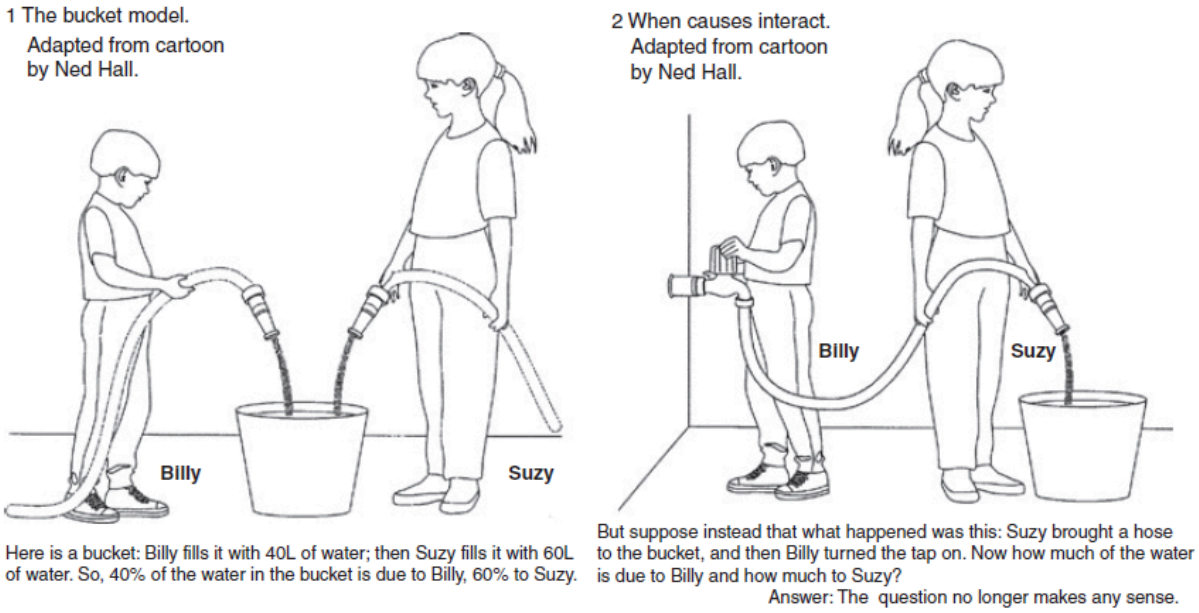
The discussion about heritability often touches on the “missing heritability” question. Generally speaking, **“missing heritability” can be thought of as a significant discrepancy between different estimators of heritability**. Some people use “missing heritability” to refer to the discrepancy between twin-based and molecular-based estimates. Some people use “missing heritability” to refer to the discrepancy between what can be explained by individual, known mutations (i.e. significant associations from a GWAS) and the total molecular-based estimate across all mutations (regardless of significance). Most of the time the term only adds confusion and obfuscates the fact that different methods are estimating different parameters. It also implicitly presumes that the missing heritability could be “found”, which of course is not certain (for example if one estimate is simply biased upwards).

1.2 | Genetics, Environment, Interactions, and Assortment

In the real world, traits are not just the sum of a *genetic value* and an independent *environmental value*, they are a function of many complex relationships. To develop an understanding of these relationships, we typically break them down into further *components* of the trait variance. These components are important to define precisely because they are often assigned, estimated, or ignored differently by different models. Most of the time, models set certain components to zero or try to quantify what can be assigned to additive genetics and then what is left. In the cartoon below, a perfect interaction between two terms would result in assigning all of the variance in outcome to one term or the other arbitrarily. Indeed, complex relationships between genetics and environment can even yield significantly *negative* estimates of heritability, which no longer have a plausible interpretation as squared correlations but can be entirely statistically valid as models of trait covariance (Steinsaltz, Dahl, and Wachter 2020).

***Cartoon thought experiment of additive versus interactive models**.*
***(left)** The trait is an abstract sum of an independent genetic and environmental component. **(right)** The*

trait is a more plausible interaction between a genetic and an environmental component. With interactions, the partitioning of variance into additive genetic and environmental terms (i.e. "nature" and "nurture") is not singularly defined and assumptions/constraints have to be made on how to partition/assign the contribution from "Billy" or "Suzy". Figure from (Moore and Shenk 2017).

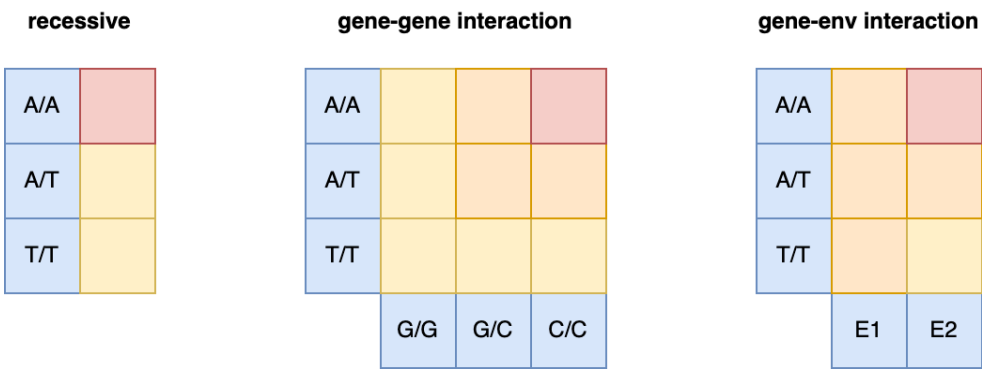


Gene-Gene Interactions (GxG)

GxG (or "epistasis") refers to the non-additive combined effects of a single or multiple causal variants. For example, a recessive effect – where a variant only impacts the trait when both hazardous alleles are present – can be thought of as a single-variant interaction. If the alleles at two different variants need to be the same for an effect on the trait, this is a two-variant (or second order) interaction, and so on for higher order interactions.

Schematic of single-locus GxG (recessive), multi-locus GxG (epistasis), and GxE.

Blue squares indicate genetic/environmental contexts and yellow/orange/red squares indicate a low/medium/high effect on the trait for that context combination. Note that in all three examples, much of the non-additive effect can still be "tagged" by an additive model but will be dampened relative to the true interaction model. A/T are the alleles of one variant; G/C are the alleles of a second variant; and E1/E1 are two environments.



Gene-Environment Interactions (GxE)

GxE refers to the interaction between genotype and environment on the trait. For example, if a mutation only has an effect on the trait in smokers and not non-smokers, this is a GxE interaction where the E (environment) is smoking. Note that E can refer to essentially any non-genetic factor/exposure. **A challenge for heritability estimation is where to assign the contribution of GxE since both factors need to be in play for the effect to manifest itself; this then becomes a modeling decision that leads to differences across different estimators**.

In addition to the simple model where a mutation has an effect in one context and not another, a more subtle "amplification" model of GxE has been proposed. Under amplification, the genetic effects between two environments are correlated but differ by some magnitude (for example, the effects of all/many alleles in older participants are 1.2x higher in magnitude than the effects in younger participants). This form of GxE would produce high *genetic correlations* but large differences in *heritability* between environments.

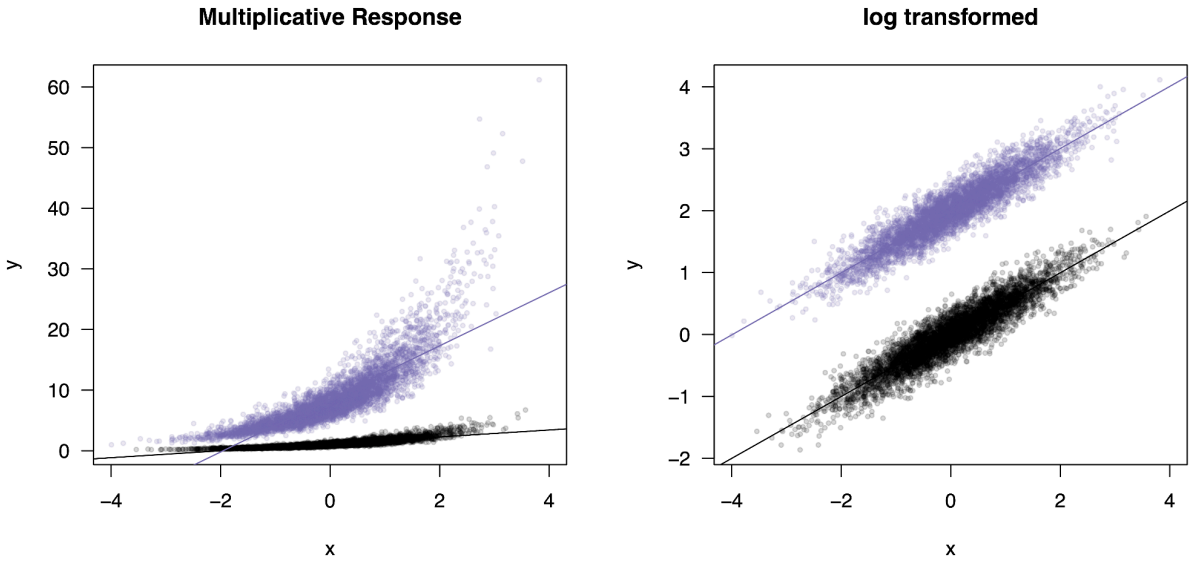
Interactions are scale dependent

It's important to distinguish between *mechanistic* interactions – non-additive effects between two mechanisms in the underlying causal model, and *statistical* interactions – significant interaction terms in an inferential model. Different ways of processing data can mask a true mechanistic interaction or induce a false statistical interaction. In general, this happens when the "scale" or "functional form" of the response variable is either unknown or distorted by data processing.

For example, let's generate data with a true multiplicative interaction ([y = x*z]) where [x] is a continuous variable and [z] is a binary group. When we fit a standard linear model to this data ([y ~ x + z + x*z]) the interaction term is highly statistically significant. Since we have two groups here, an interaction model is equivalent to testing for a difference in slope between them, and when we plot the two groups (below) we can indeed see a significant difference in slope. If we *instead* log transform the data first, a very common practice to "stabilize" features with high variance, we have turned the outcome into [y = x + z] and the linear model no longer identifies an interaction. Moreover, the transformed data actually produces a better fit to the features, so a "data-driven" analysis would tell us that the transformation is more parsimonious and no interaction is present.

Data transformation masks a true mechanistic interaction.

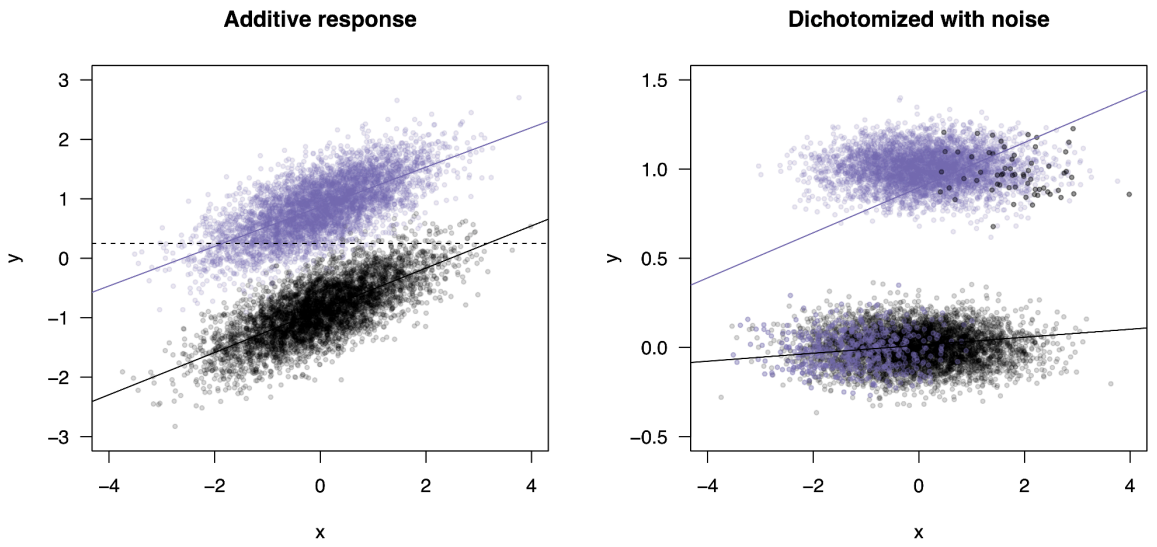
On the left, the true generative process for a continuous variable interacting with a binary group (purple/black). On the right, the same data is log transformed and the true interaction disappears (and the fit improves).



Now let's consider the opposite effect. We first generate data without an interaction ([y = x + z]) and fit a standard linear model. As expected, the slopes are the same in the two groups and no interaction is identified. Next, we dichotomize the data based on an arbitrary cutoff; let's say individuals above a certain value of [x] are cases and the rest are controls. In a linear model, the slope in each group will depend on the fraction of cases in that group, so if one group has many fewer cases (for example, they are systematically healthier but the influence of [x] is the same) the effect of [x] will *appear* weaker. In a linear model, this yields a significant statistical interaction term. Statistical interactions become even more complicated to interpret for ordinal, count-based, or survival processes (Domingue et al. 2020).

Analysis of a binary variable with a linear model induces a statistical intearction.

On the left, a generative process for two groups (purple/black) with no interaction with the continuous variable (x-axis). On the right, the continuous variable is transformed into a binary variable based on a threshold (dashed line in the left plot) that produces case imbalance. This induces a significant interaction between the variable and the group.



In short, a statistical interaction is neither necessary nor sufficient evidence of an underlying mechanistic interaction. Statistical interactions can still be useful for modeling; for example by improving predictive accuracy, adjusting for undesirable artifacts, or evaluating counterfactuals/interventions (Thompson 1991). But additional mechanistic evidence is needed for a causal interpretation; goodness of fit alone is not enough. Data that are highly non-linear or exhibit strong class imbalance are particularly sensitive to modeling assumptions.

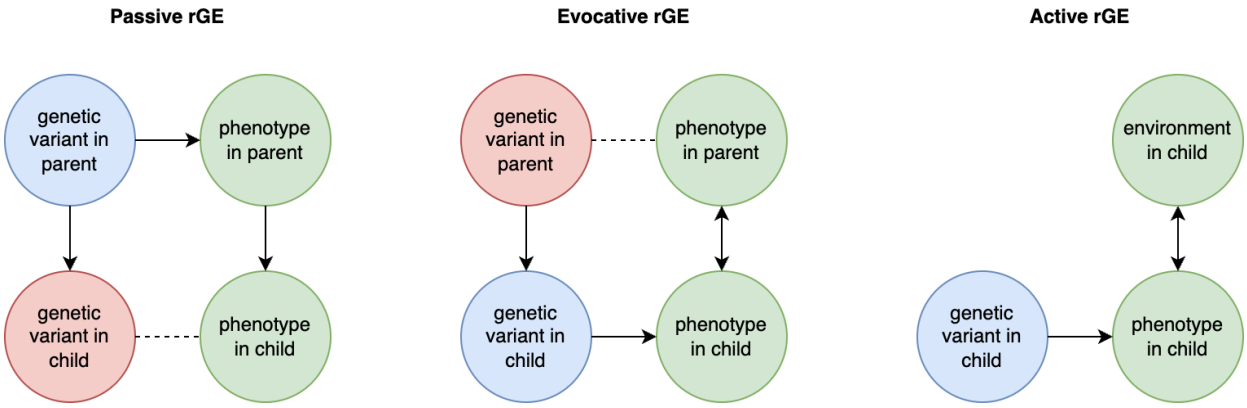
Gene-Environment Correlations (rGE)

rGE refers to correlations between genetics and environment which may or may not be caused by genetics. An example I will refer to frequently is a genetic variant that causes allergies, which nudges people to move from rural to urban areas. In a rural parent, this variant has a direct causal effect on the trait. In their urban off-spring, this variant will now be correlated with everything else they experience in that urban setting. Even generations later when allergies have been cured, the allele may still be slightly elevated in – and thus correlated – with the urban environment. This example may seem far-fetched, but in a biobank of half a million individuals such subtle changes are detectable, and in fact just such an allergy variant was recently identified and associated with geography (rs5743618, one of the strongest associations with hayfever) (Hu et al. 2023). Another example is that of genetic variants that influence parental behavior (for example, variants that are associated with postpartum depression). In parents, the variants influence the environment for their children. When passed down to those children, the variants will be correlated with the trait consequences of that environment, even though it is no longer playing a causal role in the child. These are both examples of “passive rGE”. Various cultural structures can substantially amplify passive rGE associations well beyond their true underlying causal effect (see [3]).

An “active rGE” correlation can arise when genetic variation causes individuals to enter specific environments that alter their trait. For example, a variant that nudges carriers to be more outgoing, which places them in more social situations, which further reinforces their outgoing or sociable nature, and so on. In this case, the genetic variant may initially appear to have little

association with the environment, but a *causal* association increases over time. Finally, when variants lead to behavior in children that then elicit certain behaviors and environments from their parents/relatives (who also share genetic variation with them), this creates a feed-back loop known as "evocative rGE". Of course, individuals who carry the variant but are not able to participate in the relevant environment will not exhibit this rGE. As with GxE, the assignment of rGE is another modeling decision that can lead to differences across different estimators.

Forms of rGE: Passive, Evocative, and Active Gene-Environment correlation.
Blue indicates causal factors; green indicates outcomes; red and dashed lines indicate non-causal factors and relationships. Bi-directional arrows reflect interactions or reciprocal effects. Adapted from (Avinun 2020)

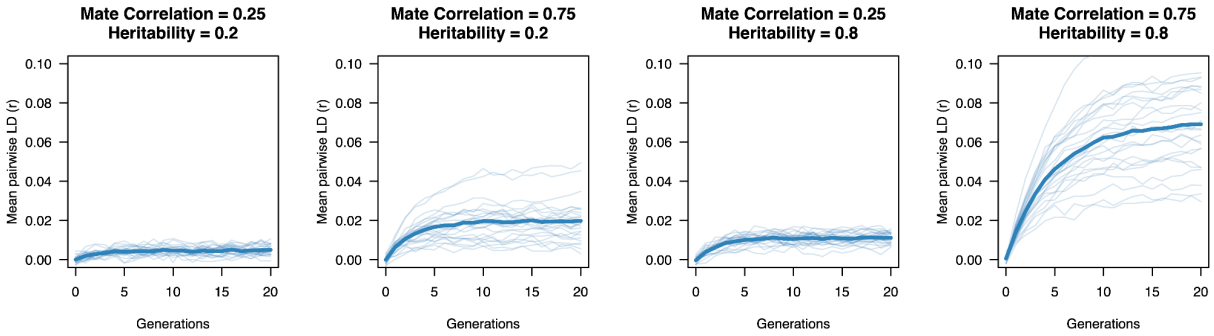


Assortative Mating (AM)

Assortative mating (also referred to as "homogamy") is a social process where partners/mates pair up based on observed or latent phenotypes (e.g. "tall people like to marry tall people"). Assortment on heritable traits is common, with the highest AM typically observed for educational attainment and other/related behavioral phenotypes. Notably, AM on educational attainment (0.48) and political values (>0.5) is higher than AM on IQ (0.23) (Horwitz et al. 2023), reiterating that AM is a social process and class signifiers can have higher AM than latent traits. AM on a heritable phenotype will influence the apparent genetic variance in offspring/family studies (i.e. siblings will be more genetically similar than expected because their parents are more genetically similar than expected) as well as the correlation between trait influencing alleles (Crow and Felsenstein 1968; Loïc Yengo et al. 2018). **AM thus further complicates the interpretation of heritability: the same exact variants and causal effects in the same exact environment will produce different values of genetic variance (and thus heritability) under different mating patterns**. In particular, the association of genetic variance with the trait (i.e. the true [Cor(**X**b,y)^2] is higher under AM than it would be with the same genetics and environment under random mating (more on this later).

When AM is constant over time, it induces correlations with each generation, roughly half of which are observed within the first generation and typically reaching "equilibrium" within five generations. Methods that account for AM typically assume that equilibrium has been reached to simplify their derivations. Lack of equilibrium (i.e. steadily increasing or decreasing AM) would cause an estimate not to generalize beyond the estimated generation.

Impact of heritability and assortative mating on correlations at putatively independent markers.
Assortative mating on a heritable phenotype leads to a sudden increase in the correlation of causal alleles in the population, which stabilizes at an "equilibrium" in ~5 generations. The correlation increases with higher heritability or stronger assortment. Simulations using 10 markers and 10,000 individuals.



A related concept is cross-trait AM (xAM), where mates pair up based on matching on different traits (for example, educated women preferentially pair up with tall men) (Border, Athanasiadis, et al. 2022). xAM will cause genetic variants influencing a trait in one partner to be correlated with variants influencing a different trait in another, and may also create apparent genetic correlations in population studies.

Genetic correlation

Genetic correlation is an estimate of the sharing of genetic variance across pairs of traits (van Rheenen et al. 2019). Formally, for two traits $\{y_1,y_2\}$ with causal effect sizes $\{b_1,b_2\}$, genetic correlation can be thought of as $Cov(X'b_1,X'b_2)/sqrt(Var(X'b_1)Var(X'b_2))$, where $Cov(X'b_1,X'b_2)$ is the genetic covariance between the traits. This is equivalent to the correlation of the genetic values $[Cor(X'b_1,X'b_2)]$ or, under very strong assumptions, the correlation of causal effect sizes $[Cor(b_1,b_2)]$. An important point about genetic correlation is that it is "normalized" for the heritability of the two underlying two traits, so two traits with very low heritability can still have very high genetic correlation if the (small influence) of genetics on each trait is highly shared across traits. Genetic correlation provides some intuition about the relationship of traits but, by definition, it cannot be interpreted *causally*. More directly, genetic correlation between two traits means one trait can be predicted from the genetic value of the other.

1.3 | Further reading

Heritability:

- (Feldman and Lewontin 1975): Seminal perspective discussing misconceptions around heritability particularly for understanding group differences.
- (Turkheimer 2000): Fundamental (though now somewhat contested) theories about behavioral genetics drawn from classic family-based analyses.
- (Moore and Shenk 2017): Conceptual criticisms of heritability as a measurement of malleability and in the context of environmental interactions.

- (R. C. Lewontin 2006): More on the importance of distinguishing causes from variances.
- (Davey Smith and Phillips 2020): Discussion of the importance and challenge of understanding causal mechanisms.
- (Baselmans et al. 2021) (and associated **interactive online tool**): Models and derivations for thinking about heritability on continuous versus case/control scales.

Environment and more:

- (Thompson 1991): Comment on interpreting statistical versus mechanistic interactions.
- (Mostafavi et al. 2020): Analysis and proposed models for differences in heritability in different environments and GxE.
- (Loïc Yengo et al. 2018): Derivation of the influence of assortative mating on variant correlations and frequencies.
- (Horwitz et al. 2023): Large-scale analysis of assortative mating across many traits.
- (van Rheenen et al. 2019): A review of molecular genetic correlations and its applications.

Molecular heritability

2.0 | Summary

- **Molecular methods enable the estimation of heritability (h2g), defined as the proportion of trait variance that can be predicted from a given set of genetic features**. These approaches generally work by regressing phenotypic covariance on genetic covariance or modeling the relationship through a multivariate normal likelihood.
- **When assumptions are met, estimators of h2g are unbiased with respect to sample size and causal/non-causal variation**. In expectation, the estimate matches the truth at any sample size and regardless of whether some variants included in the estimator are not associated with the trait.
- **Estimates of h2g correspond to the maximum prediction r2 that can be achieved with a linear predictor or PRS/PGI and assumptions can thus be verified in held-out data**. As an example, the estimate of h2g of 0.45 for height in 2010 with 4,000 individuals was

eventually confirmed by a saturated GWAS of 5.4 million individuals in 2022 yielding a PRS with out-of-sample r2 of 0.45.

- **Assumptions for h2g estimators can be violated if**: closely related individuals are retained in the analysis or population structure is otherwise not accounted for (confounding through rGE), the distribution of causal variants is significantly different from the distribution of tested variants (LD/genetic architecture bias), assortative mating distorts the observed genetic variance.
- **The h2g of rare coding variant burden (defined as the fraction of trait that can be predicted by the same) can be estimated using Burden Heritability Regression**. Likewise, other genetic components (GxE, GxG) can be reframed as "variants" in the relatedness matrix and their h2g quantified.
- **Simulations show that recent population structure can inflate conventional estimates of rare variant h2g**. Very subtle demographic models may also inflate common variant h2g estimates and may be indistinguishable from gene-environment correlation without causal models.

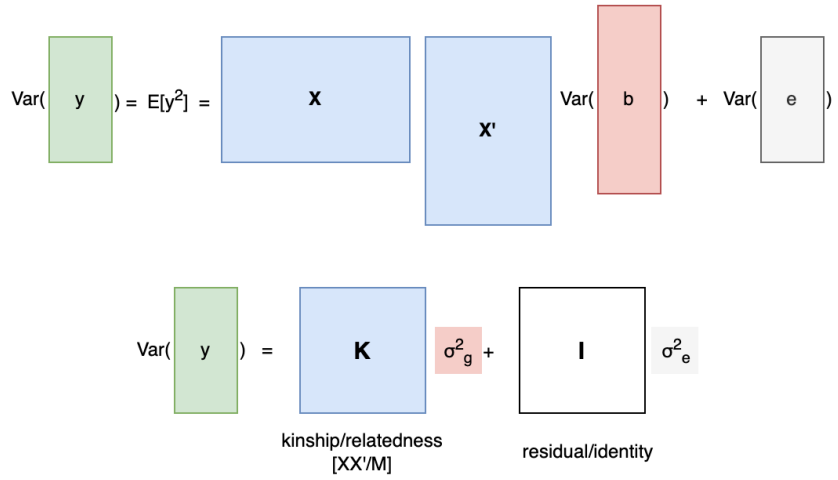
2.1 | Definition

Heritability formulated as above naturally lends itself to estimation with molecular methods, where the genetic variation in [**X**] can be typed and correlated with [y] directly. These molecular estimates are often called SNP or "chip" heritability (from here on out referred to as h2g for "genetic"). In contrast to approaches that use closely related individuals, h2g is typically estimated using putatively unrelated individuals for whom the genetic (or "realized") relatedness is inferred directly from the molecular data. This means that if we want to understand how much genetic variation is correlated with a given trait, we can simply collect data from a lot of random people and then apply some math.

A little bit of math: Returning to our generative model of the trait as the sum of a genetic value and an environmental value [y = Xb + e], we can further derive the variance of y as [Var(y) = Var(Xb + e) = (**XX'**) Var(b) + I Var(e) = (**XX'**/M) h2g + **I** Var(e)], where [**I**] is the identity matrix, [M] is the number of variants in [**X**], and h2g is our parameter of interest. Here [XX'/M] is the genetic relatedness matrix (i.e. a pairwise, symmetric matrix where each entry is the correlation across genotypes for that pair of individuals) and we can see that [h2g = M*Var(b)] or the total variance (sum of squares) of the causal effects. As before, h2g corresponds to [Var(X'b)/Var(y)] or the squared correlation between [X'b] and [y]**.** It can thus be interpreted as "the variance in the trait that can be assigned to all genetic variation in the relatedness matrix and anything that variation is correlated with".

Derivation of the relationship between heritability and trait variance from the additive model.

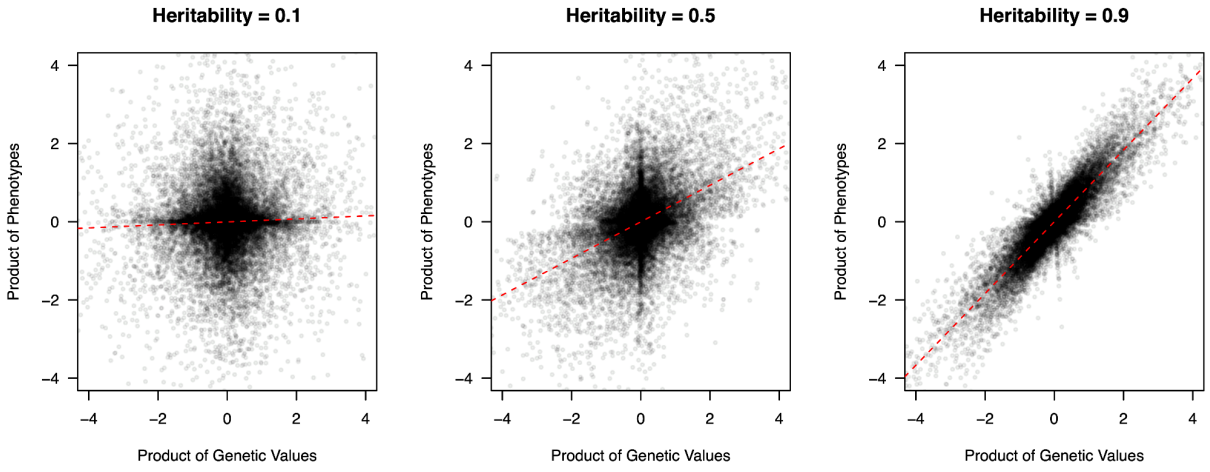
[y]: the trait; [X]: a matrix of genotypes; [b] the vector of causal effects; [e] a random environmental term; [K] the kinship / relatedness matrix; [I] the identity matrix. Note this derivation explicitly assumes that [b] and [e] are uncorrelated (i.e. no rGE), which drops any cross-terms between [X] and [e].



There are several unique aspects of this definition. First, unrelated individuals are more likely (but not entirely) to be unconfounded by shared environments and require fewer environmental assumptions. Second, h2g corresponds directly to the maximum prediction r^2 that can be achieved by a linear model using all the variants in [**X**]. Specifically, for a given training size N, and number of variants M, the expected prediction accuracy can be derived as [$r^2 = (h2g * h2g)/(h2g + M/N)$] (Dudbridge 2013; Daetwyler, Villanueva, and Woolliams 2008) (see also (Okbay et al. 2022) for an alternative derivation). **h2g can thus be validated by predicting into independent samples and comparing the observed and expected prediction accuracies**. This may seem like a simple point but it has quite profound implications: any time we make an estimate of h2g we can, in principle, confirm that the estimate has *predictive* validity simply by constructing a linear score and testing it out of sample (International Schizophrenia Consortium et al. 2009). While this does not guarantee that the estimated h2g is causal or free of confounding, it does enable an independent check on the estimating assumptions.

Visualization of three simulated trait heritabilities.

Three populations with simulated phenotypes under different heritabilities. The product of genetic values between pairs of individuals (x-axis) is correlated with the product of phenotypic values. This approach can, in fact, be used to estimate molecular heritability in real data (see: Haseman-Elston regression below).

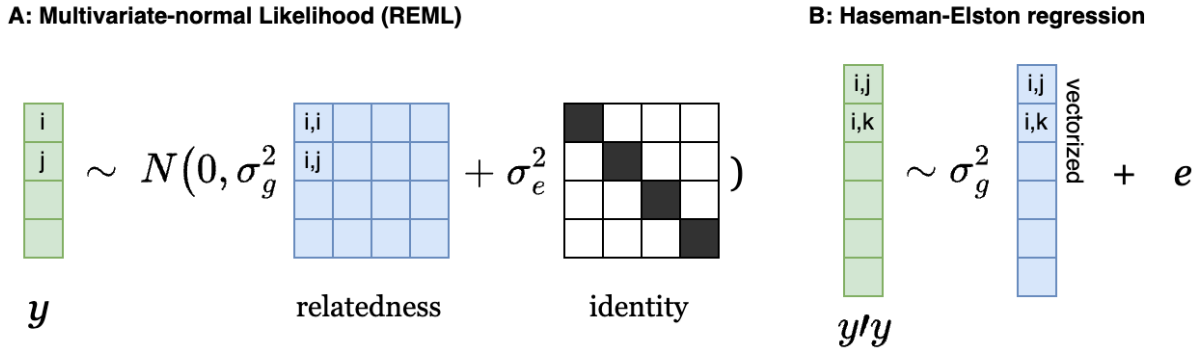


2.2 | Estimation

Individual-level estimation (GREML)

Multiple methods can estimate h2g directly from molecular data, typically by relating the covariance in phenotypes to the covariance in genotypes in a population. *GREML/GCTA* uses a "variance component" approach where the trait is modeled as a multivariate normal [$y = N(0, (\mathbf{XX'}/M)\ \sigma^2_g + I\ \sigma^2_e)$] and [$h2g = \sigma^2_g/(\sigma^2_g + \sigma^2_e)$] is learned by maximizing the corresponding likelihood (Yang, Lee, et al. 2011). The use of "GCTA heritability" to describe h2g is somewhat confusing and will be avoided here, because GCTA is a *tool* that can in fact be used to estimate a variety of different variance components. *Haseman-Elston (HE) regression* uses a "method of moments" approach by simply regressing each element of the product of the phenotype [y'y] on the relatedness matrix [**XX'**/M] to estimate h2g by ordinary least squares regression (Golan, Lander, and Rosset 2014). The differences between these approaches are mainly in how they handle unusual trait distributions (e.g. case-control traits) and how efficient they are: GREML is generally more precise than HE regression at a fixed sample size because it makes use of information across individuals more efficiently.

Two common methods for estimating heritability (h2g).
*(**a**) Estimation with REML under a Multivariate normal likelihood: green is the phenotype vector and blue is a matrix of sample relatedness. (**b**) Estimation with Haseman-Elston regression: green is a vector of the product of phenotypes between individuals, and blue is the vectorized relatedness estimates between the corresponding pairs.*



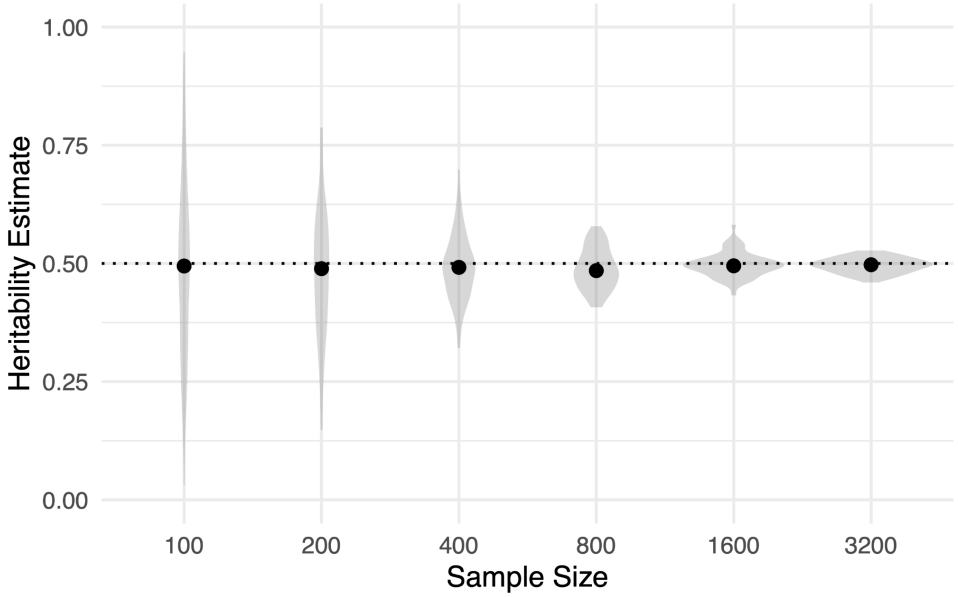
Properties

An important point about estimators of h2g is that (when assumptions are met) they are "unbiased", meaning the estimated parameter equals the true parameter in expectation (i.e. as sample size increases) for the variants in [**X**]. This is in direct contrast to the individual associations identified in GWAS or the accuracy of polygenic scores, which are highly dependent on sample/training size. In the figure below, a trait with h2g of 0.5 is simulated and estimated across data from different sample sizes. The estimates remain *accurate* and unbiased even at very low sample sizes (i.e. they correspond to the true estimate on average over many simulations). The only quantity that changes is *precision* around the estimate – the level of

certainty – which increases with sample size as one would expect. This may seem counterintuitive if you are used to models "overfitting" to data when the number of data points is smaller than the number of features. But h2g methods are only estimating a *single* parameter, they are not estimating individual effect sizes, and thus remain unbiased when model assumptions are met regardless of sample size.

Heritability (h2g) estimates remain unbiased regardless of sample size.

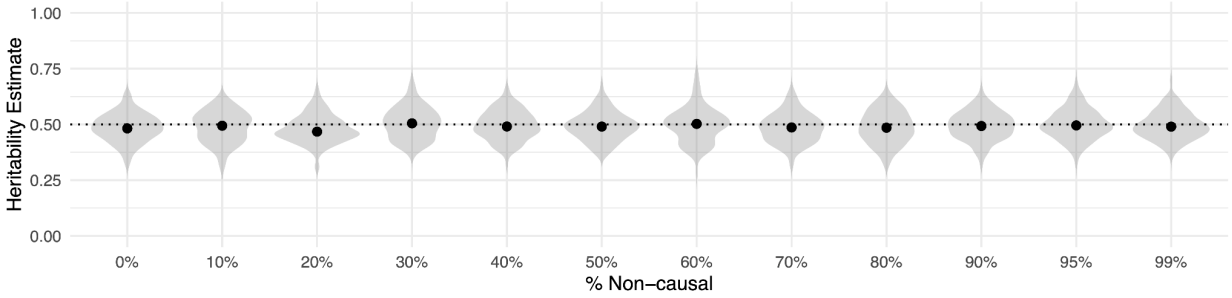
Each violin reflects Haseman-Elston regression estimates from 100 simulations of a 50% heritable trait estimated at the (x-axis) number of individuals. Points represent the mean.



h2g estimates are likewise unbiased by the inclusion of variants in [**X**] that are non-causal or unassociated with the trait. This is a mathematical consequence of estimating the sum of the squared causal/associated effect sizes, which remains the same in these simulations regardless of the causal fraction. In the figure below, different traits are simulated under a wide range of causal/non-causal variant proportions, starting from 100% of variants being causal to 99% of the variants being non-causal. In all instances, the total h2g estimate from a relatedness matrix that includes all variants (causal and non-causal) is consistent with the true value.

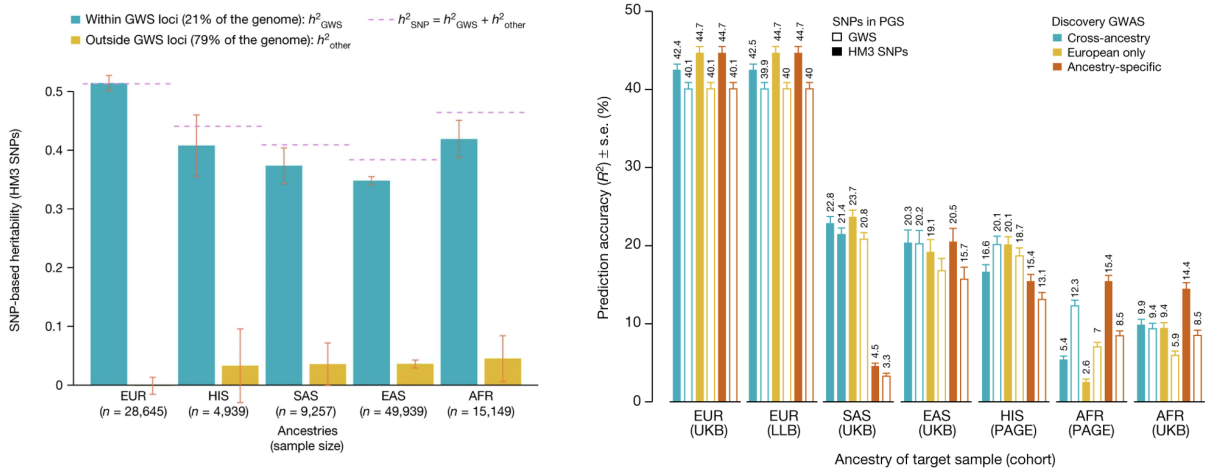
Heritability (h2g) estimates remain unbiased with an increasing number of non-causal variants.

Each violin reflects Haseman-Elston regression estimates from 100 simulations of a 50% heritable trait with the (x-axis) fraction of non-causal variants. Points represent the mean.



An illustrative real data example comes from one of the earliest molecular heritability estimates in humans: the h2g of 0.45 for height, estimated from ~4,000 individuals in 2010 (Yang et al. 2010). At the time, very few individual associations had been identified, and this study energized the human genetics community by forecasting that a much larger number of associated variants were hiding below the level of statistical sensitivity. Over a decade later, the estimate was confirmed at the individual variant level in a GWAS of height from 5.4 million individuals (Loïc Yengo et al. 2022). The 2010 h2g estimate also corresponded to the r^2 of ~0.45 for the out-of-sample prediction accuracy that could be achieved for height in the 5.4M study (assuming ~60k effective variants, we can use the above derivation to compute expected r^2 = 0.45*0.45/(0.45+60e3/5.4e6) = 0.44, right on the money!). **Thus, h2g estimated in the year 2010 provides verifiable claims about genetic studies and prediction accuracy for the year 2022**.

Estimated trait h2g matches observed trait prediction for height.
*(**left**) A massive GWAS of height in 3.5 million individuals identifies individual associations that confirm the total estimated h2g (h2snp), with some underestimation in other populations. (**right**) The estimate snph2 also translates nearly perfectly to the achieved out-of-sample prediction accuracy using genome-wide significant SNPs (GWS) or all SNPs, with a substantial drop in non-European populations. Figure from (Loïc Yengo et al. 2022)*



Misinterpretation

What exactly h2g is estimating is thus often misinterpreted. First, h2g is sometimes described as a “biased” estimator of the total trait heritability; this is not the case, as h2g does not intend to estimate the total trait heritability but only the heritability attributable to the variants in the relatedness matrix (Yang et al. 2016). Likewise, h2g is sometimes described as a “lower bound” on the total trait heritability, this again is not the case: if all causal variants are included in the relatedness matrix then h2g will be an unbiased estimator of the total heritability. Indeed, several studies have attempted to estimate the “total” h2g by sequencing the entire genomes of participants and using all of their variants in the relatedness matrix. Finally, h2g estimators, like any other models, rely on certain modeling assumptions and when those assumptions are violated the estimator can be biased either upwards or downwards and thus provide no bound at all.

Until recently, most h2g analyses focused on common variation, which can be assayed at scale with cheap genotyping arrays. As a consequence, the most comprehensive understanding of trait heritability is for common variants (i.e. “common h2g”). Common variation (and thus common h2g) will not capture the contribution of most rare variants, both because they will not be directly included in the relatedness estimate and because they tend to have low correlation with common variants and so will not be “tagged”. The extent to which common h2g is an estimate of “all” h2g (or the total association with trait of all genetic material) is thus a question of the extent to which variants in [$\mathbf{X}_{common}$] include or correlate with all causal variants.

2.3 | Biases in estimation

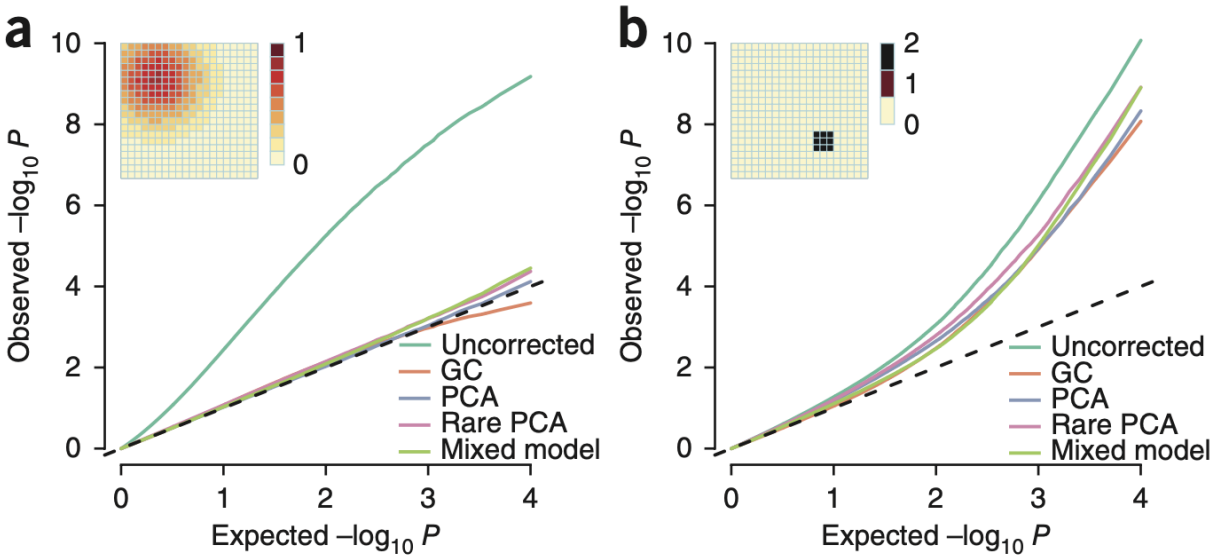
No estimator is perfect, and estimators of h2g make several modeling assumptions and can produce biased estimates when those assumptions are not met. **In short, the biases that are of most concern are: upwards bias from rGE/indirect effects and (primarily for rare variants) upwards bias from unmodeled population structure**. The full set of putative biases is as follows, roughly in order of most to least important:

rGE and "indirect" genetic effects. When genetic variants present in the relatedness matrix are correlated with variants present in other individuals that influence the participant's environment, those effects will also be captured in the h2g estimate. For example, if variants inherited by a participant from their mother influenced their phenotype through their maternal environment, then the effect of those variants will get counted in the h2g estimate even though it is "indirect" (i.e. mediated by parental genetics). This may be interpreted as an upward bias as such "indirect" effects are not strictly causal (altering them in the participant would not lead to a change in phenotype in expectation). Another way to think about this is that rGE makes genetically similar individuals look more phenotypically similar than if there was no environmental structure. Distinguishing direct and indirect factors will be discussed in much more detail in the next section.

Subtle population stratification. Population stratification is the incidental correlation between genotypes (typically due to genetic drift) and environment (typically due to environmental separation). Estimators of h2g account for stratification through the inclusion of covariates for genetic ancestry. If these covariates do not fully capture the stratification the GCTA estimate will be biased, generally upwards (J. Huang et al. 2023). In general, including a large number of ancestry covariates is seen as an effective way to address stratification (Goddard et al. 2011). However, accounting for recent population structure may be challenging for studies of rare variants (Zaidi and Mathieson 2020; Mathieson and McVean 2012).

Rare variant stratification is difficult to account for and inflates heritability (in simulation).
*(**a**) A common genetic variant that has accumulated in a geographic region (shown as a cloud in the grid) can be properly accounted for with a variety of methods for controlling stratification (all colored lines, except “Uncorrected”, match the dashed null). (**b**) A rare genetic variant arising in a very specific environment (shown as a point in the grid) leads to inflation association estimates (all colored lines deviate*

from the null). In all cases, the variant is not causally associated with the environment/trait. Figure from (Mathieson and McVean 2012).

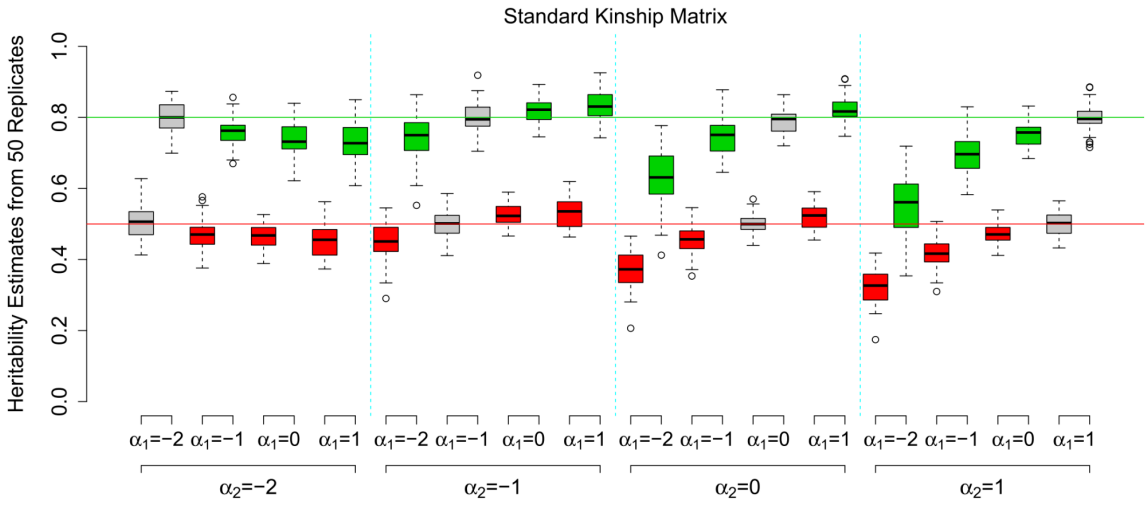


Residual genetic or environmental relatedness. h2g is defined assuming a homogenous population with an independent and identically distributed environmental term. This assumption is violated if related individuals and/or individuals with substantially shared environments are included in the data (Zaitlen et al. 2013). In this case, the h2g estimate will additionally capture the contribution of any genetic variation correlated with the genetic relationship: either direct genetic effects or correlated environment. This is typically accounted for by restricting to stringently unrelated individuals (who are unlikely to share environments) and including covariates for known environmental structure.

The distribution of causal variants is systematically different from the distribution of variants included in the relatedness matrix (even if all causal variants are included in the relatedness matrix). For example, if causal variants are systematically at a higher/lower frequency or in higher/lower correlation than all genotyped variants (Speed et al. 2012). This can produce either an upwards or downwards bias depending on the relationship between the causal variants and variants used. In general, this potential bias can be addressed either by partitioning the heritability into multiple frequency-based components (Yang et al. 2015) or by using alternative estimators that do not require variant scaling/weighting (Hou et al. 2019).

Moderate GREML biases when the genotyped and true causal variant frequencies are systematically different.

Each panel shows the results from simulations where a_1 is the true causal model and a_2 is the estimation model. a_2=-1 (the default in real data) produces fairly minor bias. Figure from (Speed et al. 2012)

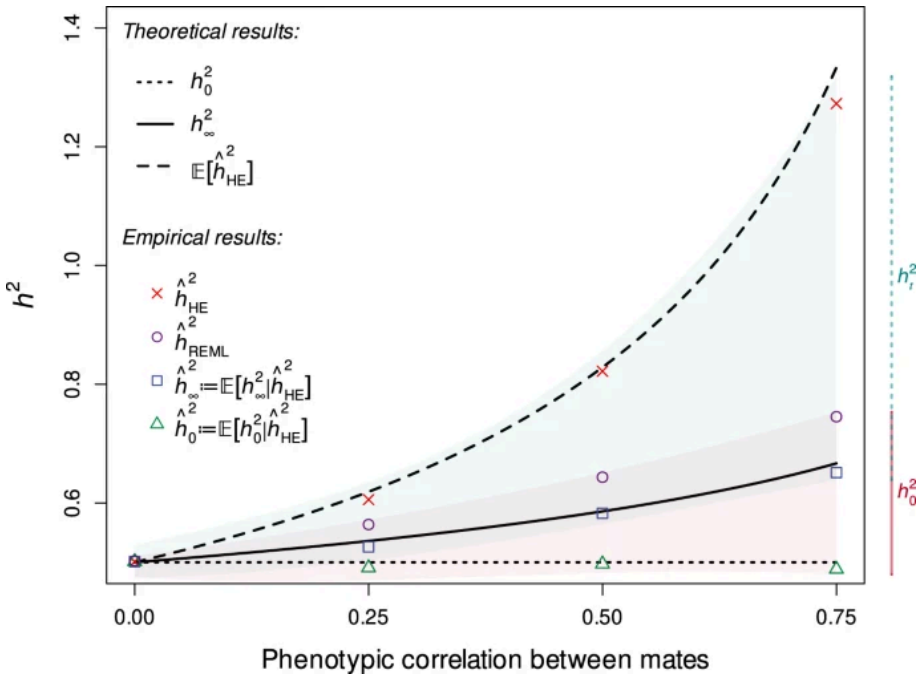


Assortative Mating. Assortative mating biases the genetic relationships towards the causal alleles, and induces an upwards bias in h2g estimators (Border, O'Rourke, et al. 2022). AM creates correlations across distant causal variants inherited from genetically correlated parents, which increases the true association of genetic variance on the trait (i.e. the true [Cor(**X**b,y)^2] is higher than it would be with the same genetics and environment under random mating). Heritability estimators do not model this excess correlation and thus the association between genetic variation and trait appears stronger than it truly is, inflating the estimate of h2g (i.e. the estimated h2g no longer reflects the true [Cor(**X**b,y)^2]). This bias impacts estimators differently and for the GREML estimator it is typically expected to be small (<10%). However, for social/behavioral traits under high assortment (educational attainment, political values, etc) AM biases need to be considered.

Moderate GREML and HE bias due to Assortative Mating of the REML estimator.

The solid line is the "equilibrium" heritability, or the heritability in the population assuming AM has stabilized. The dashed line is the hypothetical "random mating" heritability in a population with no AM. h2HE is the estimator in the contemporary population using Haseman-Elston regression; h2REML is the estimator in the contemporary population using REML. Purple dots are estimates from REML/GCTA and red x's are estimates from HE/LDSC.

Figure from (Border, O'Rourke, et al. 2022)

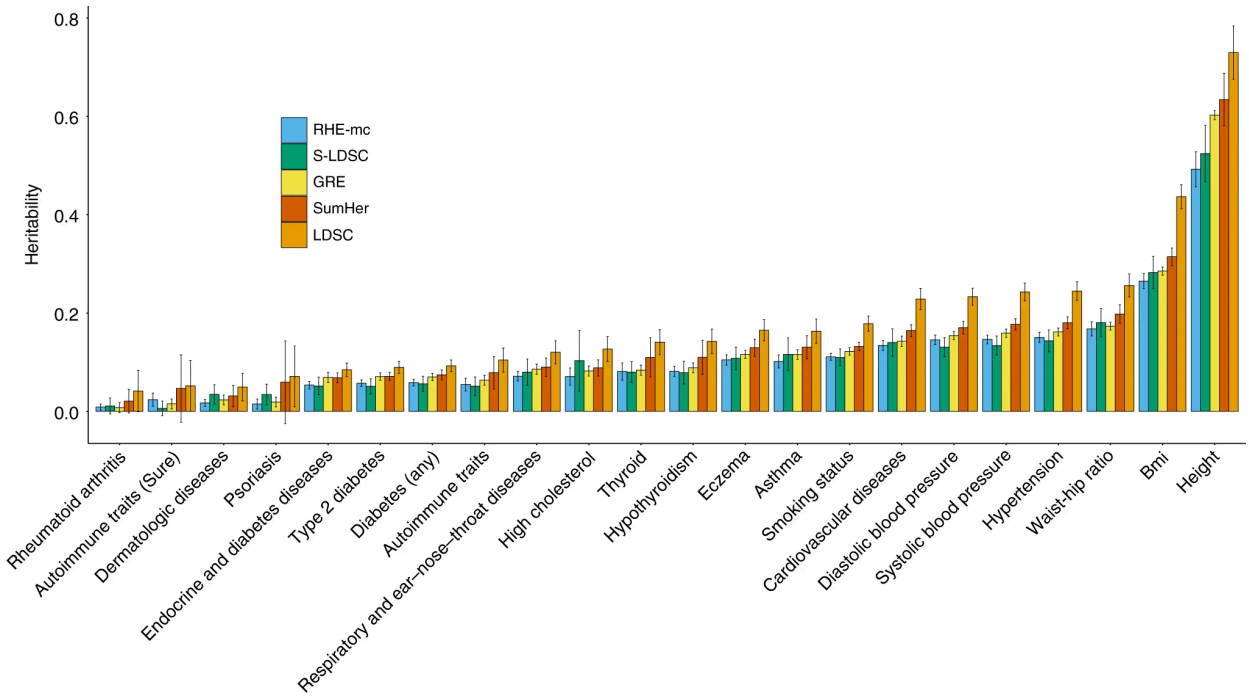


Case/control versus continuous traits. For mathematical reasons, estimates of case-control phenotype heritability under ascertainment (i.e. cases are overrepresented relative to the population) may be biased when using REML but not HE-regression (Golan, Lander, and Rosset 2014). Estimates for case-control phenotypes also typically need to be converted to a "liability scale" parameter, based on assumptions about the population prevalence of the trait and the underlying trait distribution.

GxG / GxE. Dominance, gene-gene, and gene-environment interactions that are independent of additive genetics are not included in h2g and do not bias the estimator. Extensions have been proposed to estimate these quantities: (i) h2 due to dominance "residuals" (the extra contribution of dominance variation not captured by common variants); (ii) h2 due to all gene-gene interactions, though the power to estimate this term is generally very low; (iii) an explicit GxE "heritability" term when the E is measured.

Parameter choices. Each algorithm for estimating h2g involves some explicit or implicit design decisions: how to scale variants, how to restrict unrelated individuals, how many components to include and how to select them, how to model covariates, etc. These choices typically produce some small differences in the resulting estimates.

Different methods for estimating common h2g generally agree.
h2g estimates from five different approaches are shown for 23 representative traits. RHE-mc: A fast, multi-component HE-regression; LDSC/S-LDSC/SumHer: Summary-based HE-like methods with different components or SNP weights; GRE: a method that does not assume a given SNP weighting. Figure from (Pazokitoroudi et al. 2020)

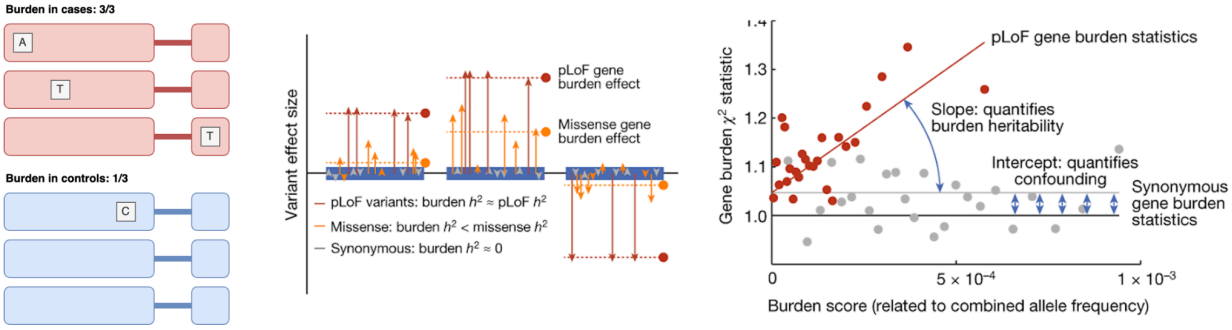


2.4 | Rare coding burden h2g

A convenient aspect of defining h2g in terms of the genetic variation in [**X**] is that one can then derive creative ways to estimate the association of specific classes of genetic variation. Recently (Weiner et al. 2023) proposed a quantity related to h2g they called “coding burden h2g”, an analog of h2g but using genes instead of variants. Rare variant studies typically employ “burden” (or collapsing) tests, which aggregate the carriers of any rare allele in a gene into a single unit. This is done because individual rare variants have too few carriers to be tested directly, and under the assumption that any large coding change to a gene is likely to have the same effect on the phenotype. In the same way that h2g is an estimate of the total trait variance associated with all the variants in [**X**], coding burden h2g is an estimate of the total trait variance associated with the burden effects across all the tested genes. Coding burden h2g thus quantifies an aspect of rare variant heritability for variants that are otherwise too rare to be counted individually. Coding burden h2g will be lower than the total rare h2g if some included variants have no effect or an opposite effect to the average effect in the gene (in contrast to common h2g, which is not biased by the inclusion of non-causal variants). Recent large-scale analyses of exomes demonstrated that 77% of associations were identified through burden tests, suggesting that burden h2g captures a large proportion of total coding h2g (Backman et al. 2021).

Schematic of a collapsed burden test and burden heritability.

***Left**: A coding burden/collapsing test applied to a single gene. **Middle**: Coding burden across multiple genes. **Right**: Estimating the rare coding burden with Burden Heritability Regression. Figure from (Weiner et al. 2023).*

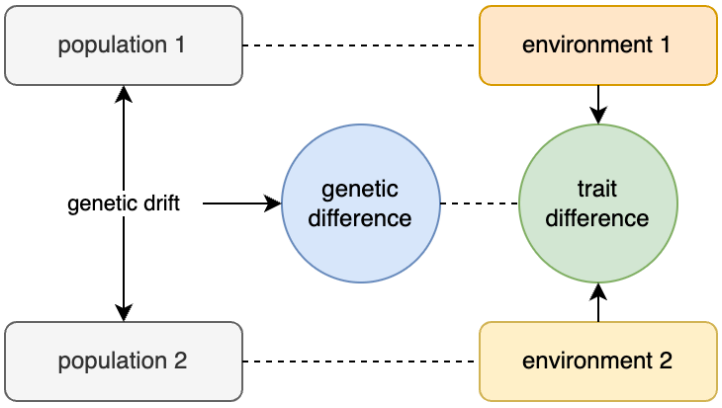


2.5 | Population stratification

Population stratification occurs when differences in the genetics between populations and differences in the environments between populations "line up" by happenstance. For example, two populations that are partially separated (e.g. by geography) and do not undergo continuous random mating will, over many generations, exhibit random genetic differences due to neutral drift (see [**8.3**]). Any trait that differs between the populations for environmental reasons will then appear to be correlated with every drifted variant, leading to the *appearance* of heritability in the total population (recall: heritability is just the correlation of genetic variation with the trait). Even though drift is weak, very large genetic studies are still statistically powered to identify subtle correlations and (in genome-wide analyses) amplify them across many sites, so population stratification in genetic analyses is a major concern. Beyond drift due to separation, other forces can induce non-causal genetic differences between populations: for example, rapid population expansion in one group will increase the number of rare variants and thus induce stratification in rare variant "burden" tests.

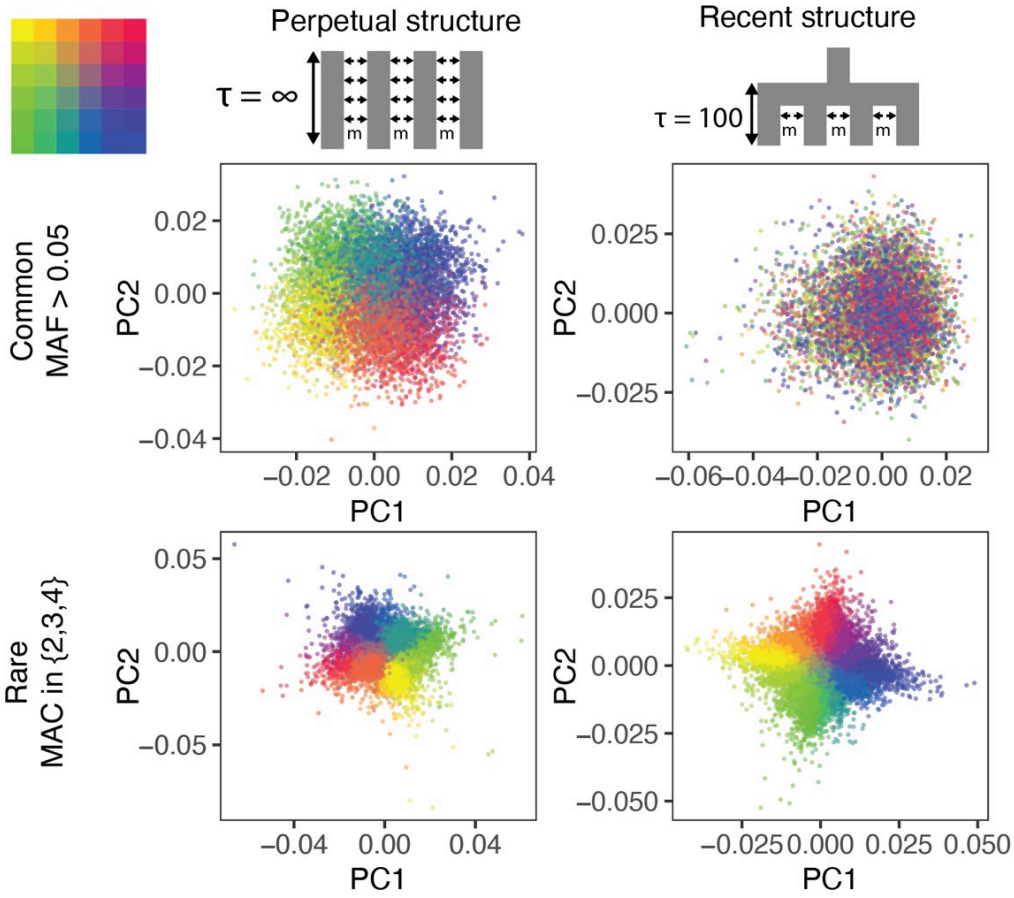
Schematic of population stratification.

Two populations (gray) separate for multiple generations leading to neutral genetic drift, which induces subtle genetic differences at all variants (blue). Two different environments (orange/yellow) influence the trait of interest in these populations (green). These two sources of stratification will then produce non-causal correlations between genetic variation and trait (dashed lines).



In neutral two-population models, stratification will lead to some population-specific allele frequency differences (or "drift") across all variants in the genome, and can thus be inferred by methods that estimate broad axes of genetic variation (e.g. Principal Components Analysis (PCA); see [**9.4**]) or by methods that model unusual patterns of linkage disequilibrium (e.g. LDSC regression; (Bulik-Sullivan et al. 2015)). However, when genetic structure is recent or non-neutral (potentially more substantial in regions of the genome under selection), identifying and controlling for stratification is challenging (Zaidi and Mathieson 2020; Mathieson and McVean 2012). In the figure below, population structure that is undetected by PCA is shown.

Visualization of population stratification on common and rare variants in simulations.
*Top row shows population structure on a grid that is either perpetual separation (**left**) or separation within the past 100 generations (**right**). Middle row shows the structure inferred from common genetic variation (principal components analysis). Bottom row show the structure inferred from rare genetic variation. Notably, recent structure is only identifiable from the analysis of rare variants. Figure source: (Zaidi and Mathieson 2020)*



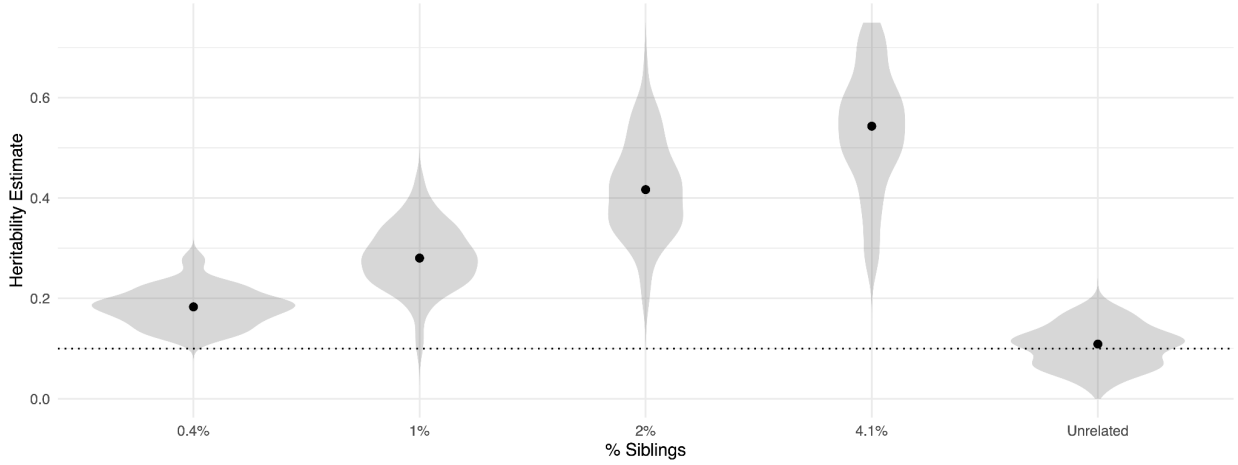
The line between "population stratification" and "passive rGE" becomes blurred as one moves further away from the causal mechanism. A rare variant that incidentally accumulated in a region with excess pollen (and thus appears to be associated with allergy) would be considered "stratification". On the other hand, a rare variant that caused individuals with allergy in prior generations to move to urban areas (and now appears to be associated with urban pollution) could be considered "passive rGE". Neither mechanism is strictly causal: the rare variant in the

first example does not increase allergy and, in the second example, does not increase environmental pollution. **Without knowing the underlying mechanisms it is not possible to distinguish even these two non-causal scenarios**.

2.6 | A word on "molecular" kinship heritability

Sometimes molecular methods are used to estimate kinship "heritabilities", which leads to confusion about what is actually being estimated. The approach generally involves applying REML/HE-regression to a kinship matrix built from pedigree relationships, or a "realized" kinship matrix built from genetic relationships among close relatives (Zaitlen et al. 2013; Speed, Kaphle, and Balding 2022; Young et al. 2018). In practice, these two procedures are nearly identical, as the genetic relationships among close relatives are very similar to the expected relationships based on their pedigrees: one is merely a data-driven estimate of the other (Zaitlen et al. 2013). Even though molecular data may be employed, the estimand is not the variance in trait that can be assigned to *genetic* variation, but the variance that can be assigned to *familial* relationships. Thus, any components of trait variance that track in families – shared environment, for example, but also rare/private genetic variation – will also be included in this kinship-based estimate (Zaitlen et al. 2013; Young et al. 2018; Kemper et al. 2021). The extent to which shared environment biases the estimate relative to h2g will be a complex function of the number of close relationships in the relatedness matrix and cannot be easily derived. This is illustrated in the figure below, where a trait is simulated with true h2g of 0.10 and the rest explained by a shared sibling environment. An estimate using unrelated individuals (i.e. one of each sibling) is unbiased, as expected. However, as more siblings are included in the analysis, the estimated heritability increases substantially, going beyond 0.5 when just 4.1% of the relationship pairs are siblings. Relatively small amounts of relatedness can thus introduce substantial biases.

h2g estimates are inflated by shared environment when including related individuals.
A simulated trait with true h2g of 0.10 (dashed line) and the rest due to shared/familial environment. Estimates become increasingly biased when increasing the number of siblings included in the analysis (x-axis: fraction of pairs that are siblings), increasing to >0.50 when 4% of the pairs are siblings. The estimate is unbiased when restricting to unrelated individuals. All estimates with HE-regression over 100 simulations.



Even in the absence of a shared environment, the kinship-based estimate will still capture genetic variation that is correlated with relationships in families that would not otherwise be correlated in unrelated individuals. For example, the fact that two siblings share half of chromosome 1 is strongly indicative of sharing half of chromosome 2; whereas the fact that two unrelated individuals share 0.001 of chromosome 1 is not informative of their relationships on chromosome 2. Thus, building a relatedness matrix from just chromosome 1 would capture the contribution of variation on chromosome 2 (and all the other chromosomes) in siblings but not in unrelated individuals. Similar intuition holds for variation on the same chromosome that's not typed/correlated with the genotyped variants. For this reason, kinship-based estimates are sometimes referred to as "h2" or "narrow-sense heritability" with the presumption that they will capture variance explained by all genetic material (Speed, Kaphle, and Balding 2022); but, as noted above, this terminology is a bit misleading due to the additional tagging of environmental components. Confusion over molecular h2g estimates in the presence of relatedness has led to some erroneous conclusions of bias (see: (Kumar et al. 2016) and responses: (Yang et al. 2016; Gamazon and Park 2017)).

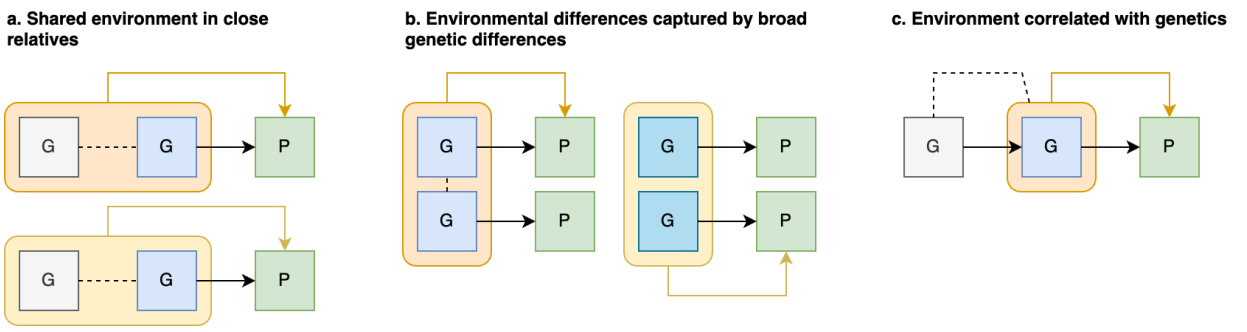
In practice, the appropriate use of kinship-based estimators is thus to *control* for the shared environment, typically as a second component in a model with otherwise unrelated individuals (Zaitlen et al. 2013; Young et al. 2018).

2.7 | Putting it together: environmental confounding in genetic studies

The preceding sections focused on general sources of h2g estimator bias, but a particularly important and poorly understood source is environmental confounding. We'll define *confounders* here in the causal sense: a variable that influences the trait and also influences the genetic variation being tested. There are three broad classes of environmental confounding in molecular h2g analyses, summarized in the figure below.

Three broad forms of environmental confounding in genetic analyses.

*(**a**) Shared environment across relatives correlated with the trait; (**b**) Environment correlated with genotype frequency due to genetic drift (shaded blue); (**c**) Environment passively correlated with parental/relative genotype and with the participant trait. G: Genotype (blue for individuals in the study, gray for related individuals); P: phenotype; rounded squares indicate environments; dashed line indicates either a causal or non-causal relationship.*



a. Confounding due to a shared trait-influencing environment among close relatives: where individuals who are closely genetically related also share environmental influences on the trait, which increases the gene-trait covariance and inflates h2g. This type of confounding is addressed by strictly pruning related individuals out of the study or including a second component for close relatedness. H2g estimates may still be inflated by subtle environmental confounding among moderately related individuals (e.g. geographic environments).

b. Confounding by population stratification: where a trait-influencing environment is incidentally correlated with genotype due to genetic and environmental drift. This type of confounding is addressed by including genetic ancestry components as covariates in the analysis, which intend to capture the axes of genetic variation that are correlated with the environment. H2g estimates may still be inflated by subtle environmental confounding with recent genetic variation that is not captured by conventional principal components or is not linearly correlated with them.

c. Confounding by parental/"dynastic" genotype that is correlated with trait-influencing child environments. This type of confounding will persist even among strictly unrelated individuals with homogeneous genetic ancestry. Methods to address such "dynastic" confounding will be discussed in more detail in [**3.0**].

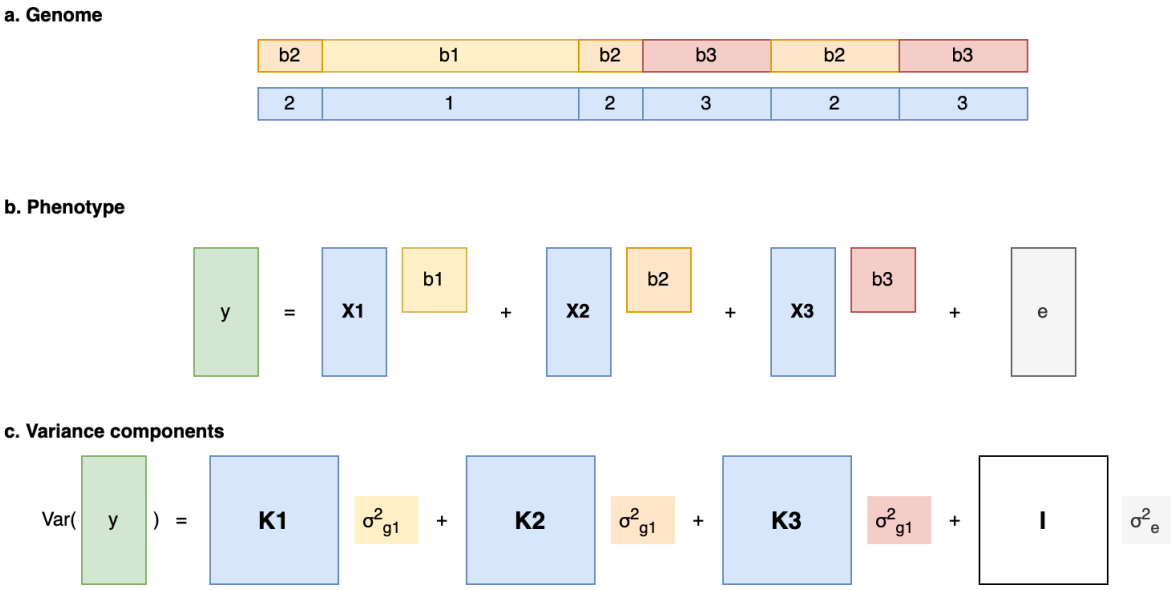
Environmental and technical variation can, of course, influence genetic analyses in other ways (for example, missing or noisy phenotypic data). If these factors are uncorrelated with genotype, however, they will lead to decreased h2g and fewer associations (i.e. false negative findings) and thus tend to be less of a concern.

2.8 | Functional partitioning of h2g

While total h2g estimates draw general interest and controversy, the field of molecular genetics is typically more interested in quantifying which parts of the genome are *relatively* important for heritability, known as *partitioned* heritability. The genome is a patchwork of different functional elements: gene exons that directly code for RNA, promoters that initiate transcription, enhancers/suppressors/insulators that regulate those genes, and so on. Knowing whether variants in certain functional regions tend to have a larger effect on the trait can thus tell us something general about which biological mechanisms are important and where to focus our efforts. Under the assumption that causal variant effects are uncorrelated (as well as the other baseline assumptions described in [**2.3**]), one can estimate the fraction of h2g that can be jointly assigned to each of a given set of annotations using multi-component models.

Modeling partitioned heritability with multiple variance components.

(a) Different regions of the genome (1, 2, 3) have different causal effects (b1, b2, b3) on the trait. For example, SNPs in 1 are in coding regions, SNPs in 2 are in regulatory elements, and SNPS in 3 are all the rest. (b) The phenotype is a sum of genotype-effect products and a random environment where b1, b2, b3 are each drawn from a normal distribution with their own variance. (c) The variance of the phenotype can be assigned to each functional partition using partition-specific kinship matrices.



This analysis is most commonly conducted with "stratified" LD-score regression (sLDSC), which requires only GWAS summary statistics (and the annotated region definitions) (Finucane et al. 2015). Under additional assumptions, these methods have also been extended to overlapping and continuous (Gazal et al. 2018) annotations, as well as annotations based on other molecular phenotypes (Yao et al. 2020; Hormozdiari et al. 2018).

In the absence of cross-annotation correlations, functional h2g estimates should also translate into the expected prediction r^2 built from a corresponding "functional" PGI (just as total h2g estimates relate to the total possible prediction r^2). However, in real data where variants in nearby annotations are highly correlated, the expected accuracy of a functional PGI is more complicated and this form of validation is no longer easily defined. Ultimately, functional h2g estimates for a given trait will need to be validated by actually mapping the individual causal variants and summing up their contribution in each functional annotation.

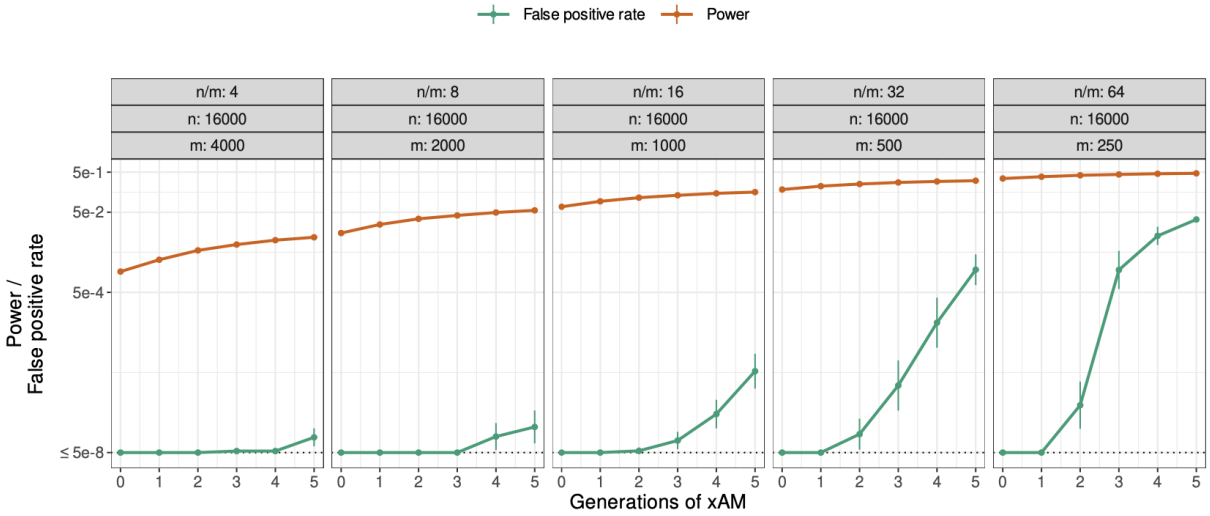
2.9 | Biases due to cross trait assortative mating

A major challenge for partitioned h2g analyses is cross-trait assortative mating (xAM). Under xAM, partners pair up based on different traits and have offspring; those offspring then inherit variation that is correlated with both traits, which in turn becomes correlated in the population. For example, if tall people (trait Y) tend to have kids with thin people (trait Z), then the variants associated with height (Y) become correlated with the variants associated with weight (Z) in their offspring (including variants that would otherwise be completely independent in the population, such as those on separate chromosomes). This presents two problems for h2g analyses, elegantly demonstrated in the recent work of (Border, Athanasiadis, et al. 2022).

First, genetic variants that are associated with trait Z but not Y in a random mating population will appear to be associated with Y in an xAM population GWAS. **This implies that functional annotations containing variants exclusively associated with trait Z will appear to be enriched**

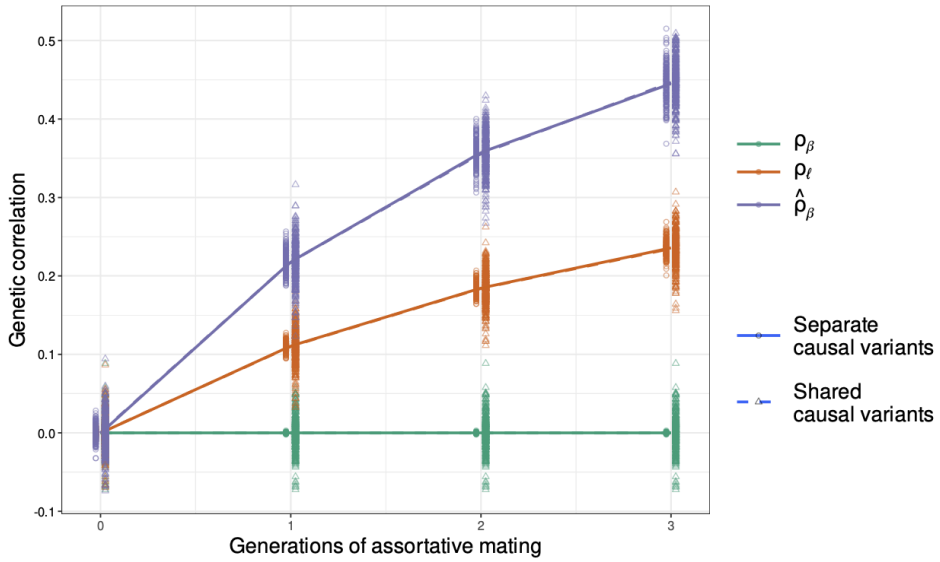
for h2g for Y. For example, if only variants near muscle-expressed genes are associated with height and only variants near adipose-expressed genes are associated with weight, these two gene sets will become enriched for both height and weight in the xAM population GWAS. In the simulations below from (Border, Athanasiadis, et al. 2022), the chance of detecting a non-causal variant at genome-wide significance increases as a function of xAM and variant effect size.

Increased false variant association under cross-trait assortative mating (xAM).
(y-axis) Power or false positive rate (with values of zero replaced with 5e-8) as a function of generations since xAM (x-axis). Sample size (n) and number of causal variants (m) are varied across the panels under fixed heritability. Larger samples and larger effect sizes (fewer causal variants) increase power and the false positive rate. Simulations with cross-mate correlation of 0.5 and heritability fixed at 0.5. Figure from (Border, Athanasiadis, et al. 2022).



Second, **traits that are caused by independent variants and would otherwise be uncorrelated in a random mating population appear to be genetically correlated under xAM**. In the simulations below from (Border, Athanasiadis, et al. 2022), traits with no shared causal variants or with independent causal effects show increased genetic correlation of observed effect sizes and of genetic values after xAM. This inflation is observed under either a marker-based or score-based definition of genetic correlation.

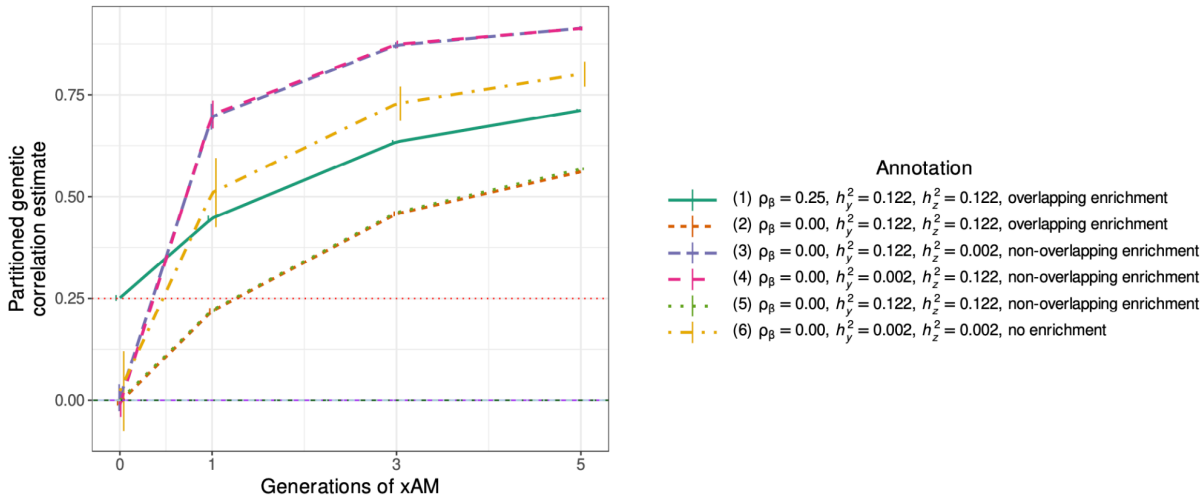
False genetic correlation induced by cross-trait assortative mating.
Genetic correlation (y-axis) as a function of generations of xAM (x-axis) for two traits with no sharing of causal effects (green line). Estimated genetic correlation across variants (purple) or across genetic values / PGIs (orange) becomes inflated relative to the truth. Traits with separate causal variants (solid lines) and shared causal variants with uncorrelated effect sizes (dashed lines) are shown and produce identical results. Figure from (Border, Athanasiadis, et al. 2022).



Third, **due to the directional effect of xAM, functional annotations that contain variants exclusively associated with trait Z will appear to be genetically correlated with functional annotations that contain variants exclusively associated with trait Y**. In other words, the false genome-wide genetic correlation also extends to the local/functional level. In the above example, local genetic correlation between height and weight will appear to be high in both muscle-expressed genes (associated only with height) and adipose-expressed genes (associated only with weight), even if no causal variants are shared between the two annotations. In the simulations below from (Border, Athanasiadis, et al. 2022), functional annotations that contain no shared causal variants still exhibit substantial apparent functional genetic correlation due to xAM.

False partitioned genetic correlation induced by cross-trait assortative mating.

Partitioned genetic correlation shown as a function of different trait architectures and xAM. (green solid line) shows the estimated genetic correlation under a model with true correlation of causal effects in the annotation; estimates are inflated relative to the true value of 0.25. (dashed lines) show different trait architectures with no correlation of causal variants and different levels of overlapping partitioned h2g; estimates are inflated relative to the true value of 0. Inflation becomes most pronounced (pink/purple) when one trait is much more heritable than the other.



It's again worth distinguishing predictive/correlative variation from causal variation under xAM. In the above scenarios, genetic variants associated with height will cause individuals to pair up with partners based on their weight and induce correlation with weight-specific effects in their offspring. Height associations in an individual are thus causally predictive of weight in their spouse and, eventually, their children (but not weight in themselves). One could consider this to be a *socially* causal cross-generational, gene-environment interaction; where the environment is defined by xAM structure and the outcome is the phenotype in offspring. **However, the effect is not directly *biologically* causal**: altering or intervening on a height-associated variant in an individual would not change their weight. Moreover, if the social structure changes (and it is of course always changing), even the socially causally effect will no longer hold.

2.10 | Further Reading

Molecular heritability:

- (Visscher, Hill, and Wray 2008): A high-level primer on estimation and interpretation of molecular heritability.
- (Yang et al. 2010): Seminal work developing and using REML/GCTA to estimate the h2g of height. (Yang, Lee, et al. 2011): Full specification of the REML/GCTA algorithm.
- (Zaitlen and Kraft 2012): Review of concepts related to the estimation of heritability using different approaches.
- (Tenesa and Haley 2013): Review of the measurement, interpretation, and misinterpretation of molecular heritability.
- (Yang et al. 2016): Commentary from the developers of GCTA describing common misinterpretations of h2g.
- (W. Huang and Mackay 2016): Discussion of the identifiability of different additive/non-additive disease architectures with heritability parameters.
- (Young 2019): Perspective on heritability estimates from different estimators and the "missing heritability" question.

Partitioned heritability, genetic correlation, and biases:

- (Speed et al. 2012): Systematic evaluation of potential biases in h2g estimates due to deviations in the causal variant distribution.
- (Finucane et al. 2015): Derivation of stratified LD-score regression for functional heritability partitioning.
- (Zaidi and Mathieson 2020): Models and analyses of potential confounding in genetic studies due to very subtle/recent population structure.
- (Border, O'Rourke, et al. 2022): Theory and methods for how assortative mating influences h2g estimators.
- (Border, Athanasiadis, et al. 2022): Theory for the influence of cross-trait assortative mating on trait heritability and genetic correlations.

Direct and indirect heritability

3.0 | Summary

- **When traits exhibit cultural transmission (parental traits influence child traits) or assortative mating, population heritability estimates will be biased (typically upwards)**. Population heritability estimates and/or indirect effects are uninterpretable: they are an amalgam of true indirect genetic effects, correlated environmental confounding, correlated environmental confounding due to assortative mating, and population stratification.
- **Assortative mating *together* with cultural transmission further amplifies indirect effect bias over generations and propagates it even after genetics/environment has changed**. In addition to bias due to cultural transmission, under assortative mating the population heritability may be capturing correlations from prior generations that are no longer active in the present generation.
- **Heritability estimators are <u>additionally</u> biased by assortative mating (even in the absence of cultural transmission / indirect effects), which is not properly modeled in the relatedness matrices**. Assortative mating will inflate population heritability estimates

and deflate within-family heritability estimates. “Bias” means the estimate no longer reflects the fraction of the trait that could be predicted with genetic features.

- **Estimation bias in h2g models can be fully corrected for only if the assortative mating has reached equilibrium and the assortment is happening on the measured trait directly**. Latent assortment on an underlying trait can further bias heritability estimates and no corrections have yet been established.
- **The direct genetic h2g (i.e. the variance in trait explained within the individual unbiased by family environment) can be estimated using within-family heritability and GWAS methods**. Relatedness Disequilibrium Regression, which requires genotyped parent/child trios, is uniquely robust to environmental confounding from siblings and also only modestly biased by assortative mating when estimated using REML.
- **The same issues of interpretation apply to polygenic scores, in addition to unique challenges due to the portability from score training to target population**.

3.1 | Concepts

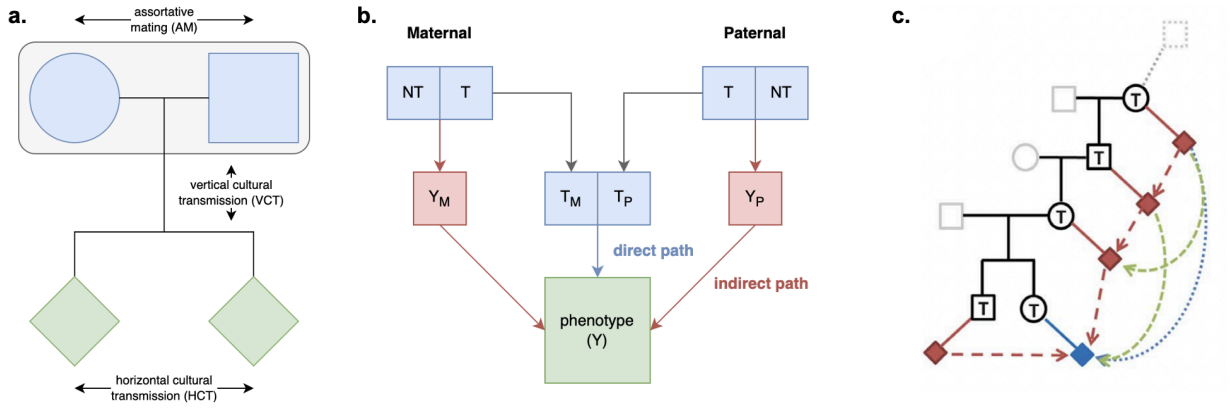
By default, h2g will include the variance from genetically correlated environments (rGE). Intuitively, h2g will include variance due to “active” rGE, where genetic variants drive individuals to create environments that influence their traits (which are causal in the sense that changing the genetic variant in that individual can change their phenotype). Less intuitively, however, h2g can also include variance due to “passive” rGE, where genotypes in parents/families influence the trait and are correlated with genotypes in the offspring. *Completely unintuitive,* however, is the fact that h2g can capture *entirely* non-causal correlations inflated by “cultural transmission” or assortative mating. Cultural transmission is the broad phenomena where traits in some individuals influence the traits in others (Cavalli-Sforza et al. 1982), for example: the language of parents is transmitted to their children (“vertical cultural transmission”, see figure below) or the habits of students are transmitted to other students (“horizontal transmission”). Cultural transmission, together with assortative mating, can mimic genetic transmission and thus confound the estimation and interpretation of heritability.

The complexity of such confounding effects was succinctly summarized in a recent GWAS of educational attainment (Okbay et al. 2022): “*The population effect captures the sum of the direct effect, indirect effects from relatives (e.g., genetic influences on parents’ education, socioeconomic status and behavior), other gene–environment correlation (i.e., correlation between genotypes and environmental exposure, with population stratification being one possible cause) and a contribution from the genetic component of the phenotype that would be uncorrelated with the PGI under random mating but becomes correlated with the PGI due to the LD between causal alleles induced by assortative mating.*”

Because genetic transmission is a “***particulate***” process, molecular h2g methods that track individual transmitted and non-transmitted variants enable us to better disentangle these components of variation, typically referred to as “direct” (i.e. genetic variants acting on the trait in the individual) and “indirect” (i.e. genetic variants correlated with everything else). **The distinction between direct genetic effects and indirect correlations is critical to developing a causal**

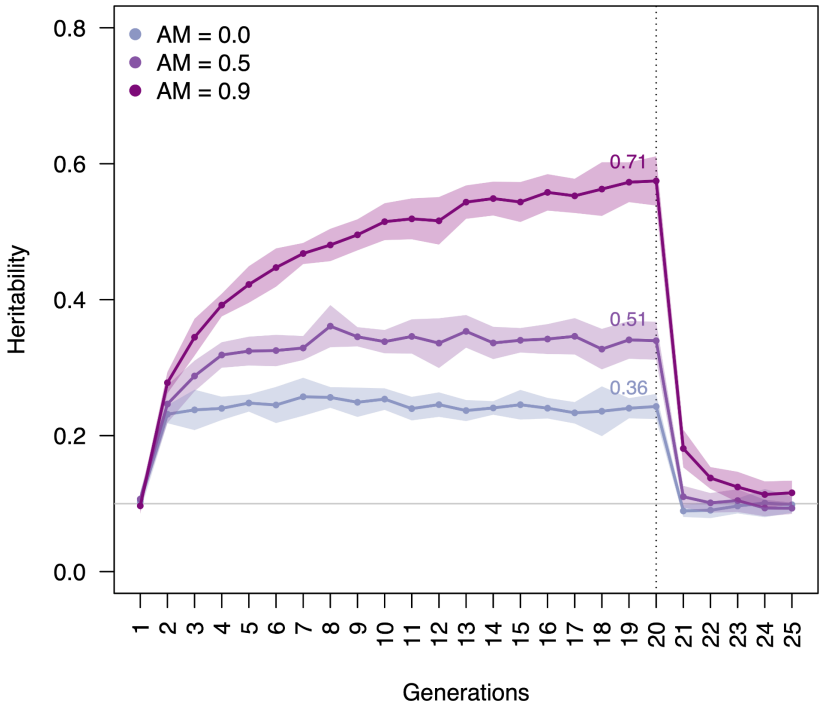
understanding of heritable traits. The figure below visualizes the underlying cultural and genetic processes as well as the genetic "particles" that can be used to track direct effects and indirect associations.

Schematics of cultural transmission leading to direct and indirect effects.
*(**a**) Definition of terms: Assortative Mating (AM) between parents; Vertical Cultural Transmission (VCT) of trait from parents (gray block) to children; Horizontal Cultural Transmission (HCT) between siblings or other individuals in the same generation. (**b**) Both transmitted (T) and non-transmitted (NT) alleles can influence a trait (Y), the former "directly" (blue line) and the latter through rGE/indirect effects (red lines via the parental phenotypes Y_M and Y_P). (**c**) A more complex multigenerational direct/indirect model including sibling effects. Figure adapted from (Kong et al. 2018)*



To emphasize this point, let's look at what happens to constant direct genetic effects on a trait in a constant environment when it is also shaped by vertical cultural transmission (VCT) from parental traits (for example, language) as well as assortative mating between parents. In the figure below, a trait is simulated with a small direct genetic effect (variance of 10%), a moderate VCT effect from the mean parental phenotype (variance of 40%), and a random environment with variance of 50%. After one generation of VCT, the true h2g (defined as the squared correlation between the genetic value and phenotype with no measurement error) immediately appears to increase to >20% under random mating. **This inflation in h2g is a consequence of correlation with parental genotypes (via cultural transmission), not an increase in the causal biological effect sizes.** The variants appear to have shaped the trait twice, once in the parents and once in the child, thus inflating the h2g.

Indirect effects increase apparent heritability even under fixed genetic and environmental variation.
A simulated trait where genetic variation is fixed and initially contributes 10% of the variance in the trait, parental traits contribute 40% of the variance ("vertical transmission"), and the rest is random. Vertical transmission is replaced with a random environment after 20 generations (vertical line). The average sibling phenotypic correlation at the end of the vertical transmission period is shown numerically for reference.



Under assortative mating, the true h2g appears to increase even further and with each successive generation. Now, due to increased correlation across many sites, the variants appear to have shaped the trait many times for each generation of assortment. A trait for which only 10% of the variance is *caused* by genetics in truth, appears as though a whopping ~60% of it's variance is associated with genetics. What happened? Individuals paired up based on their phenotypes, increasing their genetic similarity, and passed on that excess similarity to their offspring. They also passed on their phenotypes through cultural transmission. Now offspring with an excess of trait altering alleles also acquired an excess of the corresponding trait, perfectly imitating genetic transmission. Over generations, this process repeats and intensifies.

To demonstrate that this apparent h2g is not causal, in the 20th generation we change the environment from VCT back to random transmission (i.e. the VCT/parental trait contribution to the trait is replaced with random variance): the apparent h2g quickly returns to ~10%, with slower decay under high AM. Even though the true h2g changed substantially, neither the genetics nor the environment actually changed; what did change was the *relationship* between phenotypes and environments across generations. Note that these quantities were all derived from the true genetic and phenotypic values with no estimation, estimators of h2g under these processes exhibit additional biases as detailed in later sections.

A naive causal interpretation of this data could lead one to conclude that the "influence" of genetics has fluctuated greatly over time: perhaps a highly beneficial mutation was rapidly sweeping through the population, or a very deleterious environmental factor was eliminated and then suddenly returned. GWAS in the earlier generations would identify large-effect variants or highly predictive polygenic scores. Yet, tragically, attempts to experimentally validate these associations or identify the right environmental context would fail to recapitulate a large effect on

the trait. How can we avoid this fate? **By explicitly incorporating models of direct and indirect effects into the way we study and quantify heritability**.

Finally, let's clarify a bit of jargon:

- Vertical cultural transmission (VCT) is the process by which traits influence traits across generations.
- Direct Genetic Effects are the effects of variants in an individual on their trait and are a consequence of biology.
- Indirect Genetic Effects are the direct effects of variants in individuals in prior generations on their trait, a consequence of VCT on a heritable trait.
- Indirect Effects / Non-Transmitted Coefficients (Young et al. 2022) are the associations of variants that were not transmitted to the individual with their trait, and will include both indirect genetic effects and biases due to population structure and assortative mating (note that transmitted variants can still have indirect genetic effects).
- The final point is important, as estimates of Indirect Effects are often conflated with Indirect *Genetic* Effects and interpreted to be genetically causal when, as we will see, they are easily confounded by non-genetic factors.

In this section, the following language will be used to distinguish various parameters:

- "True population h2g": the true squared correlation between the genetic value and phenotype in the unrelated population (also the squared correlation one would expect from a PGI estimated without error).
- "True direct h2g": the true squared correlation between the genetic value and phenotype in the unrelated population *conditional on the true genetic values in the parents (i.e in a joint model)*. This is also what one would get from a proper within-family analysis using a PGI estimated without error.
- "True indirect effect": the true squared correlation between the average genetic value in the parents and the phenotype in the child *conditional on the true genetic value in the child (i.e. in the same joint model as above)*.

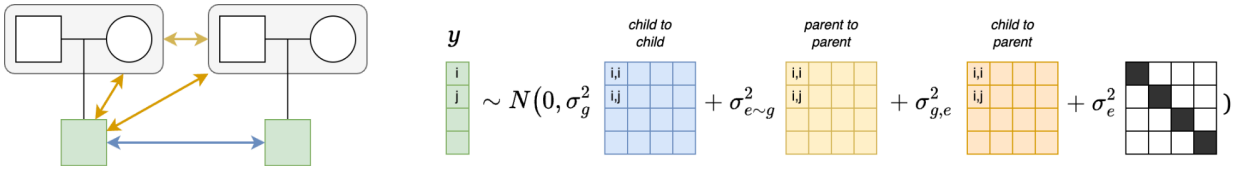
3.2 | Estimation

In general, molecular methods partitioned direct effects by quantifying the association between the trait and the *deviation* of transmitted alleles from their expected familial values. For example, genotyping parent-child "trios" and estimating the association between a trait and the genetic variants in the child while *conditioning* on the variants in the parents. Since parents are the source of genetic variation in children, their genotypes are sufficient to account for all indirect genetically correlated variation. However, it is important to keep in mind that just because parents are used to estimate the indirect effects does not mean the indirect effects were causal in the parents (see below for more on interpretation).

Relatedness Disequilibrium Regression (RDR): direct heritability using families

Relatedness Disequilibrium Regression (RDR) (Young et al. 2018) is an elegant and intuitive approach to estimating direct/indirect h2g: extending molecular h2g estimates from a single component of cross-participant relatedness with additional components for the effect of parental relatedness on the participants' phenotype. If we think of each participant's trait as derived from the sum of (i) a genetic component in the individual (direct), (ii) parental traits and environment that are correlated with parental genotypes (indirect), and (iii) an uncorrelated environmental component, RDR partitions the additive contribution of each component, while conventional h2g estimators collapse the genetic associations of (i) and (ii). The figure below shows how the various child and parental relationships map to specific components in the RDR estimator (note the blue "child-to-child" component here is exactly the same as the genetic component for population h2g estimation in [**2.2**]).

Schematic of the four component RDR model to partition direct/indirect heritability.
*(**left**) A schematic of the relationships between families modeled by RDR with blue, yellow, and orange arrows. Gray rectangle indicates the average parental relationship (maternal versus paternal effects are not modeled). (**right**) The RDR variance components: phenotype (green) is modeled as a multivariate-normal function of the child-child relationships (blue), the parent-parent relationships (yellow, capturing the indirect association from parents), the child-parent relationships (orange, capturing the covariance of direct and indirect effects), and the uncorrelated environmental component (white).*



$$y \sim N(0, \sigma_g^2 \begin{bmatrix} i,i & \\ i,j & \end{bmatrix} + \sigma_{e\sim g}^2 \begin{bmatrix} i,i & \\ i,j & \end{bmatrix} + \sigma_{g,e}^2 \begin{bmatrix} i,i & \\ i,j & \end{bmatrix} + \sigma_e^2 \begin{bmatrix} & & & \\ & & & \\ & & & \\ & & & \end{bmatrix})$$

While the primary estimate of interest is the direct h2g, RDR additionally estimates the variance in the phenotype associated with the genotypes in the parents and thus correlated with parental environment ([$v_{e\sim g}$], i.e. the "indirect" effect) and the covariance between the direct and indirect terms ([$v_{g,e}$]). Significant values of [$v_{e\sim g}$] are indicative of genetic variation correlated with familial environments, and significant positive/negative values of [$v_{g,e}$] are indicative of an alignment/misalignment between direct and indirect effects. **As noted above, "indirect effects" are not necessarily causal genetic effects and can be confounded by other non-genetic processes, as we will see.**

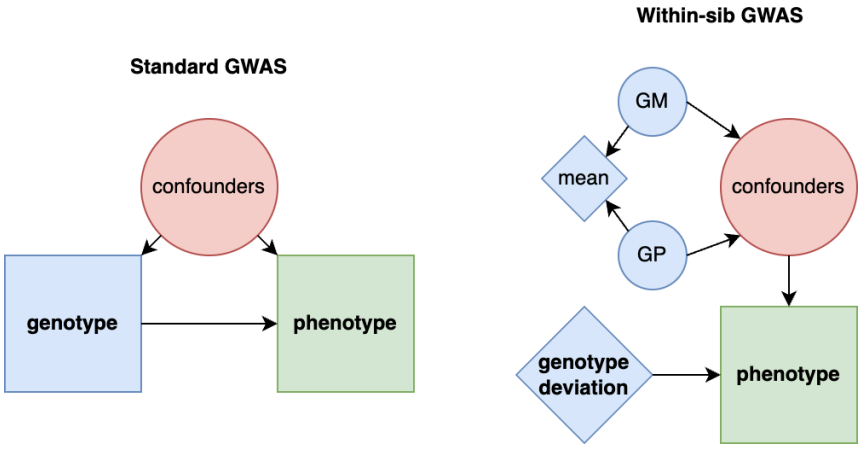
Finally and very much in the weeds, RDR (and, to some extent, other molecular h2g methods) can estimate two forms of direct h2g (recall that h2g is formally defined in relation to the variants included in the genotype or relatedness matrix): (1) using identical-by-descent (IBD) segments between individuals, which are expected to capture all transmitted material that arose prior to the most recent relative from which the segment arose (including most rare variants) (Kong et al. 2008); (2) using common polymorphisms between individuals, which are primarily expected to capture common variants and variants they "tag". In simulations, IBD-based RDR captured ~88% of the variance explained by rare SNPs (between 0.1% and 1%), with the remainder being very recent variants acquired after relatedness. In contrast, SNP-based RDR captured ~30% of the

variance explained by rare SNPs, as expected from the generally low correlation between rare and common variants. **Thus, IBD-based RDR provides the closest value to the direct effect of all transmitted genetic material**. As a practical matter, high quality IBD inference is only available in very specific datasets and populations, so the application of IBD-based RDR has been limited.

Within-family GWAS: Individual direct associations using siblings/trios

In the same way that RDR uses genotyped parents to estimate direct h2g, within-family GWAS designs enable the estimation of the direct effects of individual variants (Abecasis, Cardon, and Cookson 2000; Brumpton et al. 2020; Spielman and Ewens 1998). The underlying model is again that of a trait that is associated with direct genetic effects in the participant as well as confounding by indirect genetic associations in their parents. When data from siblings is available, the average of the siblings will capture the shared genetic variation correlated with their environment vertically, and the deviation in each sibling from that average will capture the direct, sibling-specific variation. In this way, within-family GWAS uses the random genetic differences between siblings to estimate direct associations without confounding from parental genotypes, which are fixed for all siblings (Young et al. 2019). These per-variant estimates can then be fed into standard summary-based methods (e.g. LDSC regression) to estimate common direct h2g. In the figure below, the standard GWAS regression of phenotype on genotype is contrasted with the sib-GWAS regression of phenotype on the "genotype deviation" from the parental or sibling mean.

Schematic for standard GWAS versus within-sib GWAS.
*(**left**) Standard population-scale GWAS can be confounded by unmodeled effects on genotype and phenotype. (**right**) Within-sib/family GWAS captures confounding through the parental genotypes and then estimates the unconfounded effect of the genotype deviation on the phenotype. Circles represent unmeasured variables; squares represent measured variables; diamonds represent computed variables in the sib-GWAS. Adapted from (Howe, Nivard, et al. 2022).*



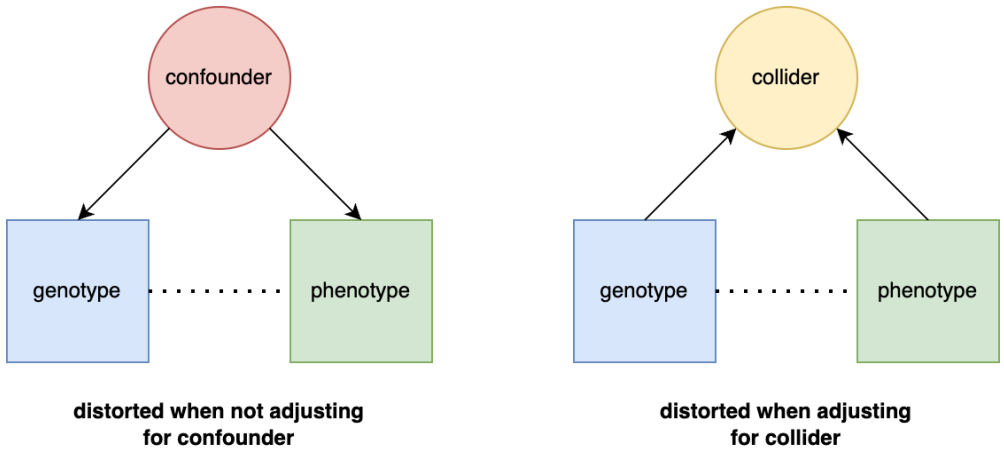
A unique advantage of within-family GWAS analysis is it is not biased by assortative mating, in contrast to variance partitioning methods like RDR (more on this in [3.5]) (Lee et al. 2018; Brumpton et al. 2020; N. M. Davies et al. 2019). A unique disadvantage is that, unlike RDR, sib-GWAS estimates will be biased in the presence of indirect sibling effects: where the genotype in one sibling influences the phenotype in the other through sibling environment. The indirect

sibling effect is effectively "overcorrected" in the sib-GWAS and introduces a corresponding negative bias in the direct effect estimates (positively correlated sibling indirect effects will deflate the sib-GWAS estimate and negatively correlated effects will inflate the sib-GWAS estimate). In contrast, RDR draws signal from individuals across families (after controlling for their parents), so will remain unbiased even with the inclusion of individuals that have siblings as long as the number of sibling pairs is smaller than the number of total pairs (which is true in any large dataset). Large indirect sibling effects have not been observed to date (Young et al. 2022), but with wide uncertainty on the estimates their precise magnitude remains an open question.

Conditional h2g: Adjusting for known environmental confounding/correlation

Perhaps the simplest way to account for rGE would be to measure the environments and include them as features in the inferential model. Indeed, this is typically how population structure is addressed, with genetic ancestry or genetic relatedness *itself* treated as a proxy for the gene-environment relationship and added as a covariate or a random effect, respectively (Price et al. 2010; Patterson, Price, and Reich 2006). Intuitively, if environmental covariates account for non-genetic environmental variance, then the h2g should increase (because the remaining environmental term has decreased); whereas if environmental covariates account for gene-environment confounding, then the h2g should decrease. This is relatively straightforward for covariates that are known to be *upstream* of genetics (e.g. parental environments) but becomes more complicated for covariates that may be mediating genetics. Simply adjusting for all available measurements can introduce new biases by distorting the estimate around non-causal relationships (commonly known as "collider bias", illustrated in the figure below). Note that collider bias can distort the estimate in either direction: if genotype and phenotype have the same (different) direction of effect on the collider, the genotype-phenotype association will be biased downwards (upwards).

Schematic of confounders versus colliders.
*When confounders are present (**left**), the estimate of the causal effect of exposure on outcome is distorted and adjusting for the confounder can recover the true estimate. However, if a collider is mistakenly adjusted for (**right**) it will induce a bias to an estimate that otherwise would be correct.*

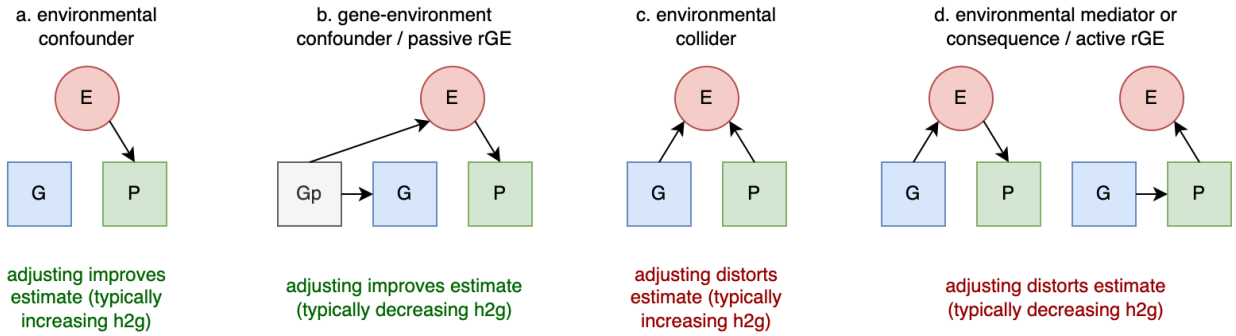


Consider the following examples (also illustrated in the figure below):

A. If urban environments influence the phenotype of some individuals with no relationship to genetics (a simple environmental *confounder*), adjusting for the urban environment will correct genetic estimates and increase h2g.
B. If ancestral individuals with allergy variants moved to urban environments and the genetic variation in their present-day children is indirectly associated with phenotypes influenced by the urban environment (a gene-environment *confounder* / passive rGE), adjusting for the urban environment will correct genetic estimates and decrease h2g.
C. If a genetic variant causally influences moving to an urban environment in contemporary individuals and a non-genetic trait also influences moving to an urban environment (a collider), adjusting for the urban environment will distort the estimate h2g of the non-genetic trait (potentially increasing it).
D. If a genetic variant directly influences moving to an urban environment which in turn influences the trait (an environmental mediator / active rGE) or a genetic variant influences the trait which in turn influences the environment, adjusting for the urban environment will distort the h2g (potentially decreasing it).

Illustrations of gene-environment relationships.

Analysis is always with respect to the effect of G (genotype) on P (phenotype) with (E) as an environmental factor. Gp are unmeasured parental/ancestral genotypes.



Thus care needs to be taken when selecting the covariates to adjust for. In instances where the phenotype occurs temporally after the covariate (for example, the covariate is place of birth) one can be more sure that no causal path exists from phenotype to covariate and thus no collider bias.

Within-family polygenic scores (PRS/PGI)

A polygenic score or index (PRS/PGI) is simply the sum of the estimated genetic effects on a trait in a single individual: i.e. $[x\hat{\beta}]$ where $[x]$ is the vector of genotypes and $[\hat{\beta}]$ is a vector of estimated causal effects of each variant (with the little hat "^" indicating an estimate) (Chatterjee, Shi, and García-Closas 2016). Although in principle PGIs correspond to the genetic value that variance partitioning methods like GREML and RDR also attempting to quantify, the correlation or LD between variants poses a major challenge that the two methods address differently: **specifically, the fact that PGIs use $[\hat{\beta}]$ rather than $[\beta]$ results in many important and sometimes counterintuitive differences**. Variance component approaches are effectively fitting all variants simultaneously and estimating their *joint* association with the trait, without needing to identify any

individual causal variants (if you look under the hood at GREML, for example, you will see equations that are very similar to Bayesian or ridge regression across all variants). In contrast, PGI approaches typically estimate each [$\hat{\beta}$] individually ("marginally") via GWAS and then perform some post processing to either select the optimal variants for the PGI or to "shrink" certain variants to contribute less. There are many strategies for selecting these optimal variants, but the general consequence is that the PGI will contain a mixture of variants that are directly causal/associated with the trait and variants that are only associated through other correlated variants. This may be a relatively minor issue when applying PGIs within homogenous populations but becomes a major issue across genetically distant populations (Martin et al. 2017).

PGIs can likewise be applied within families to estimate components of the direct and indirect effects, by jointly analyzing the PGI computed in an offspring and the PGI computed in their parents for association with the offspring trait (Kong et al. 2018). While there are analogs between most within-family PGI designs and within-family h2g estimators, PGIs are often used because the weights [$\hat{\beta}$] can be trained/estimated in much larger cohorts of unrelated individuals and then applied within smaller family-based studies. Within-family PGI analyses also do not exhibit additional *estimation* bias due to assortative mating (see [**3.3**]) (Herzig et al. 2023). However, the estimation and application of PGI from one population to a different within-family study leads to several unique challenges for interpretation:

- In contrast to h2g estimators which are unbiased by sample size, PGI accuracy is biased by training sample size (because the individual [$\hat{\beta}$] will be noisier when learned in smaller studies). PGIs will thus also be less accurate if they were derived from smaller studies and cannot be easily compared across different training sets even for the same target set.
- PGIs will, by definition, reflect the studied population, so if either the environment or the genetic variation differs between the training and target population the PGI will no longer reflect the genetic value in the target population.
- PGIs trained in a population GWAS will capture both direct and indirect effects, if these effects are not perfectly identical the resulting PGI will be an arbitrary mixture of the two.
- Using a population-trained PGI in parents to capture "indirect" effects will likewise account for both direct and indirect effects and may over- or under- correct depending on the influence and correlation of these effects.
- Direct PGI effect estimates in siblings may be biased by indirect effects *from* siblings.
- As with within-family GWAS (see above), within-family PGI estimates of direct effects are **not** biased by assortative mating (Lee et al. 2018; Brumpton et al. 2020; N. M. Davies et al. 2019).
- Indirect PGI effect estimates are biased (typically upwards) by assortative mating (Balbona, Kim, and Keller 2021), as discussed for other methods in the next section.
- A PGI trained using within-family weights (i.e. a "direct" PGI) but predicted into a population-level target dataset will still be correlated with and confounded by indirect effects. **Within-family controls must also be applied in the target data to control for environmental confounding**.

In short, PGI-based analyses further sacrifice interpretability for increased statistical power and fewer biases under assortative mating (more on this in the next section).

3.3 | Estimation bias due to assortative mating

Theory

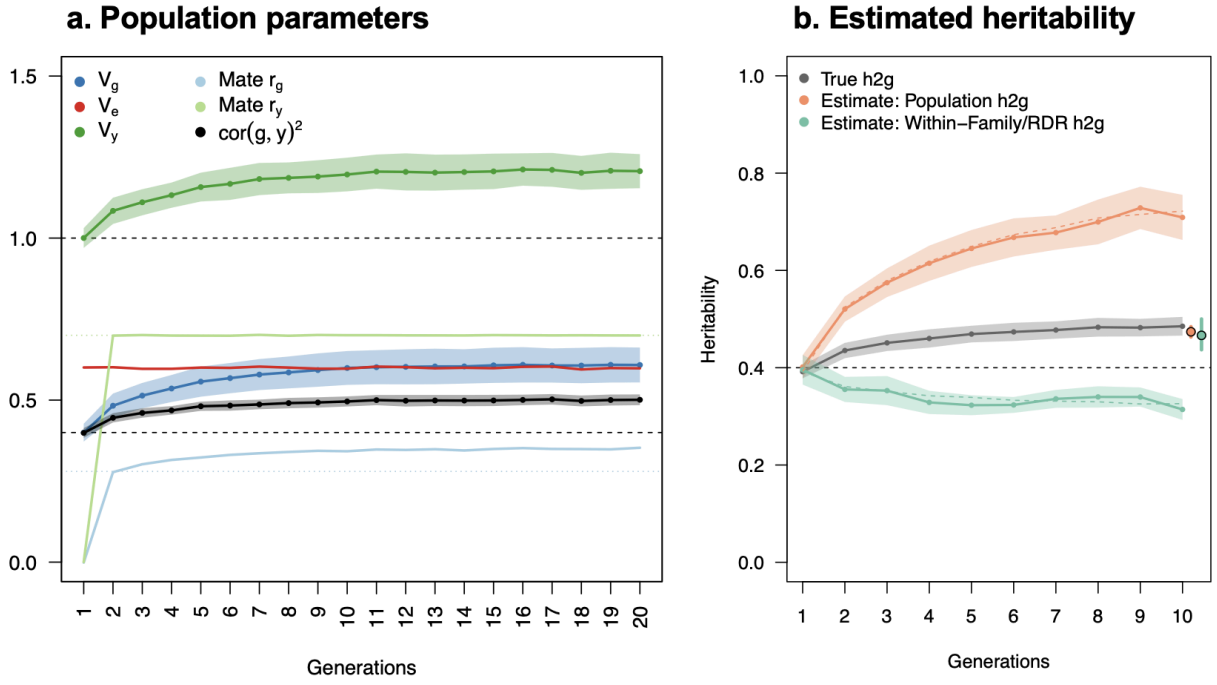
Assortative mating increases the genetic variance relative to what would be observed in a random mating population by inducing excess covariance across putatively independent sites. **Conventional estimators of h2g (either direct or population) do not properly account for this covariance and so are additionally biased in the presence of AM**. This bias means the estimated h2g no longer corresponds to the true [Cor(**X**b,y)^2] in the population.

For population-scale estimators of h2g, the estimate is biased upwards by a factor of [$V_{g,eq}$ / $V_{g,0}$], where under positive assortment the genetic variance at equilibrium ([$V_{g,eq}$]) is larger than that in the random mating population ([$V_{g,0}$]) (Border, O'Rourke, et al. 2022). For within-family (e.g. RDR/sibling regression) estimators of h2g, the estimate is likewise biased downwards by the reciprocal, a factor of [$V_{g,0}$ / $V_{g,eq}$] (Kemper et al. 2021). In both cases, the estimated h2g is a mix of random mating and equilibrium variances. Because the estimators are not aware of the excess genetic covariance (which occurs at trait increasing alleles we generally do not know), the population-scale estimate sees individuals as less related than they actually are (and increases h2g to compensate) whereas the within-family estimate "over-corrects" for genetic correlation in siblings/parents sees siblings/parents as more related than they actually are (and decreases the h2g to compensate).

In the figure below, we can observe this behavior in simulations for a heritable trait with only direct effects undergoing assortative mating. On the left, genetic and phenotypic mate correlations increase immediately after assortment starts (i.e. we model AM as an instantaneous process starting in generation 2). Genetic variance increases more slowly and reaches equilibrium at ~5 generations; total trait variance thus also increases because environmental variance remains constant by construction. Finally, "h2g" (black) increases slightly due to the increase in genetic variance relative to fixed environmental variance. **Here we again see a trait with identical genetic effects and identical environmental effects exhibiting different apparent h2g in different cultural contexts**. On the right, heritabilities are estimated at each generation using a population estimator (HE regression) and a within-family estimator (RDR), starting without bias (generation = 1) and slowly inflating (population estimate) and deflating (within-family estimate). Again the true h2g (squared correlation of [Xb] and [y]) is shown in black, with neither estimate matching the true value. The expected bias, based on the variance ratios described above, is shown with colored dashed lines calculated from the true genetic variances and matches the observations through the entire trajectory. Note that this simulation includes only direct effects and so all biases are due to assortative mating.

Consequences of strong assortative mating on trait variance across generations.
(a) *A simulated trait with random mating direct genetic variance of 0.4 and phenotypic assortative mating of 0.7. V_g: variance of the genetic value; V_e: variance of the environment (fixed); V_y: variance of the total phenotype; Mate r_g: correlation of genetic values between mates; Mate r_y: correlation of phenotypes between mates; cor(g,y)^2: "heritability" or correlation between genetic value and phenotype.* ***(b)*** *Estimates*

of population (orange) and within-family (green) h2g relative to the true h2g (gray, defined as true [Cor(Xb,y)^2]). Black dashed line shows the random mating h2g; colored dashed lines show the expectation based on variance correction factors. The two rightmost points show bias corrected estimates at equilibrium (see below). All results are averages over 20 simulations with n=10,000 and m=100.



Lastly, AM biases (and thus AM corrections) do not apply equally to all inference algorithms. The above ratios are derived for HE-based estimators which follow basic mathematical properties. REML-based inference of population h2g has generally less pronounced bias but can be biased upwards or downwards relative to equilibrium heritability (Border, O'Rourke, et al. 2022). REML-based inference of direct h2g with RDR also exhibits less pronounced bias in the presence of indirect associations (see below). Contrasting REML and non-REML estimates has even been proposed as an approach to evaluate the influence of AM on population-based estimates (Border, O'Rourke, et al. 2022).

Bias correction

If the true values [$V_{g,t}$ / $V_{g,0}$] were known, the estimated h2g could be corrected by their respective ratios in any generation [t]. At equilibrium, the [$V_{g,0}$ / $V_{g,eq}$ = (1 - $r_{g,eq}$)] where [$r_{g,eq}$] is the correlation of genetic values between mates, so just one parameter needs to be known. In real data, however, we do not know these values and have to employ approximate corrections based on the values we do observe. Unlike [r_g] which is unknown, the observed phenotypic assortment [r] can be measured from spousal correlations, and under the assumptions that (a) the trait is polygenic, (b) assortment is operating through the observed trait, and (c) the trait is at equilibrium, then [$r_{g,eq}$ = r h^2_{eq}]. Population estimates of h2g can thus be corrected using [h^2_{eq} = $h^2_{est,pop}$ / (1 + r $h^2_{est,pop}$)], as derived in (Border, O'Rourke, et al. 2022); and within-family estimates can be corrected using [h^2_{eq} = (1 - sqrt(1 - 4 r $h^2_{est,fam}$))/(2 r)] as derived in (Kemper et al. 2021). For example,

an estimated within-family h2g of 0.17 and an [r] of 0.45 would correspond to a true equilibrium h2g of 0.19 (which would also correspond to an uncorrected population-level estimate of 0.21).

While polygenicity and equilibrium may be reasonable assumptions, the assumption that [r_g] is related to the observed assortment through [$r\ h^2_{eq}$] is more likely to be violated (Torvik et al. 2022; Keller et al. 2009; Young 2023). As we saw in [**3.1**], increased [r_g] can occur as a simple consequence of AM coupled with vertical cultural transmission (VCT), which increases genetic similarity beyond what is expected from the direct h2g. In other words, with VCT and AM on the observed trait, [r_g] will equal [$r\ h^2_{eq}$] instead of [$r\ h^2_{eq,direct}$] and a closed-form correction to recover [$h^2_{eq,direct}$] has not been derived. Increased [r_g] can also occur through assortment on an unobserved phenotype that is much more heritable and genetically correlated with the observed phenotype (for example, latent phenotypes of conscientiousness and grit that manifest as a less heritable phenotype such as college attainment); or assortment on highly heritable related traits in families/siblings, where individuals with low observed phenotypic correlations still pair up based on the latent genetic correlations they observe in relatives. On the other hand, [r_g] could also be lower than expected from [$r\ h^2_{eq}$] if AM is occurring through "horizontal" cultural transmission, where individuals pair up based on correlations in their non-genetic environments/culture rather than the heritable trait itself. For example, all individuals in a given social class go to college regardless of their genetic predisposition and then marry other individuals of their social class who attend college (phenotypic mate correlation without genetic mate correlation). More sophisticated methods to interrogate these assumptions, estimate [r_g] from data, and correct for latent assortment are actively being developed (Young 2023; Bilghese et al. 2023; Herzig et al. 2023).

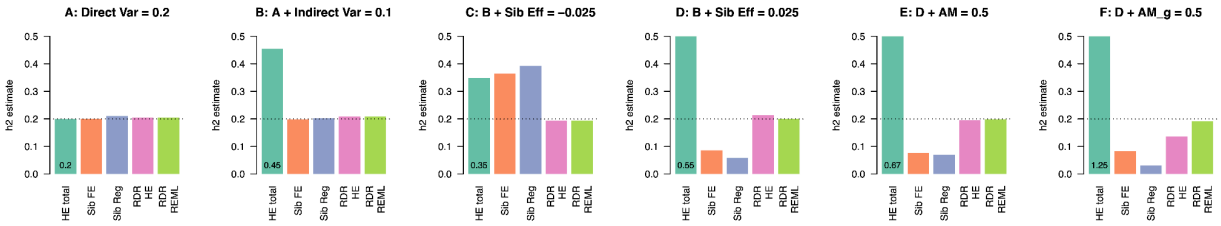
In short: AM induces a downward bias in within-family estimates of direct h2g; correcting for AM requires knowing the true underlying genetic correlation between mates; and corrections should be applied to HE estimates which behave as expected from theory. The focus on assortative mating may seem highly technical, but for a small number of traits undergoing substantial assortment, these technical details often limit the ability to draw clear conclusions about the underlying estimates.

Putting it all together: direct heritability estimators and their biases

With all of the above estimators and potential biases in mind, let's look at what happens in simulation as we increase the levels of confounding. To make things simple, we'll fix the true direct h2g at 0.2 and set all of the direct/indirect/sibling effects to be perfectly correlated (or anti-correlated), so their presence only increases or decreases the observed genetic variance. Then we estimate direct h2g using the molecular methods described above.

Influence of increasing levels of confounding on direct heritability estimates in simulation.
*From left to right additional confounders are added: (**A**) no confounders, only direct h2g; (**B**) indirect effects, (**C,D**) negative or positive sibling effects, (**E**) phenotypic assortment, and (**F**) genetic assortment. True direct h2g is always at 0.2 and shown with a dotted line. [HE total]: Haseman-Elston regression estimate of total/population h2g (values above 0.5 are not shown and reported numerically inside the bar)); [Sib FE]: Sibling Fixed Effect analysis evaluating the sibling-family deviation in PGIs (assumed to be free of error); [Sib Reg]: Sibling regression estimate of direct h2g; [RDR HE/REML]: RDR estimate of direct*

h2g using Haseman-Elston/Least Squares (HE) or REML. Each bar reports the mean over 10-100 simulations depending on method.



- **A**: When genetic effects are direct every method recovers an accurate estimate of the true h2g.
- **B**: When parental indirect effects (with variance of 0.10) are added, the standard population-level estimate of h2g is inflated (it's inflated by more than 0.10 because of the perfect correlation between direct and indirect effects here further increasing the true genetic variance) but all within-family estimates remain unbiased. This is the utility of within-family designs.
- **C/D**: When (negative or positive) sibling indirect effects are added (explaining 0.025 of the variance in trait, or a quarter of the parental indirect effects), both sibling fixed effect models and sibling regression are biased due to overcorrection in the familial effect. RDR, which draws signal primarily from the variation across individuals, remains unbiased.
- **E**: Adding phenotypic assortative mating of 0.5 deflates all within-family estimates and inflates the population estimate further. Because true h2g is low, the decrease due to AM is very slight.
- **F**: Adding genetic assortative mating of 0.5 (i.e. parents mate based on correlated genetic values) more substantially deflates the within-family estimates and further inflates the population estimate. A milder effect is observed of RDR REML, which models all relationships simultaneously rather than as pairs.

In short, RDR REML provides the most accurate molecular estimate of direct h2g, with biases due to assortative mating that are slight in the presence of indirect effects.

Bias for within-family PGIs

As noted above, the bias due to AM in PGIs behaves a bit differently from h2g estimators because the latter is estimating regression coefficients rather than partitioning variance. Under AM, within-family indirect/non-transmitted PGIs correlate with excess variation across chromosomes that would otherwise be independent in a random mating population, and are thus biased upwards (by a factor of $[1 - r_{g,eq}]$; (Lee et al. 2018; Okbay et al. 2022)). In contrast, within-family direct PGI effects are estimated without AM bias because the transmission of variants within families is random and cross-chromosome correlations are broken (Brumpton et al. 2020; N. M. Davies et al. 2019; Okbay et al. 2022). Because the relationship with assortative mating has been somewhat confusingly described in the literature, a cheat sheet across different study designs is provided below. Broader conceptual issues with direct/indirect estimates are discussed in the next section, and the adoption design is discussed in more detail in [**5.11**].

Biases in different PGI study designs.

Each row reports a different PGI estimator and each column reports a potential source of confounding. The population PGI is ill-defined as an effect estimator in the presence of any confounding. Population stratification is not included as it can bias all designs. [*] Adoption direct effects are only unbiased if there are no prenatal effects.

	Bias under different scenarios				References
PGI / study design	**No AM No VCT**	**AM**	**VCT**	**AM and VCT**	
Population	Unbiased	Biased	Biased	Biased	(Kong et al. 2018)
Within-Family Direct	Unbiased	Unbiased	Unbiased	Unbiased	(Brumpton et al. 2020; N. M. Davies et al. 2019; Okbay et al. 2022)
Within-Family Indirect	Unbiased	Biased	Unbiased	Biased	(Balbona, Kim, and Keller 2021; Okbay et al. 2022)
Adoption Direct	Unbiased	Unbiased	Unbiased*	Unbiased*	(Demange et al. 2022)
Adoption Indirect	Unbiased	Unbiased	Unbiased*	Biased	(Demange et al. 2022)

3.4 | Interpretation of direct heritability and indirect associations

Direct effects: still environmentally specific

The same issues regarding misinterpretation of h2g across environments apply to interpreting direct (within-family) effects across families (Coop and Przeworski 2022a). Direct effects are not informative as to the malleability of a trait in a different environmental context: a "strong" direct effect in one environment may be completely abrogated by a shift to a different environment or an intervention. Direct effects also do not explain variance across families: a direct effect within families may be completely swamped by environmental differences between families or, alternatively, amplified by environment/indirect effects correlated with those direct effects.

Specific to within-family studies is the fact that individual direct effects are estimated at positions that are heterozygous in the parents (thus providing within-family genetic variation). If such positions are not randomly distributed with respect to the environments in the population (for example due to stratification or ascertainment), then they will not reflect the true population level direct effect sizes (Veller and Coop 2023).

Correlations between direct and indirect effects, which are common and can be both positive or negative, further complicate interpretation by inducing causal consequences across successive generations (more on this later).

Lastly, while direct effects may be statistically causal, they should not be interpreted as "biologically" causal: a direct effect on educational attainment in a society that discriminates

based on skin/hair pigment would still be mediated by within-family differences in pigmentation (i.e. causal via discrimination).

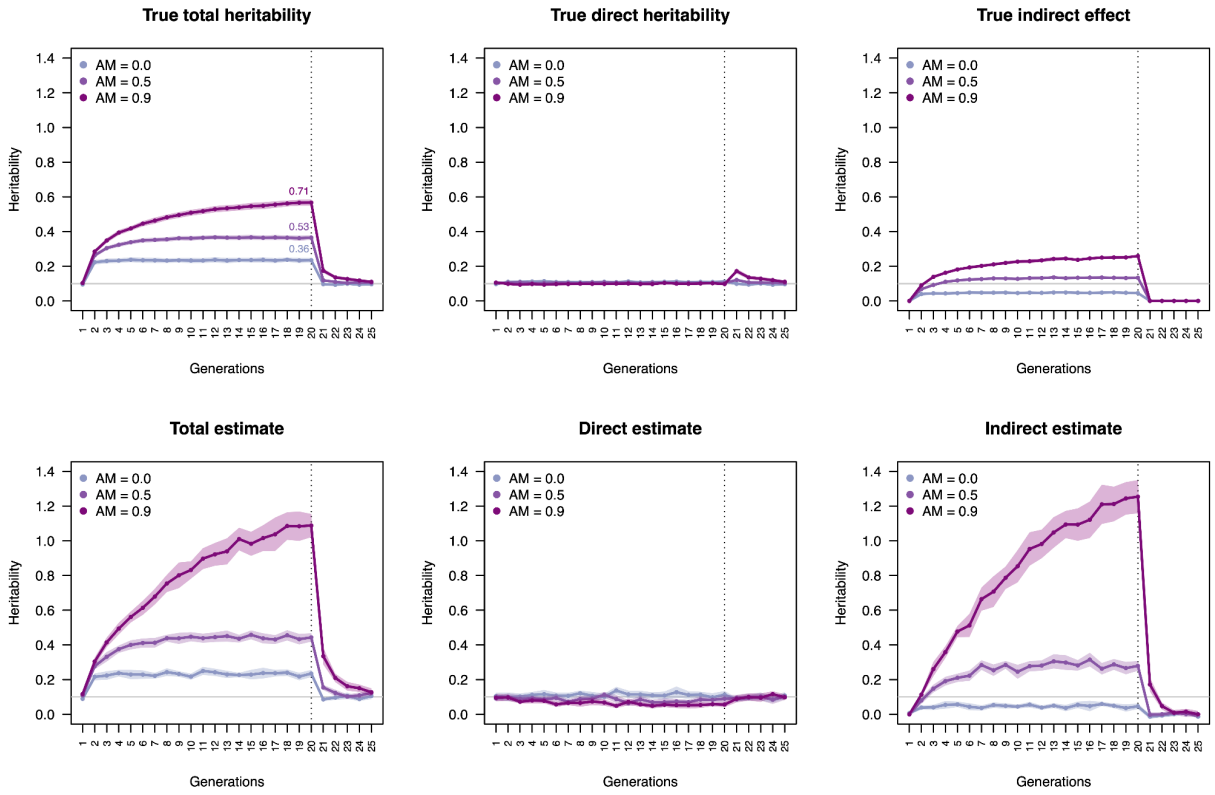
Indirect effects: neither “effects” nor “indirect”

While there is at least some causal notion to the direct effect, **there is no such interpretation for indirect effects** because indirect effects do not control for confounding by environment, assortative mating, or stratification (Veller and Coop 2023; Okbay et al. 2022). In a simple semi-casual scenario, a genetic variant that induced allergies many generations ago and nudged carriers to move to the cities (i.e. classic passive rGE), would now contribute to indirect effects on urban pollution even though it has no causal effect on the trait in the current generation whatsoever. In the more complex scenario with VCT and AM, large indirect effect estimates can be observed with no causal relationship in *any* generation. It is very tempting to treat indirect effects as simply genetic causes in the parents (sometimes even referred to as “genetic nurture”) but as we have seen repeatedly, entirely non-causal processes can create or inflate the indirect effect and estimate.

To illustrate the point, let’s revisit the above simulation of h2g in the context of AM and VCT and use within-family RDR to estimate direct h2g and the [$v_{e^{\sim}g}$] parameter. Recall that the causal effect of genetics is 10% of the trait variance, the VCT is 40%, and the remaining 50% is random; AM is induced for 20 generations; then in the 21st generation VCT is replaced with 40% random variance. We compute the “true” values of each parameter by regressing the trait on the genetic value in the child (population h2g) or on the genetic value in the child and their parents jointly; and we *estimate* their values from the data using RDR.

Estimation of components of heritability with changing assortative mating and vertical cultural transmission.

*Population (“total”) h2g (**top left**) with sibling correlations shown numerically; direct effect (**top middle**); and indirect effect (**top right**) in the same simulation of AM + VCT followed by no VCT as in [**3.3**]. (**bottom**) Corresponding estimates from the population (Haseman-Elston regression) or within-family (RDR). Confidence intervals across 15 random simulations shown in shaded regions. Each simulation used 10,000 samples and 100 variants.*



In the figure above, the estimate of direct h2g (bottom row, middle panel) generally reflects the true 10% direct genetic effect (top row, middle panel), or is biased down by assortative mating. Likewise, with random mating, the indirect estimate is roughly proportional to the fraction of the trait in the child correlated to the genetic values in the parents (2*0.4*0.1). But with AM, the indirect estimate ([$v_{e\sim g}$]) becomes wildly inflated, even exceeding 1.0 when mate correlation is very high. This estimate is now some amalgam of the (non-causal) correlation of parental genetics with child traits via parental traits, inflated by the excess correlated genetic variance in the parents due to assortative mating. Note that even if the true population or indirect estimates could be resolved (as in the top panels, computed by regressing the phenotype of the child on the true genetic value – estimated without error – of the child and their parents jointly), they too are inflated by AM, though less substantially.

This example highlights why indirect effects, [$v_{e\sim g}$] from RDR, or indirect PGI terms should not be interpreted as the effect of "genetic nurture" or even as an "effect" at all. Absent AM, these parameters can reflect "effects" in distant generations or bias due to population stratification. In the presence of AM, they can reflect inflated correlations due to mating patterns both as inferred by family models and in truth (i.e. with perfectly estimated genetic mate correlations). These issues will be further compounded in the context of cross-trait assortative mating, which can induce inflation via the relationships between the studied trait and other traits (Border, Athanasiadis, et al. 2022).

3.5 | Biases in population heritability under AM and VCT

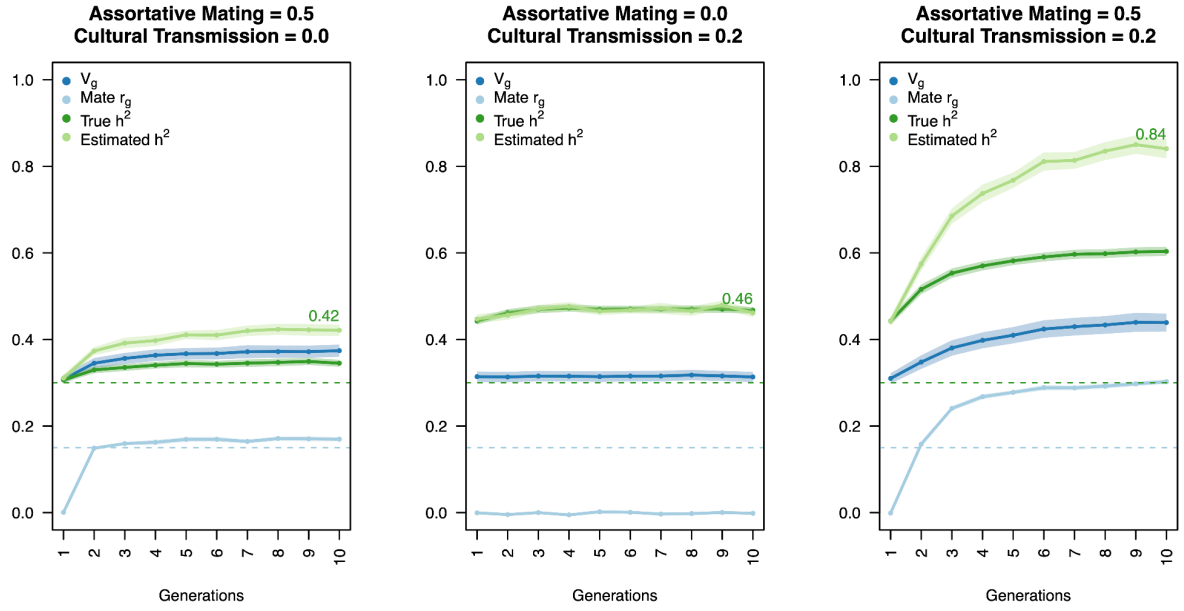
While the above analyses have primarily focused on the direct h2g estimate, which can be interpretable (if slightly biased) under complex cultural scenarios, let's now re-examine what happens to the population h2g estimate in the presence of both AM and VCT. Conceptually we should expect (a) AM to induce genetic correlation between spouses and excess heritability and (b) VCT to induce gene-environment correlation across generations and excess heritability. How do they act together?

Compounding effects

Population h2g estimates in the presence of AM and VCT will be a complex mix of the direct causal effects, the indirect confounded effects (including both AM and VCT), and AM-induced estimation bias. In the figure below, a trait with a fixed causal genetic variance (30%) is simulated under scenarios with only AM (left), only VCT (right), or both.

True and estimated h2g under varying levels of AM and VCT.

A simulated trait with 30% direct genetic variance (green dashed line) and either mate correlation of 0.5 (left) or VCT of 20% (middle) or both (right). "True h2g" is the true squared correlation between genetic value and phenotype without measurement error. Population h2g estimated using Haseman-Elston regression. Results averaged across 15 simulations with 10,000 samples and 100 markers each.



AM alone (left) induces excess genetic variance which increases the true population h2g (green), as well as additional bias in the h2g estimate (light green). As expected, the genetic mate correlation [rg] (light blue) is approximately equal to the product of the observed mate correlation [r] and the true [$h2_{eq}$]. Thus the estimated h2 can be corrected based on observed mate correlations as described above. VCT alone (middle) does not increase the genetic variance, but instead increases the gene-environment correlation and thus both the true and estimated h2 equally. As expected, VCT alone does not produce genetic mate correlations and would thus yield unbiased estimates using within-family estimators. Finally, both AM and VCT (right) compound to introduce a complex set of biases. Both the genetic variance and the correlated

environmental variance increase, leading to a large increase in the true h2 and an even larger inflation in the estimated h2: increasing from a direct value of 0.3, to a true population h2 value of ~0.6, and an estimated population value of >0.8. The estimated h2 can still be corrected to the true h2 based on the observed mate correlation [0.84/(1+0.84*0.5) = ~0.6], however this population h2 still does not reflect the direct causal heritability. Thus strong AM and moderate VCT can compound to substantially increase true population h2 and inflate the population h2 estimate.

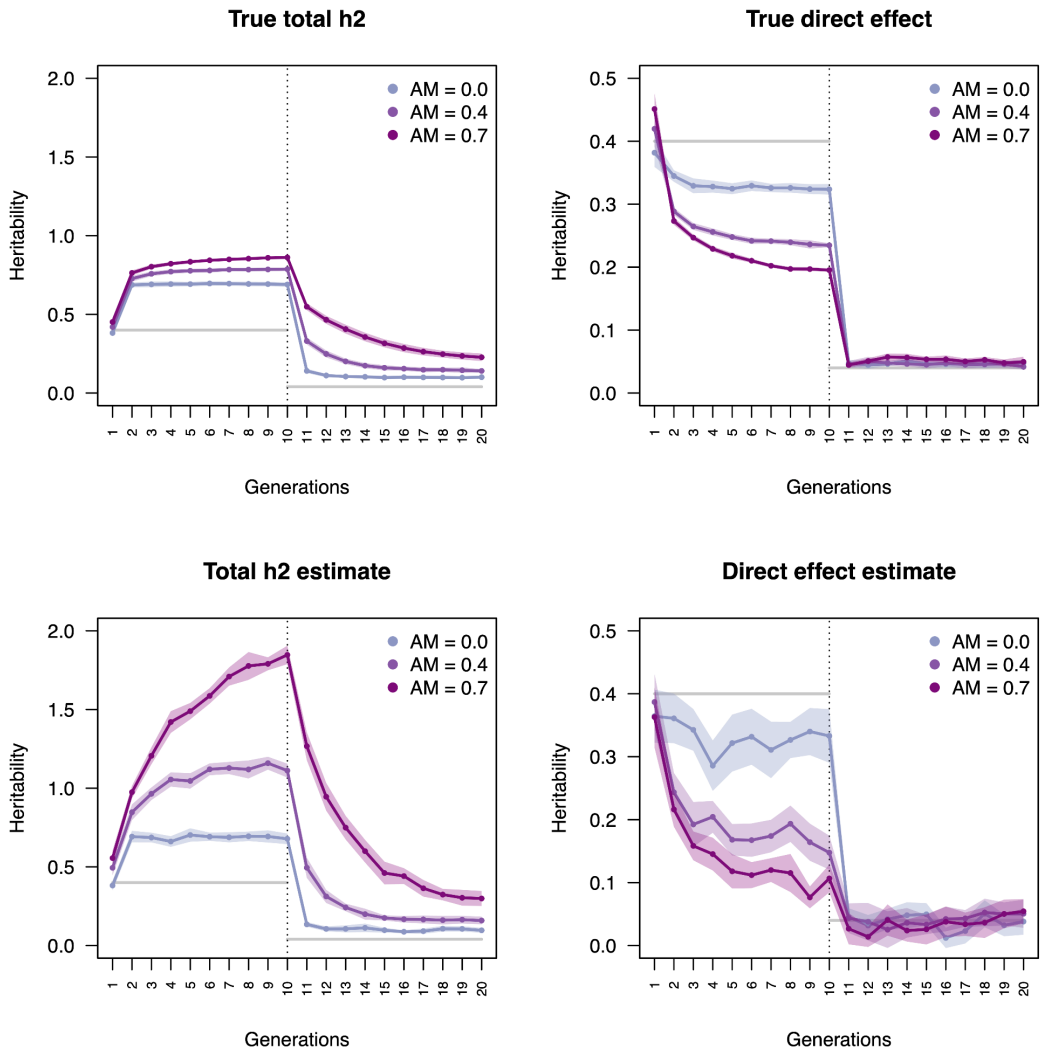
Persistence of bias across generations

An important aspect of AM is that it can cause genetic variance to build up over time (due to increased correlation across putatively independent markers) and then dissipate over generations. This means that population/indirect estimates of h2g from current data may be biased by the buildup of variance from historical cultural structure even when the modern-day genetic architecture is substantially different. To highlight the persistence of such biases, let's modify the simulation in [**3.4**] from fixed genetics with changing environmental structure to changing genetics with a fixed environmental structure. Imagine that for a long period of time skin pigment strongly influenced whether a person would go to college via discrimination, producing a high direct h2g for college attainment; additionally, college attainment is culturally transmitted from parents to children (VCT), and spouses tended to pair up based on college attainment (AM). At some point, laws are passed that end discrimination and the direct influence of pigment genes on college attainment is substantially diminished, but cultural practices (VCT and AM) remain.

To formalize this scenario, we start with a trait where genetics causally contributes 40% variance, VCT (i.e. mean parental trait) contributes 40% variance, and random environment is 20%; random mating occurs for 10 generations; then in generation 11 the genetic variance is shrunk to just 4% (and the environment increased to 56%). As above, we calculate the true heritabilities using either a marginal regression of the trait on the genetic value, or a joint regression of the trait on the genetic values of the child and the sum of the parents. Finally, we estimate population h2g using HE regression and direct h2g using within-family RDR, with results shown in the figure below.

Estimating heritability with assortative mating, vertical cultural transmission, and changing genetic effects.

*(**left**) Population ("total") h2g values (**top**) and estimates (**bottom**). (**right**) Direct h2g values and estimates. Traits are simulated with VCT, AM, and 40% causal genetic variance (horizontal gray lines) for 10 generations and then 4% causal genetic variance for 10 generations. Gray horizontal bars show the simulated direct causal h2g and vertical line highlights the last generation of high genetic variance. Confidence intervals across 15 random simulations shown in shaded regions. Each simulation used 10,000 samples and 100 variants.*



In the top left, we again see how VCT (and, to a lesser extent, AM) increases the true h2g (that is, the squared correlation between genetic value and phenotype). In the bottom left, the estimated population h2g reflects the true h2g under random mating but substantially biased upwards under AM, even reaching out-of-bounds values >1 when mate correlation is high. This would not be resolved by established AM corrections because existing corrections assume no VCT (though see: (Young 2023)). Moreover, when genetic variance drops to 4% in generation 11, the estimated population h2g decreases very slowly under AM and never returns to the true value due to the ongoing VCT. With spousal correlation of 0.4 (similar to that of educational attainment), for example, the estimated h2g is 0.5, 0.3, and 0.27 in generations 11, 12, and 13 and eventually asymptotes at ~0.17. In contrast, both the true direct effect and the estimated direct effect from RDR is generally consistent with the true value of 0.04. In other words, not only is population h2g inflated by gene-environment correlations in the current generation (i.e. converging to 0.17 due to VCT, >4x higher than the true direct effect) population h2g can even be substantially inflated by rGE from *previous* generations (i.e. starting at 0.5, >12x higher than the true direct effect).

Thus, in the presence of AM or VCT, only the direct effect estimate has any interpretation in the current generation; the population (and indirect) estimates will reflect an unknown amount of additional genetic variance accumulated from prior generations. Similar issues will be relevant for PGI-based estimates, especially when evaluated without family/genetic controls, though without the extra inflation due to HE regression bias.

3.6 | A word on ongoing challenges for within-family analyses

The field is beginning to understand the relationships between AM, VCT, direct heritability, and indirect correlations but many challenges to fully interpretable genetic estimates still remain:

- **Assortment on a latent phenotype**. As noted above, correction for AM requires knowing the underlying genetic correlation between mates. If AM is occurring on an unmeasured, more heritable, and genetically correlated trait then this will induce higher genetic correlation in mates than expected. Understanding whether and when latent/genetic assortment has occurred is thus important to properly correct estimates for AM. Related work: (Torvik et al. 2022).
- **Confounded direct/indirect correlations under ascertainment**. Several studies have observed puzzling and highly significant negative correlations between direct effects and indirect associations (Cheesman, Eilertsen, et al. 2020; Barcellos, Carvalho, and Turley 2021; Bjørndal et al. 2023; Eilertsen et al. 2021; Young et al. 2022; Young 2023). Such effects may have a causal explanation: the variation in parents that increases the trait in them also decreases the trait in their children (for example, variants that influence identifying depressive symptoms in children may also reduce depression in parents, as hypothesized in (Cheesman, Eilertsen, et al. 2020)). An alternative non-causal explanation was proposed in (Young et al. 2022), wherein collider bias is induced by ascertaining on a phenotype (e.g. education) that is caused by direct and indirect effects and thus deflating the true correlation between the two. In both cases understanding this process is important as it's either a complex negation of causal effects or a technical cofounder.
- **Ascertainment and participation bias**. A more general issue is the influence of ascertainment and participation in the study on within-family estimates. As noted in (Veller and Coop 2023), within-family direct effects are estimated from variants for which parents are heterozygous, and will be biased relative to the population if those variants are non-randomly distributed across family environments. This bias may, for example, be induced by variants that correlate or cause participation in the study itself. Related work: (Benonisdottir and Kong 2023)
- **Cross-trait assortment**. Most of the above findings consider AM and VCT on a single trait, however, more complex scenarios exist when individuals mate on different traits (e.g. wealthy men marry tall women), which will induce apparent non-causal relationships between traits in children and the population. Similarly, cross-trait VCT (e.g. early cancer in parents impacts education in children through socioeconomic status) could induce apparent heritability in the children that has nothing to do with the focal trait (transmitted variants that influenced cancer in the parents appear associated with education in the

children). Related work: (Border, Athanasiadis, et al. 2022; Bilghese et al. 2023; Veller and Coop 2023)

- **Sibling indirect effects**. Indirect effects from siblings (i.e. where a heritable trait in a sibling influences the trait of the other sibling) will confound sibling difference / sibship studies and estimates. Quantifying of sibling indirect effects has been limited, although large effects have so far not been observed. Birth order may also play an important role in these effects (e.g. older siblings having a stronger influence on young sibling traits). Related work: (Young et al. 2022; Howe, Evans, et al. 2022).
- **Larger and more accurate within-family GWAS**. While many large population-scale GWAS studies have been conducted and produced PGIs that approach the predictive limit of heritability, within-family/sibling GWAS have so far been much more limited and "direct" PGIs relatively weak. As a simple practical matter, larger family GWAS are needed to characterize individual direct effects and construct more accurate PGIs. More accurate direct PGIs would, in turn, provide an alternative approach to estimating components of heritability that may be less susceptible to bias from AM. Related work: (The Within Family Consortium, n.d.)
- **Properly accounting for subtle population structure**. Several studies have contrasted PGIs with geographic parameters to draw conclusions about rGE. This approach is particularly vulnerable to biases from uncontrolled population stratification. Recent work has shown that controlling for a large number of common variant principal components, as is typical practice, may not be sufficient to address stratification. Related work: (Hu et al. 2023)
- **Accurately estimating direct effects without family data**. Large-scale family data is difficult to obtain and unavailable in all circumstances. In principle, knowing the genetic correlations between direct and indirect effects as well as their precise variance estimates may be sufficient to approximate direct effect estimates in population scale data. Alternatively, decomposing direct effects into those that are entirely uncorrelated from indirect effects may enable estimation of a population-scale "uncorrelated direct" component.
- **Analytical recovery of true parameters**. Many of the above analyses are shown through simulations because analytical derivations of trait variance have mostly not been derived for both AM and VCT. This also poses a challenge for interpreting within-family results, which are often presented as being possibly explained by AM or VCT or "genetic nurture" or some mixture of all three, even though these mechanisms have substantially different implications. Related work: (Herzig et al. 2023; Young 2023).

3.7 | Further reading

Methods/analysis:

- (Kemper et al. 2021): Evaluation of heritability across different family designs and derivation of assortative mating corrections.
- (Kong et al. 2018): Seminal analysis of non-transmitted influences through polygenic scores.

- (Young et al. 2018): Relatedness Disequilibrium Regression (RDR) and analysis of direct/indirect heritability.
- (Howe, Nivard, et al. 2022): Large, within sib-ship GWAS to estimate direct/indirect heritability across many traits.
- (Torvik et al. 2022): Methods for estimating and modeling assortative mating in family data.

Theory:

- (Veller and Coop 2023): Modeling and interpretation of potential biases in within-family studies.
- (Herzig et al. 2023): Derivation of h2g inflation under assortative mating and cultural transmission.

Commentary:

- (Feldman and Ramachandran 2018): Essay discussing classical estimates of heritability in the context of cultural transmission.
- (Young et al. 2019): Overview of genotype/phenotype association models including direct and indirect effects.
- (Burt 2022): Primer on the use of polygenic scores in behavioral genetics and critique, together with several related commentaries and rebuttals.
- (Coop and Przeworski 2022a): Difficulties in interpreting direct and indirect effects as explanatory variables for between-family differences.

The genetic architecture of common traits

To orient ourselves and set expectations, let's review what has been broadly observed regarding the heritability and "genetic architecture" of common complex traits.

4.0 | Summary

- **Most common traits have modest but non-zero common SNP heritability (h2g)**. In a large analysis of ~2,000 traits across ~500,000 individuals in the UK Biobank, the mean h2g was 0.10, with ~90% of well-powered measurements having significantly non-zero heritability.
- **Most common traits are highly polygenic**. The typical common trait is caused by thousands of common variants and behavioral/psychiatric/anthropometric traits are typically caused by tens of thousands of common variants, each of very small average effect (O'Connor et al. 2019; Zhang et al. 2018).
- **Most common variant h2g is non-coding**. Coding variants explain <10% of the common h2g for typical traits (Finucane et al. 2015), with the remaining heritability localized to "regulatory" elements active in relevant tissues (Finucane et al. 2018) as well as broadly in the body (Boyle, Li, and Pritchard 2017).
- **The non-additive contribution of common dominance/recessive effects is negligible.** Multiple studies estimated the contribution of dominance h2g (on top of additivity) to be in the range of 0.001-0.001, or 100-200x lower than additive h2g (Palmer et al. 2023; Pazokitoroudi et al. 2021).
- **The contribution of indirect effects to common h2g is typically low (<10%) for non-behavioral traits.** However, several traits stand-out as exhibiting a substantial proportion of h2g attributable to indirect effects including: height, educational attainment, cognitive function, and related behavioral traits (Howe, Nivard, et al. 2022). Shared environmental effects not correlated with genotype in unrelated individuals are also substantial on average across representative traits (Zaitlen et al. 2013).
- **The contribution of geographic rGE to common h2g is typically low (<1%) for non-behavioral traits.** However, socioeconomic and cognitive traits exhibit substantial apparent h2g explained by either passive rGE/stratification (>10%) or active rGE or some mix of both (>20%), estimated through birth/residential addresses (Abdellaoui, Dolan, et al. 2022).
- **Common traits appear to be under weak trait-specific selection with a proportionally low contribution from rare variants.** Evolutionary theory indicates that neutral traits are expected to have very little rare variant heritability (Simons et al. 2018). On average across traits the rare variant (<0.01) contribution to h2g is expected to be 5-20% (Schoech et al. 2019).
- **Selection is likely to be pleiotropic across many traits.** Estimates of selection across traits exhibit lower variability than expected, suggesting that selection may be acting indirectly through an underlying "latent" phenotype (Schoech et al. 2019; Simons et al. 2018). Models with a single underlying selective process and a small number of parameters fit the observed data from many traits very well (Simons et al. 2022).
- **Low frequency (0.005-0.05) variants explain less h2g and are much more likely to be coding.** Low frequency variants explain ~3% additional h2g on average, compared to 20% for common variants (Gazal et al. 2018), consistent with weak selection. 27% of

low-frequency h2g is coding variants, compared to 8% for common h2g, most of it in highly enriched non-synonymous variants.

- **Rare coding burden h2g is typically very small**. (Weiner et al. 2023) estimated an average rare coding burden h2g of ~1% across 22 common traits using large-scale exome sequencing data. Common and rare coding h2g was correlated at 0.79, consistent with weak and pleiotropic rather than trait-specific selection.
- **In the first study of total h2g using sequencing data, the majority (>70%) of h2g was common for both height and BMI, though the uncertainty was very high**. The rare variant heritability was also almost exclusively observed in coding variants (Wainschtein et al. 2022).
- **Twin and family-based estimates of (total, additive, direct) heritability are consistently inflated**. Twin study estimates of direct additive heritability are >2x inflated relative to molecular estimates using RDR across a variety of traits (Young et al. 2018). Kinship estimates (which may also include the effect of shared environment) are ~1.3x inflated. Inflation in twin-based estimates has been observed with a variety of methods: (Zaitlen et al. 2013; Kemper et al. 2021; Robinson et al. 2017; Coventry and Keller 2005).

4.1 | Common variant population h2g

Here's what we can expect from common variant population heritability for a typical common trait:

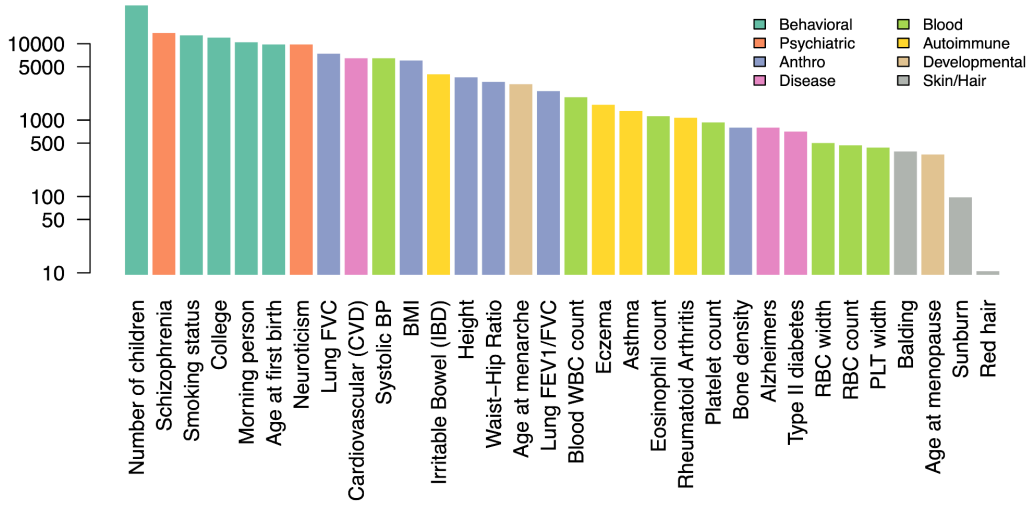
Moderately heritable. Nearly every trait has some small but non-zero common variant h2g. In a massive analysis of 2,419 unselected measurements across ~500,000 individuals the UKBiobank, the mean h2g across all measurements was 0.10, and 89.9% of measurements with >100,000 samples (i.e. well-powered phenotypes) had significantly non-zero heritability estimates. On the one hand, this implies that one should be generally aware of potential genetic influences for any phenotype of interest. On the other hand, a typical common h2g of 0.10 also means that other factors are generally much more important.

Highly polygenic. Most common traits appear to be highly *polygenic*, that is to be driven by an extremely large number of causal variants. Multiple approaches exist for estimating polygenicity (O'Connor et al. 2019; Weissbrod et al. 2020; Zhang et al. 2018; Zeng et al. 2018), typically by studying the distribution of observed association statistics and matching them up to some model. For a fixed total heritability, a "wider" distribution with more weak effects implies a higher polygenicity. These approaches agree that most common traits are associated with thousands to tens of thousands of common variants. For example, (O'Connor et al. 2019) estimated the "effective number of causal variants" across a variety of representative traits, with a mean estimate of 4,900. Behavioral traits were estimated to have the largest number of causal variants (>10,000) and skin/hair/pigmentation estimated to have the lowest (100's). These numbers are likely an underestimate of the "true" polygenicity of the trait, given an expected long tail of very weak effects which will contribute little to the "effective" number.

As GWAS sample size grows, polygenicity can be inferred directly by simply counting up the number of independent associations. A recent GWAS of height was one of the first studies to

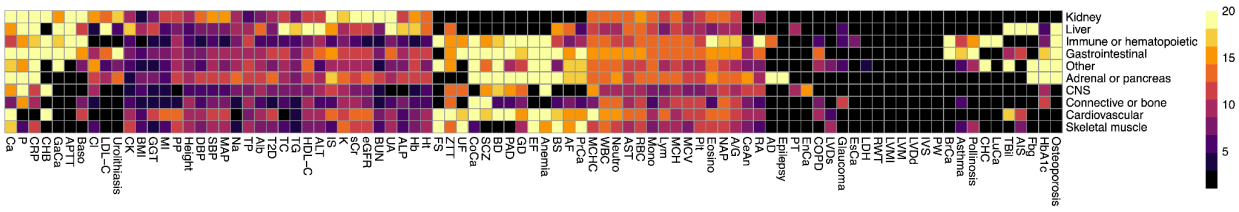
identify nearly all individual common associations, using a sample size of 5.4 million individuals (Loïc Yengo et al. 2022). In total, this produced a staggering 12,111 independent associated SNPs within 7,209 non-overlapping genomic segments.

Effective number of causal variants estimated across a variety of common traits.
Traits are color-coded by broad phenotypic groups. Most traits are highly polygenic particularly for behavioral/psychiatric traits. Data from (O'Connor et al. 2019)



Largely non-coding. In addition to quantifying the genome-wide h2g, we may be interested in knowing whether certain regions of the genome harbor more or less of the h2g than others (see [**2.8**]). Indeed, such "functional partitioning" analyses have revealed that ~90% of common trait heritability resides in parts of the genome that do not directly code for genes, but rather "regulate" the activity of nearby genes (Maurano et al. 2012; Finucane et al. 2015; Gusev et al. 2014). The fact that most trait-altering variants seem to operate through subtle regulatory changes rather than direct genic effects has been one of the more surprising and challenging aspects of common traits revealed by molecular data. In hindsight this is a logical consequence of extreme polygenicity: if there are tens of thousands of variants influencing each trait and many "traits" making up each human, it makes sense that these variants are acting in parallel via millions of subtle shifts in expression rather than summarily turning genes "on" or "off".

Heritability enrichment in regulatory elements across 89 traits and 10 cell type groups in the BioBank Japan.
Significant common h2g enrichments (p<0.05) were averaged across multiple regulatory element types for each trait - cell group pair. Enrichment defined as (% h2g / %SNP). Non-significant enrichments shown in black. Data from (Kanai et al. 2018).



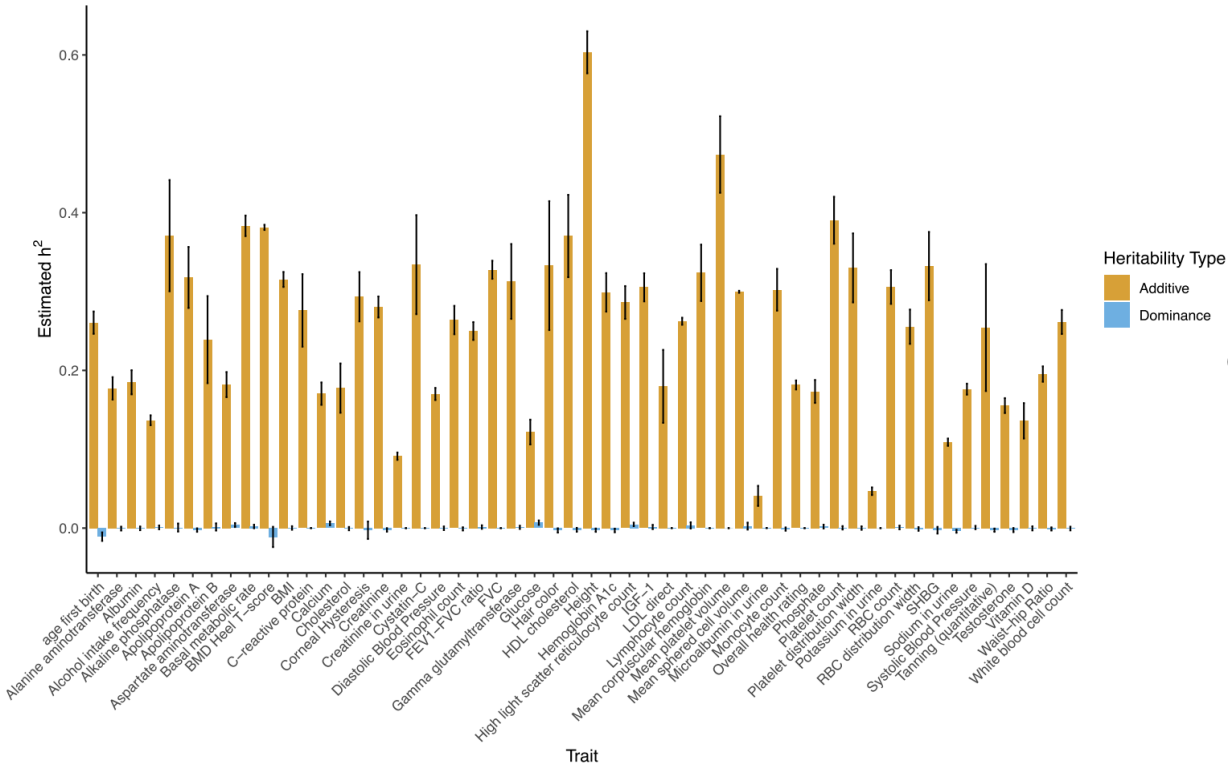
While trait h2g is enriched for regulatory elements that are generally active in the expected tissues (e.g. in brain for neurological disorders; (Finucane et al. 2018)) it is still *largely* explained

by regions that are broadly active across many tissues (Boyle, Li, and Pritchard 2017). As we can see in the figure above, neuro/psychiatric traits like schizophrenia (SCZ), and bipolar disorder (BD) are highly enriched for regulatory elements in the brain (CNS), as expected, but also for elements in connective, adrenal, and gastrointestinal tissues. Likewise, brain/CNS tissues also show enrichment for phosphorus levels (P) and anemia. In short, while trait h2g is highly functionally enriched, individual traits still appear to operate through highly complex and multifactorial mechanisms broadly active across tissues.

The combination of moderate common h2g, extreme polygenicity, and largely non-coding mechanisms continues to be a major challenge for mapping common traits. A truly causal understanding of genetic mechanisms will require data from very large sample sizes to identify the catalog weak effects, as well as better models of the non-coding "grammar" by which regulatory variants lead to trait differences.

A negligible contribution of dominance. Multiple studies have demonstrated nearly zero contribution of common variant dominance to common trait h2g beyond that which is already tagged by additive effects (Pazokitoroudi et al. 2021; Palmer et al. 2023). Roughly speaking, these approaches work by converting additive SNPs into "dominance residuals" (the bits of dominance that are not explained by an additive effect) and then adding those residuals into h2g estimators as if they were new variants. An LDSC-style analysis of summary-statistics from ~1,000 phenotypes in the UK Biobank found that mean dominance h2g was 0.00076 compared to a mean additive h2g of 0.088 (Palmer et al. 2023). An HE-regression-style analysis of individual-level data across 50 representative heritable traits similarly found a mean dominance h2g of 0.0013 compared to a mean additive h2g of 0.22 (Pazokitoroudi et al. 2021), shown in the figure below.

Negligible dominance h2g for common heritable traits.
Additive h2g estimates shown in orange and compared to dominance h2g estimates shown in blue. Figure from (Pazokitoroudi et al. 2021)



The negligible contribution of dominant (or recessive) effects has been another genetic surprise: why don't some variants function only when both copies are present (or absent)? But together with common h2g being largely non-coding and modifying traits through subtle changes in transcription, additivity – that two copies generally just do twice as much as one copy – seems quite plausible.

4.2 | Direct heritability

The most accurate and comprehensive estimates of *total* direct h2g to date were obtained in (Young et al. 2018), by separately applying RDR to IBD segments (total genetic material) and SNPs (common genetic material) across a wide range of traits known to be heritable. On average across the traits, RDR-IBD estimated total direct h2g at 0.30, which was 1.15x higher than the average RDR-SNP estimate of common direct h2g at 0.26, indicating that ~15% additional direct heritability may reside in rare variation that is not tagged by common SNPs (not counting the very rare variation RDR-IBD cannot capture). Interestingly, twin study estimates (which intend to quantify the direct additive component and partition indirect effects into a separate shared environment component) were 2.1x higher than RDR. As posited in (Young et al. 2018), these findings indicate that twin studies systematically and greatly overestimate additive heritability.

Average estimates of total heritability from different methods across 9 traits.

RDR and Twin methods intend to estimate the direct additive effect of all variants; RDR-SNP estimates the direct additive effect of common variants; Sib-Reg intends to estimate the direct additive and non-additive effect of all variants; RELT-SNP estimates the total (direct and indirect) additive effect of common variants; and Kinship estimates some mix of genetic and environmental effects. Due to the analysis of multiple

traits, assortative mating was not adjusted for, but all family conditional estimates (RDR, RDR-SNP, Sib-Reg, Twin, and to some extent Kinship) will exhibit similar downward bias from AM. Averages reported over 9 traits that had estimates from all methods. RDR-IBD: RDR from IBD segments; RDR-SNP: RDR from common SNPs; RELT-SNP: REML from common SNPs with adjustment for relatedness; Kinship: relatedness only; Sib-Reg: Within sibling regression; Twin: Additive term from classical twin study. Data from (Young et al. 2018)

RDR-IBD direct total h2g	RDR-SNP direct common h2g	RELT-SNP common h2g	Kinship "h2"	Sib-Reg h2	Twin (A)
0.30	0.26	0.30	0.41	0.36	0.63

While the RDR analysis was unique in leveraging IBD to estimate total direct h2g but was hampered by large standard errors for individual traits, (Howe, Nivard, et al. 2022) estimated common direct h2g using a much larger within-family GWAS across 178,086 pairs of siblings. Average shrinkage of direct to population common h2g across all traits was just 0.98, indicating that population-scale GWAS heritability is typically estimating a similar quantity to within-family (i.e. direct) GWAS heritability. However, several traits stood out in having significantly lower within-family h2g: height, IQ test ability, educational attainment, and age at first birth (often correlated with socioeconomic status). All but height are behavioral traits where indirect/environmental influences are to be expected. For traits not undergoing AM, the excess population h2g relative to within-family h2g can be interpreted as evidence of vertical cultural transmission (VCT) (see [**3.5**]). However, many behavioral traits do show evidence of strong AM (in particular IQ test ability, educational attainment, and socioeconomic status) which complicates this interpretation. These estimates will be considered in more detail in subsequent sections.

***Population and within-family estimates of common h2g for traits with substantial shrinkage**.*
The average across all 25 evaluated traits shown at the bottom. Confidence Intervals shown in parenthesis. Traits for which confidence intervals do not overlap are shown in bold. Data from: (Howe, Nivard, et al. 2022)

Trait	Population h2g	Within-Family h2g	% reduction
Height	**0.41 (0.37, 0.45)**	**0.34 (0.30, 0.38)**	**17%**
IQ test ability	**0.24 (0.18, 0.30)**	**0.14 (0.05, 0.22)**	**42%**
Educational Attainment	**0.13 (0.12, 0.15)**	**0.04 (0.02, 0.05)**	**77%**
Age at first birth	**0.07 (0.04, 0.10)**	**0.00 (-0.07, 0.07)**	**100%**
Depressive Symptoms	0.05 (0.03, 0.08)	0.04 (-0.01, 0.10)	-
Smoking	0.05 (0.01, 0.10)	0.07 (-0.02, 0.16)	-
Average of 25 traits:	0.12	0.11	

An interesting incidental finding came from the analysis of population structure, which was thought to be accounted for by within-family analyses. Surprisingly, the influence of stratification on within-family heritability was estimated at 21%, lower than the 42% estimated for population-level analyses but still substantially higher than zero. The explanation for this structure remains unknown and could be as simple as the covariates used in the GWAS or mismatch in the way LD was treated in estimating h2g, but it does suggest that **stratification (and likely some inflation in h2g) may still be an issue even in within-family analyses**.

Shared environment effects in the absence of indirect effects

Why don't we see indirect effects for environmentally mediated traits like cholesterol levels or asthma? The lack of large-scale indirect effects on most non-behavioral traits should not be interpreted as the *complete absence* of shared environmental effects. Population scale h2g estimates of unrelated individuals are only biased by environmental confounding that is correlated with genotype in unrelated individuals (i.e. through vertical cultural transmission from their parents). **Environmental influences that are shared across relatives but are uncorrelated with genotype or dissipate at the population level will not be captured by either population h2g or within-family h2g and will simply be attributed to random environmental variance (see [2.7])**. To investigate shared/familial environments (Zaitlen et al. 2013) estimated heritability across a wide range of relationship pairs in an Icelandic cohort under a model with no environmental sharing. Across 17 representative (and largely non-behavioral) phenotypes, they observed multiple relationship classes with significant differences in heritability estimates, with closer relationships consistently yielding larger heritability estimates. For example, heritability estimated between siblings (expected to be twice their phenotypic correlation under a model with no shared environment) was 0.14 larger than heritability estimated between a child and grandparent. These decreases in estimated heritability were not consistent with either dominance or epistasis effects, and were thus attributed to a substantial contribution from the shared environment.

Differences in estimated "heritability" from different relatedness classes.
Each row shows a pair of relationships; the difference in heritabilities estimated using relationship 1 minus that estimated using relationships 2; as well as the standard error and p-value for the difference. Significant positive differences indicate that either shared environment or non-additive genetic effects are increasing the apparent heritability at close relatives. Data from (Zaitlen et al. 2013).

Relationship 1	Relationship 2	h2 in Rel1 minus h2 in Rel2	s.e.	p-value
sib	half-sib	0.02	0.06	*NS*
sib	first-cousin	0.04	0.03	*NS*
sib	grandparent	0.14	0.04	2.9E-04
sib	parent	0.08	0.03	1.4E-03
sib	avuncular	0.15	0.03	3.7E-09
half-sib	first-cousin	0.02	0.06	*NS*
half-sib	grandparent	0.12	0.06	3.0E-02
half-sib	parent	0.06	0.06	*NS*

Relationship 1	Relationship 2	h2 in Rel1 minus h2 in Rel2	s.e.	p-value
half-sib	avuncular	0.13	0.06	3.0E-02
first-cousin	grandparent	0.10	0.04	2.0E-02
first-cousin	parent	0.04	0.04	*NS*
first-cousin	avuncular	0.11	0.04	4.2E-03
grandparent	parent	-0.06	0.03	5.0E-02
grandparent	avuncular	0.01	0.03	*NS*
parent	avuncular	0.07	0.02	7.6E-05

Several main conclusions can be drawn from this analysis. First, the shared environment clearly impacts the phenotypic relationships across close relatives (even if it is mostly not observed in population-scale h2g estimates). Second, estimators of heritability that include close relatives will be confounded by shared environment correlations and are not, in and of themselves, indicative of genetic influences. Third, estimators of heritability that focus on very close relatives, or that ignore relationships between more distant relatives, will be even more confounded by the shared environment.

4.3 | Heritability explained by environmental confounding/rGE

To investigate the components of common h2g that could be explained by rGE through measurable environments, (Abdellaoui, Dolan, et al. 2022) utilized "conditional" GWAS and heritability analyses adjusted for geographic location across a wide range of traits. Granular regions, clustered to be geographically and economically homogeneous, were used as proxies for passive environments, and considered for both birth and current address (the latter potentially capturing both passive and active rGE). What should one expect from such an analysis? If geographic location captures environmental variation that is independent of genetics, then h2g should increase; whereas if geographic location captures environmental variation that is correlated or confounded with genetic variation, then the h2g should decrease (see [**3.2**]).

The results exhibited a striking pattern between conventional anthropometric traits (height, weight, blood counts) and behavioral traits (education, IQ test performance, work satisfaction). Behavioral trait h2g decreased substantially: by 12% after adjusting for birth region and 24% after adjusting for birth and current region. In contrast, anthropometric trait h2g decreased ~3% after adjusting for both birth and current region. Note that current address adjustments will account for both passive and active rGE and may potentially induce some collider bias. Overall, these findings provided clear evidence for either confounding or mediation between genetics and environment for behavioral traits.

Heritability estimates before/after conditioning on birth region, current region, or both.

Average of estimates for two classes of traits. Raw estimate corresponds to no correction except standard covariates and ancestry. Each estimate is followed by the % of heritability relative to the raw estimate.

Results shown for the MSOA analysis, which produced larger deviations. Data from (Abdellaoui, Dolan, et al. 2022).

	Raw	Birth Region		Current Region		Birth + Current	
	h2	h2	%	h2	%	h2	%
Anthropometric & Cardiovascular	0.19	0.19	99%	0.19	97%	0.19	97%
Cognitive & Socioeconomic	0.10	0.09	**88%**	0.08	**80%**	0.08	**76%**

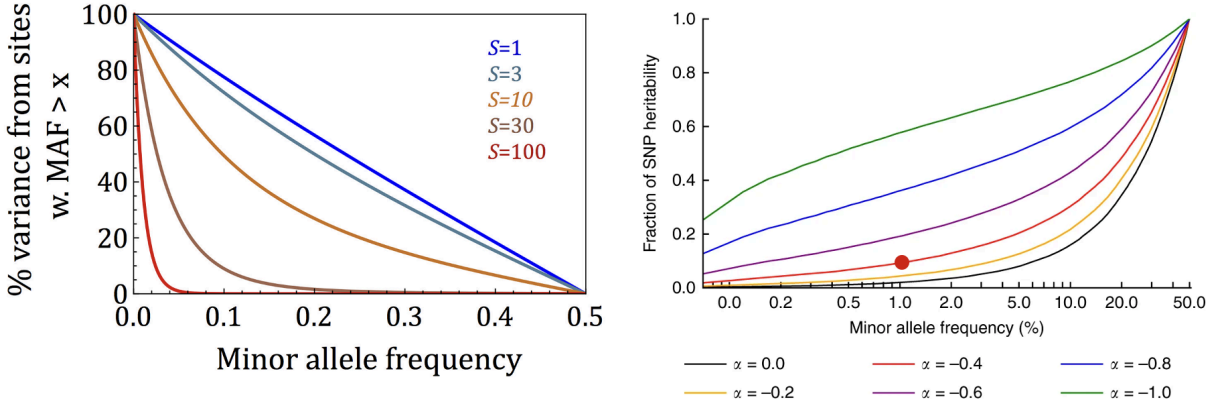
It is possible that the decrease in h2g is evidence of population stratification rather than rGE and this possibility was investigated through sensitivity analyses. First, the depletion in h2g was much lower when adjusting for longitude/latitude instead, suggesting that geography alone did not capture the environmental confounders at play here (as would be expected from simple geographic stratification). Second, the inclusion of a large number of genetic ancestry components also did not substantially alter the results. The proposed mechanism for passive rGE was that heritable behavioral traits drive individuals to live in certain environments, which in turn shape the behavioral traits in their offspring and induce a gene-environment correlation. It's worth noting that association of genetic variation for behavioral traits is generally very small: after adjusting for both regional values, the mean common h2g was only 0.08 (compared to 0.19 for anthropometric traits). It remains to be seen to what extent the excess variance attributed to rGE can either be explained by unmodeled stratification or further amplified with more granular socioeconomic/environmental measurements.

4.4 | Natural selection and expectations for rare variants

While natural selection is often classically thought of as influencing individual variants, the primary mode of selection on common variation in complex traits appears to be weak *polygenic* selection. Polygenic selection acts on the trait optimum value and can thus subtly shift the entire distribution of trait-affecting variants. For large-effect variants that shift the trait away from the optimum, negative selection will drive them to lower frequencies (Simons et al. 2018). At a fixed trait heritability, we should thus expect traits under stronger selection to have more "rare heritability" compared to traits under weaker selection (or, alternatively, for the fraction of common h2g to be lower). As an extreme example, one can think of rare mendelian disorders for which the total heritability is explained by a handful of very rare mutations.

Several approaches have been used to estimate the evidence for selection on complex traits, typically by evaluating whether large-effect variants tend to be rarer than expected. (Schoech et al. 2019) inferred a scaling parameter relating frequency to effect size and estimated a mean scaling coefficient of −0.38 (s.e. 0.02), corresponding to weak selection where variants <1% MAF explain only 8.9% (s.d. 2.7%) of total h2g (see figure). This estimate may be an upper bound, as the model was shown to overestimate the contribution of rare variants in simulated models of natural selection.

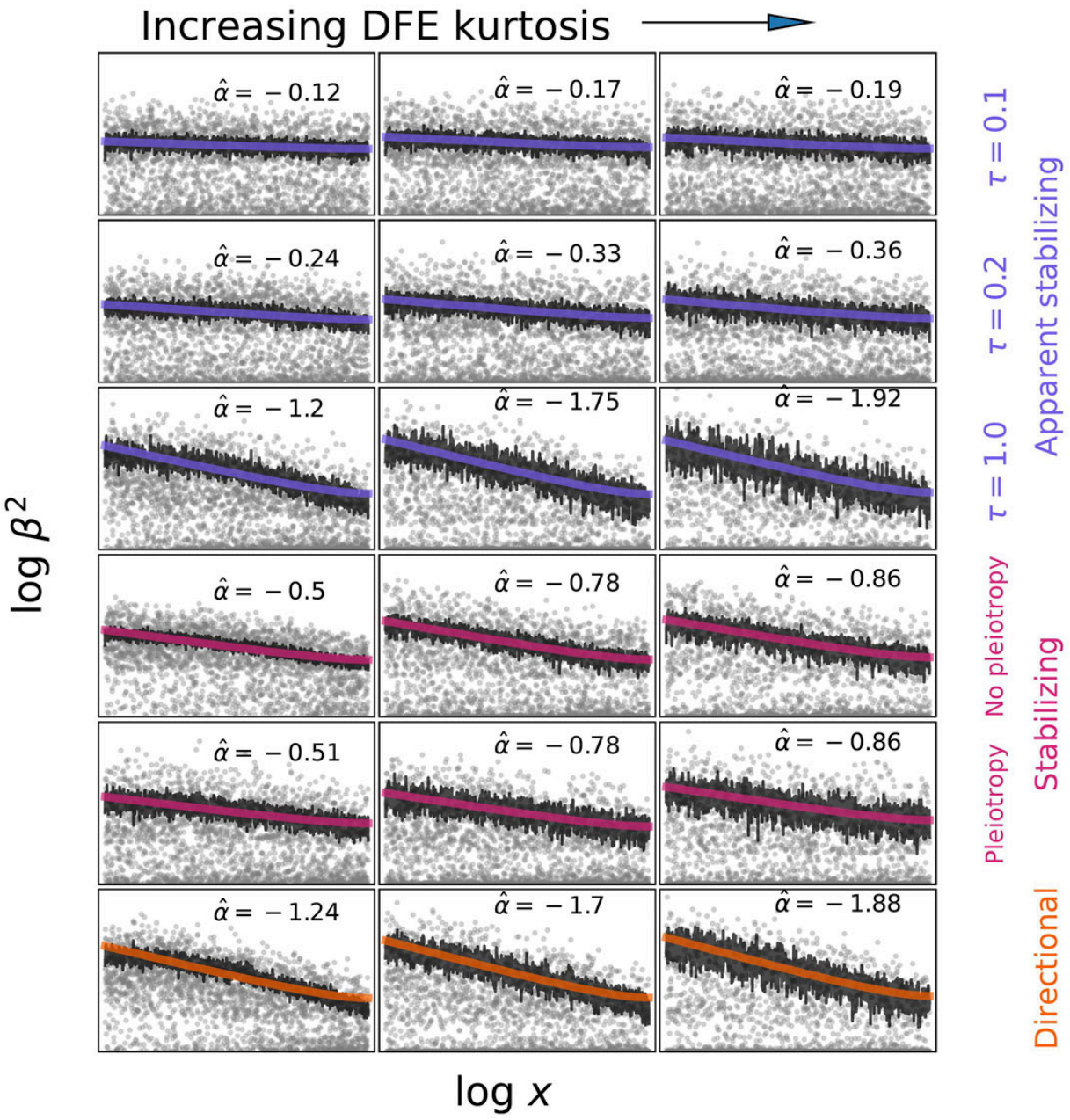
Expected h2g explained by rare variants under different levels of selection in simulations.
(left) *Expected fraction of h2g from sites more common than (x) for different selective coefficients: neutral (S=1), weak (S<30), strong (S=100). (**right**) Expected fraction of h2g from sites less common than (x) under different frequency-effect relationships. When variant effects do not increase with allele frequency (a=0), the contribution of rare variants to total h2g is very small (<1%). Mean estimate across 25 traits is −0.38, marked with a red dot, corresponds to 8.9% of the trait heritability attributable to rare (MAF<1%) variants. Left panel from (Simons et al. 2018); right panel from (Schoech et al. 2019)*



Across traits, (Schoech et al. 2019) also observed that the variance in the estimated scaling parameter was significantly lower than expected, consistent with "pleiotropic" selection either acting similarly on multiple traits or on an underlying correlated latent "fitness" trait. More recently, models have been proposed that relate heritability and polygenicity to selection *across* traits (Simons et al. 2022). When applied to real data, a small number of parameters can provide a good fit to the effect size distribution for many common traits, lending further evidence for pleiotropic selection. Thus apparent selection on any individual common trait is expected to be weak and indirect.

It is worth noting that the scaling parameter merely defines the relationship between frequency and effect size and it is not a complete evolutionary model. Even though strong directional selection may be ruled out, one parameter can still be compatible with many different models of natural selection (see (Koch and Sunyaev 2021) and figure below). This is especially true when stabilizing selection is pleiotropic and fitness effects are driven by unobserved genetically correlated traits (see much more discussion of natural selection in [**8.0**]).

Relationship between the alpha model and the true distribution of fitness effects (DFE) in simulations.
Each panel shows the relationship between trait effect sizes (β^2), allele frequency (x), and the inferred scaling parameter (alpha, listed) under a variety of evolutionary models. Figure from: (Koch and Sunyaev 2021)

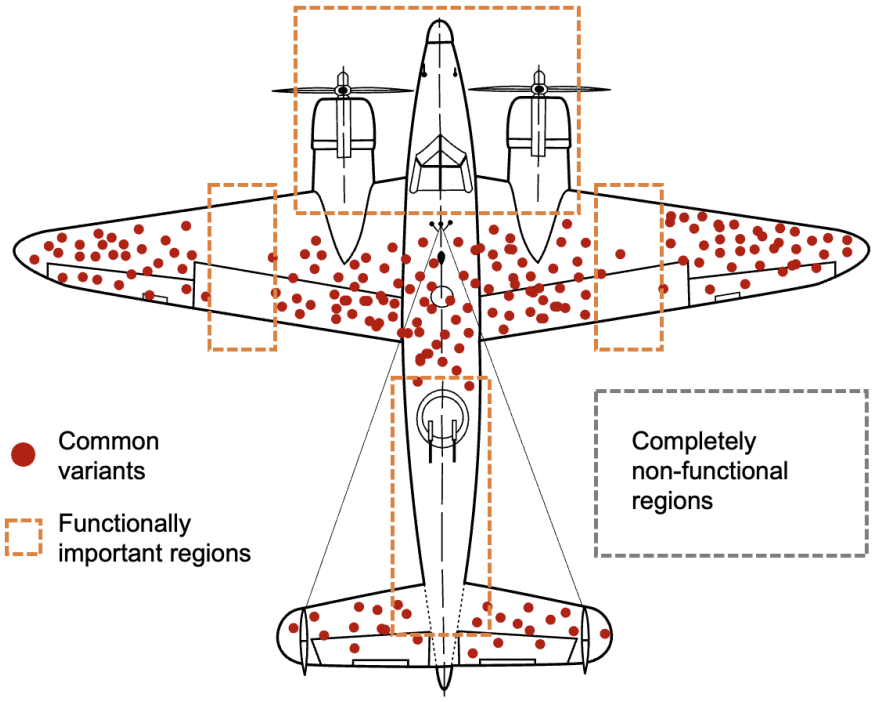


4.5 | Low-frequency variant h2g partitioning

Another way to evaluate the influence of selection is by contrasting variant frequencies in functionally important versus less important regions (for example, coding versus non-coding). We can think about this like the classic Survivorship Bias example, where bullet holes on an airplane that has returned safely from battle point to the parts of the plane that are not important to its function. Common standing variation that has survived negative selection is likely to be operating through functional elements that are less important to the trait. In contrast to the airplane though, trait associated variants will, by definition, reside in regions that do *some thing* (as we saw from the enrichment of heritability in regulatory elements above), but there will be fewer of them in regions that do *important things* and regions that do important things will explain less heritability

in total. As we move to lower frequency variants, which will include more variants doing important things that have been "pulled down" by negative selection, we expect to see more variants in the important regions of the genome and larger per-variant effects on the trait. **For lower frequency variants, proportionally more of the trait heritability will be explained by variants in important regions**. In contrast, under complete neutrality we would expect to see similar functional enrichments across all frequencies as functional variants drift around arbitrarily. Note that "*importance*" here is always in the context of selection and overall fitness; regions or traits that are irrelevant to fitness will operate as if under neutrality.

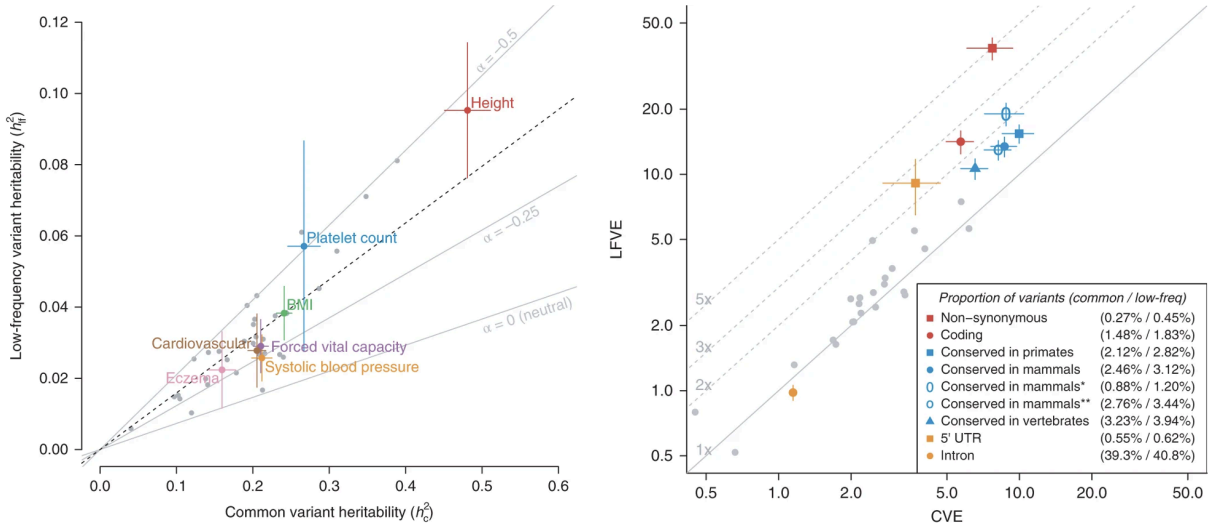
Illustration of "survivorship bias" on common variant heritability under negative selection. *Common variants (red) and heritability will be enriched in regions that are functional relative to those that are completely non-functional (gray) but there will be fewer common variants in regions that are very important (orange) and they will tend to contribute less to heritability in total. Low frequency and rare variants will be more numerous in very important regions, have larger effect sizes, and contribute proportionally more to heritability.*



The functional enrichment of heritability in low-frequency variants (0.5%-5%) was estimated and contrasted with common variant enrichment in (Gazal et al. 2018) across 40 traits in the UK Biobank. First, common variants had >6x more h2g (0.20) on average compared to low frequency variants (0.03), even though the total number of common variants (5.3M) was only 1.6x larger than the total number of low frequency variants (3.4M). This is consistent with weak selection allowing most trait heritability to be common.

Low-frequency trait heritability and functional enrichment across 40 common traits.
(left) *Total low frequency (y-axis) and common frequency (x-axis) h2g for each trait. Solid lines show different frequency/effect-size relationships and the dashed line corresponds to the average across traits, roughly consistent with -0.38 observed in (Schoech et al. 2019). (**right**) Low frequency (y-axis) and common*

frequency (x-axis) functional enrichment across different functional categories (colors) averaged across all traits. Figure from (Gazal et al. 2018)



Second, consistent with the action of negative selection, low-frequency coding variants were more enriched for low-frequency heritability (14x, 26% of $h2g_{LF}$) than common frequency coding variants (6x, 8% of $h2g_{CF}$). The difference was even more striking when restricting to non-synonymous variants: 38x (17% of $h2g_{LF}$) compared to 8x (2% of $h2g_{CF}$), consistent with more low-frequency enrichment at more "important" sites. Extrapolating out, we should thus expect low total h2g for rare variants as well as a greater fraction of (>26%) in coding regions and, specifically, at non-synonymous positions in coding regions.

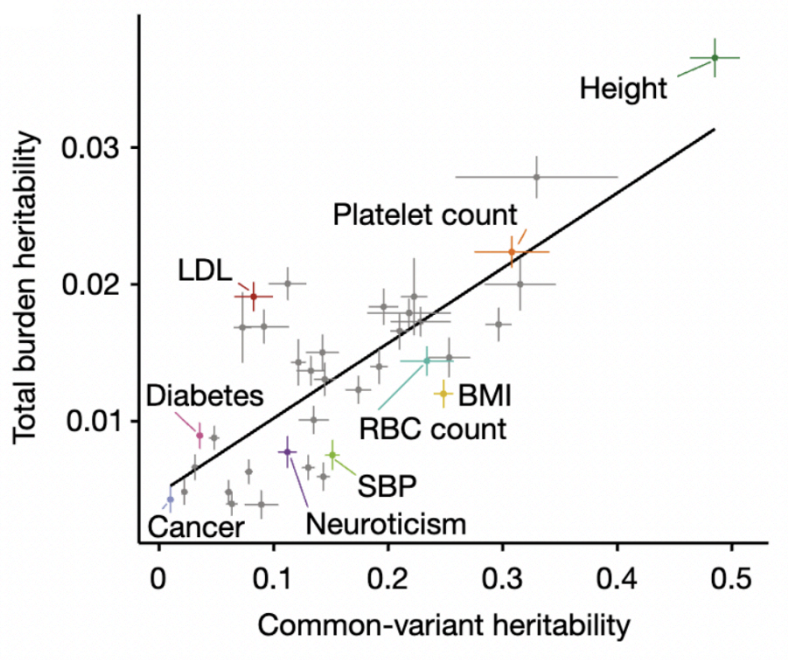
4.6 | Rare coding burden h2g

Rare variation is primarily measured using whole-genome sequencing or whole-exome sequencing, the latter capturing only mutations in coding regions. To date, large-scale rare variant analyses have focused on exome-sequencing studies due to their lower cost. As noted above, theory indicates that coding regions should capture a large fraction of rare variant heritability, particularly for traits under selection, and thus exome analyses provide a useful snapshot of rare variant heritability.

Recently, a comprehensive analysis of rare variant burden h2g was carried out applying Burden Heritability Regression (see [**2.4**]) to ~300,000 exomes from the UK Biobank (Weiner et al. 2023). Across 22 common traits, rare coding variant burden h2g was 1.3% (s.e. 0.03%) on average, most of which was explained by ultra-rare loss-of-function mutations. Average common variant h2g across these same traits was 16%, thus common variants explained 12x more h2g than rare burden, and (as reported in the previous section) 6x more h2g than low-frequency variants; consistent with weak selection allowing most trait-affecting variants to remain common or low-frequency. Moreover, common and rare burden h2g estimates were highly correlated (Pearson r=0.79), indicating that low common h2g traits generally have low rare h2g and again consistent with pleiotropic rather than trait-specific selection. Taking the 26% of low-frequency

h2g that was assigned to coding regions from (Gazal et al. 2018) as a lower bound, this would set an expectation of 1.3% / 26% = 5% of trait variance or less explained by all rare variants on average.

Estimates of common variant and rare coding burden heritability across 22 common traits.
Mean common h2g of 16% compared to mean rare coding burden h2g of 1.3% and a correlation of 0.79. Figure from (Weiner et al. 2023).



While these estimates are highly precise, they are still restricted to a single cohort, a relatively small number of traits, and merit further replication with other approaches. However, the general finding that coding variant h2g is low does appear to be consistent with several independent analyses:

1. Analysis of common variants in the n=~220k FinnGen cohort identified 275 independent GWAS associations across 15 selected diseases (~18 per trait) (Kurki et al. 2023). In contrast, analysis of rare coding variants in n=~650k exomes combining both FinnGen and UK Biobank identified 975 associations across 744 disease endpoints (~1.3 per trait). A 3x larger rare variant association study still produced >10x fewer associations per trait.
2. Common variant GWAS has generally identified many more associations than rare variant analyses. For example, GWAS of height in the UK Biobank identified 2,098 independent associations (Loh et al. 2018); compared to rare exome analysis in the same data identifying just 61 genes (Backman et al. 2021). Statistical power to detect rare variant associations is lower than for common variants, so this observation is necessary but not sufficient evidence of low rare h2g.
3. (Fiziev et al. 2023) constructed polygenic scores using functionally weighted rare coding variants and common GWAS variants across 78 quantitative phenotypes in the UK Biobank. On average common scores explained 10.1% of phenotypic variance, compared to just 0.4% for rare burden scores. Individual rare variants often had large effects, but collectively explained very little of the trait variance.

In short, multiple lines of evidence indicate that the contribution of rare coding variants to the heritability of common traits is very low.

4.7 | Whole-genome h2g

Few studies have quantified the total (rare and common) population h2g for common traits, which requires the measurement of every variant in the genome across tens of thousands of individuals. The most extensive analysis so far was conducted by (Wainschtein et al. 2022) for height and BMI in ~25,000 whole-genomes from individuals of European ancestry. Collecting and studying that many genomes was a remarkable feat, producing a trove of 31.3 million variants, of which the vast majority – ~25 million – were rare variants below 1% frequency.

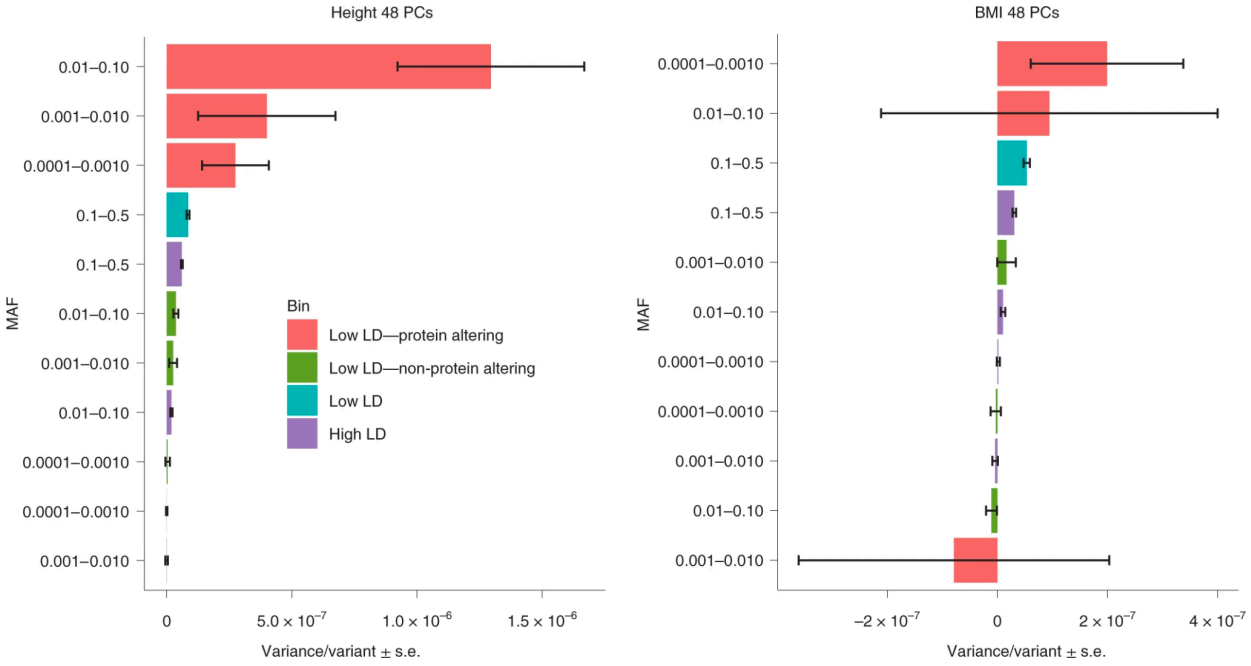
What did these 25 million rare variants reveal about heritability? The results were both consistent with expectations and surprising. The total h2g of height was estimated at 0.68 (of which 70% was common) and the total h2g of BMI was estimated at 0.32 (of which 75% was common). Both estimates were significantly lower than values that had been observed in prior family or twin studies: 0.82 (family), 0.93 (twins) for height (Kemper et al. 2021); and 0.50 (family), 0.75 (twin) for BMI (Robinson et al. 2017). Note that all estimates were determined using GREML, which is not expected to be strongly impacted by assortative mating at this sample size (Border, O'Rourke, et al. 2022). Thus, as observed in (Young et al. 2018) and other studies, twin-based estimates continued to show 1.5-2x upward bias relative to these total h2g estimates.

Common and rare population h2g estimates for height and BMI from whole-genome sequencing data. *Total h2g: Primary reported result from an analysis of 12 GRMs and 48 WGS principal components. Functional: Secondary result using 11 GRMs but splitting protein-altering and non-protein-altering variants. Common h2g: Estimate from ~1M representative common variants only. UKBB: Estimate in the UK Biobank using rare coding variants from exome sequencing and common non-coding SNPs. Previous kinship/twin: Estimates from family-based studies (including shared environment) and classical twin studies in prior work. All "h2g" estimates are population-level (not direct). Data from (Wainschtein et al. 2022).*

Trait	Total h2g	Total h2g (functional partition)	Common SNP h2g	% Common	UKBB SNP+exons h2g	Previous kinship h2	Previous twin h2
Height	0.68 (0.10)	0.61 (0.10)	0.48 (0.02)	70%	0.59 (0.04)	0.82 (0.04)	0.93
BMI	0.32 (0.10)	0.24 (0.10)	0.24 (0.02)	75%	0.31 (0.04)	0.50 (0.03)	0.75

Further partitioning the heritability into coding/non-coding variants and by allele frequency revealed that rare variant h2g was almost exclusively in coding variants, with the contribution specifically assigned to rare non-coding variants not significantly different from zero for either height or BMI (see figure below). This matched the expectation from prior analyses and theory that the proportion of coding heritability would increase for lower frequency variants.

Heritability per variant for different functional, frequency, and LD variant classes.
The h2g per variant/SNP is shown on the x-axis for different variant classes and frequencies. Coding variants highlighted in red. Figure from (Wainschtein et al. 2022).



The big surprise here was the total rare variant h2g accounting for an additional 25-30% of total h2g, when prior models had anticipated only 5-10%. The higher than anticipated rare variant h2g could imply that (a) selection is stronger than expected, (b) models from common/low-frequency variants do not capture the full complexity of the evolutionary process, (c) population stratification across rare variants was not fully addressed, (d) simply that the whole-genome estimates are still very uncertain. The estimates are also frustratingly reliant on somewhat ad hoc parameter choices. The study employed heritability partitioning across a large number of components to address potential frequency/LD biases (see [**2.3**]) but different parameter values could substantially change the estimates. For example, a sub-analysis that simply further divided the coding variants into components for protein-altering versus non-protein-altering (as in the figure above) reduced the total h2g for height from 0.68 to 0.61 and for BMI from 0.32 to 0.24. Whereas removing outlier individuals from the relatedness matrix substantially increased both estimates. With the confidence interval on the estimate for height ranging from 0.48 (implying no rare heritability) to 0.88 (implying a large rare variant contribution), the definitive estimate of rare variant h2g remains to be quantified with larger data and for more traits.

4.8 | A word on heritability in animals

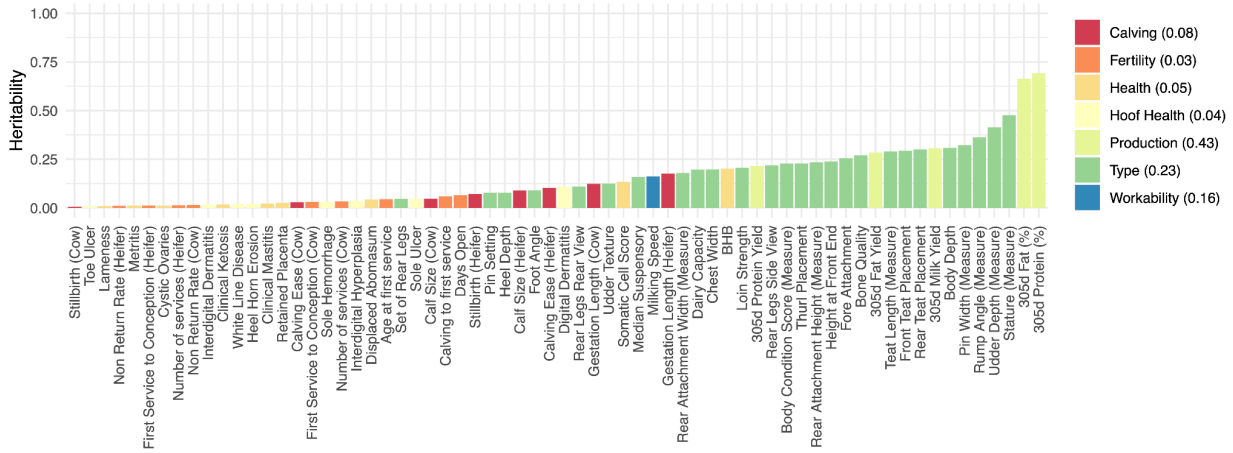
[🔥I am a human geneticist and this is just a cursory survey of findings from animal genetics]

Finally, it may be of interest to contrast the h2g estimates we see in humans with heritability estimates in non-human animals. In agriculture, very large pedigrees and detailed phenotypic records enable highly accurate estimates of pedigree heritabilities (“h2”; which are expected to

capture the *total* genetic contribution to the phenotype as well as any environmental confounding [see **2.6**]). (Oliveira Junior et al. 2021) recently estimated the pedigree heritability across >500,000 records and 67 traits in Canadian Holstein cattle. For many trait classes these estimates were surprisingly similar or even *lower* than estimates from humans: biometric traits (height, length, etc) had mean h2 estimates of 0.23; health traits had mean h2 estimates of 0.05; and fertility related traits had mean h2 estimates of 0.03-0.08. Only traits related to milk production, which are critical for profitability and thus under careful optimization by the industry, had an appreciable mean h2 of 0.43 largely driven by high h2 for fat and protein content. **Of course, the level of environmental control and health management is substantially different in the farm setting, but it is notable that non-production traits often have pedigree h2 < 10% and even many production traits have pedigree h2 < 50%.**

Pedigree heritability for 67 traits from Canadian Holstein cattle.

Estimates taken from (Oliveira Junior et al. 2021)



Observations in natural animal populations have demonstrated that h2 estimates can be substantially impacted by the amount of environmental heterogeneity, indirect (particularly maternal) effects, and the statistical methods used (L. E. B. Kruuk 2004). In particular, estimates from close relatives were consistently higher than from variance components across the full range of relatedness (aka the “animal model”) for example: a mean of 0.41 from parent/offspring regression versus a mean of 0.28 from the animal model (L. E. B. Kruuk 2004); or a mean of ~0.58 from full-sib regression versus a mean of ~0.30 from the animal model (Postma 2014). This mirrors a similar observation across relative classes in humans (see [**4.2**]). The h2 of personality and behavioral traits, in particular, has been studied across a range of organisms, with a large-scale meta-analysis reporting a mean h2 of 0.24 for personality traits in domesticated populations and 0.34 for wild populations (Van Oers and Sinn 2013); and a similar mean h2 of 0.31 for behavioral traits (Stirling, Réale, and Roff 2002). Interestingly, and in contrast to human molecular estimates, major components of behavioral h2 were explained by dominance, particularly for the domesticated animals (Stirling, Réale, and Roff 2002); dominance heritability may alternatively be conflated with shared environmental effects or vice versa (X. Chen et al. 2015). See much more discussion of potential environmental confounding in animal studies in [**8.11**]. **In short, h2 estimates in animals are generally on the low/moderate side with variance component/”animal model” estimates significantly lower than classical family regression**

estimates and impacted by the modeling of dominance: all suggesting that shared environment confounding is at play.

4.9 | Further reading

Broad overview:

- (Price, Spencer, and Donnelly 2015): Broad review of progress in disease genetics.
- (Lappalainen and MacArthur 2021): Broad review of functional findings from disease genetics.
- (Visscher et al. 2012, 2017; Abdellaoui et al. 2023): Periodic review of findings from GWAS.

Representative analyses:

- (Kanai et al. 2018): Representative analysis of heritability across many traits and functional features in the BioBank Japan.
- (Howe, Nivard, et al. 2022): Largest multi-trait within-family GWAS to date with multiple follow-up analyses.
- (Weiner et al. 2023): The first rare coding burden heritability quantification, across many traits in ~300,000 exomes from the UK Biobank.

Conceptual models of trait architecture:

- (Boyle, Li, and Pritchard 2017): A perspective and analysis on a proposed “omnigenic” model of disease where nearly every region harbors an association that is active in many tissues/cell types.
- (Wray et al. 2018): Response to the above perspective piece arguing that common disease is unlikely to be explained by network effects on a smaller number of “core” genes.
- (Simons et al. 2022): Model of pleiotropic balancing selection on multiple traits.

The heritability of educational

attainment

Across the genetic architecture of common traits [**Section 4**], behavioral traits consistently stand out in exhibiting large rGE mediation and indirect effects. It is not a coincidence that behavioral traits also tend to exhibit environmental specificity, cultural transmission, and assortative mating – all factors that lead to gene-environment confounding. Educational Attainment (EA) is, in this sense, the prototypical confounded trait: it has some of the highest assortative mating of any measurement (r=0.45), almost as high as birthplace or parental age, and much higher than cognitive phenotypes like IQ test performance (r=0.23) (Horwitz et al. 2023); it exhibits substantial, complex, and multigenerational cultural transmission (Kroeger and Thompson 2015); it is geographically clustered (Domingue et al. 2018), and correlates with many downstream outcomes (Zajacova and Lawrence 2018). EA is also relatively straightforward to define, measure, and conceptualize and has thus been extensively studied in genetic analyses including some of the largest GWAS of any trait. EA thus presents an opportunity to understand patterns of heritability for an important culturally driven phenotype with ample data and statistical power.

5.0 | Summary

- **The total effect of genetics on Educational attainment (EA) is very small.** The best molecular estimate of the direct additive effect of all genetic variation on educational attainment is 9-17% (Young et al. 2018). Conservatively correcting for potential bias due to extreme latent assortative mating still produces an estimate of 15-16%.
- **For common variants, the direct heritability of EA is just 4%, estimated within siblings** (Howe, Nivard, et al. 2022)**, compared to an environmentally confounded population heritability of ~15%.** EA has some of the lowest direct SNP heritability and the largest environmental confounding of any tested phenotype.
- Consistent with confounding via dynastic/family environment, **PGI prediction accuracy (i.e. the association of genetics) decreases by 50-75% after accounting for parental genetic values** (Kong et al. 2018; Young et al. 2022) **and by 50% when evaluated in adoptees** (Cheesman, Hunjan, et al. 2020).
- **Gene-environment confounding can be entirely** (Willoughby et al. 2021) **or largely** (Kong et al. 2018; H. Liu 2018; B. Wang et al. 2021) **explained by cultural transmission of EA from parents.** Further attenuation is also observed when adjusting for EA/socioeconomic status composites or geographic regions. Cultural transmission is thus supported by orthogonal approaches including: (1) within-family AM correction, (2) environmental conditional analyses, and (3) adoption studies.
- **Cultural transmission and environment is much more important than genetic transmission.** Under models of phenotypic assortative mating and cultural transmission, cultural transmission explains 2-6x more variance than genetic transmission. Other

environmental factors can explain 7-18x more variance in the trait than genetic factors, consistent with the low direct h2g. (🔥: estimates from a simple cultural model).

- **The association of common genetics with EA becomes weaker in higher resource environments**: Multiple large studies have found that the common h2g of EA decreases by as much as 2x when measured in a high-SES versus low-SES environment (Mostafavi et al. 2020). The within-family predictive accuracy of the PGI *decreases* 4x between the lowest achieving and highest achieving schools (Cheesman et al. 2022). Resources appear to make genetics less, rather than more, important. (🔥: statistical interactions may not reflect biological interactions: see [**1.2**]).
- **The genetic association of EA with other traits is also largely through indirect/environmental correlations.** While statistically significant, the contribution is negligible: the most accurate EA PGI explains <3% of the variance in non-EA phenotypes and <1% in non-behavioral phenotypes after accounting for indirect associations.
- **Studies interpreting PGI-offspring associations as "natural selection"** (J. P. Beauchamp 2016) **are getting the causality backwards and the direct genetic of EA on fertility is negligible at just ~0.3%.**
- **After controlling for population stratification, recent natural selection on EA is not significantly different from zero** (Howe, Nivard, et al. 2022)**.** Under weak natural selection, the vast majority of EA heritability is expected to be common.
- **EA variants are broadly active in many tissues.** While genes/regulatory elements expressed in the brain are the most *enriched* for EA h2g, they explain less h2g *in total* than broadly expressed genes. It remains unknown to what extent these variants may be acting through explicitly non-cognitive mechanisms such as discrimination on pigment/height/weight.
- **In a study of 300,000 sequenced exomes, rare variants contributed negligibly to EA heritability and entirely via developmental disability genes** (C.-Y. Chen et al. 2023)**.** The rare burden h2g (see [**2.4**]) for EA was estimated at <0.0025. All six rare variant genes associated with EA had negative effects, four of which were previously identified in studies of neuro/psychiatric disorders.
- **The most recent EA PGI achieves 88% of the theoretical maximal predictive accuracy, current PGI-based findings are thus close to the highest achievable associations.**

5.1 | Rationale

Let's start with the basics: how is EA defined? In the most recent GWAS (Okbay et al. 2022) the definition is very simple: educational steps are recoded as a continuous variable roughly corresponding to the years of schooling. Genetic variation is then tested for association with this continuous "Edu Years" value or a second "College Attainment" phenotype. We can already see some challenges for interpretation since educational milestones are, in truth, more like ordinal transitions rather than continuous values: is the difference between high school and "some college" (2 points) really half the difference between a bachelor's degree and a doctorate (4 points)? These milestones also differ by country and time of measurement (see also [**5.4**] below): for example, in the UK CSEs were replaced by GCSEs; which are both treated as equivalent to

"less than high school" in the US. **In short, the final phenotype is something like a relative/rank quantification of how many major *milestones* of education the participant has attained**.

***Phenotypic coding of Educational Years in** (Okbay et al. 2022)*

23andme	
Category	**Coding**
Less than high school	10
High school	12
Associate/vocational/some college	14
Bachelor degree	16
Master/Professional	19
Doctorate	22

UK Biobank	
Category	**Coding**
None of the above	7
O levels/GCSEs or equivalent	10
CSEs or equivalent (GCSE predecessor)	10
A levels/AS levels or equivalent	13
Other professional qualification eg: nursing, teaching	15
College or University	20
NVQ or HND or HNC or equivalent (2yr/4yr vocational degrees)	*Age left school minus five*

The rationale for collecting this crude phenotype is, essentially, that it's easy and accessible (Rietveld et al. 2013). Since extremely large studies are needed to identify genetic associations with polygenic traits (for example, 5 million individuals to saturate the common genetic architecture of height in (Loïc Yengo et al. 2022)) and EA is routinely collected in biobank surveys, it presents an opportunity for very large and well-powered analyses. Of course, EA is not just *any* phenotype, it is often presumed to be a proxy for "intelligence" (however you define that) or at least "test taking/IQ" and thus a "backdoor" into the genetics of cognitive function (Flint and Munafò 2013) (we will interrogate whether this assumption was supported by the data in later sections).

Should we expect educational attainment to be heritable at all? First, as we saw in [**4.1**], nearly every common trait has some non-zero h2g (at least population-level h2g), so the baseline answer is "yes". Second, we know both common and rare genetic variants exist that predispose individuals to various diseases, some of which occur early in life and make it difficult to move through the steps of educational attainment. These causal genetic associations may have nothing to do with cognitive function whatsoever, simply imposing physical/structural barriers for an individual to advance from high-school to college and so on. Since h2g alone does not tell us the mechanism, the genetic variation associated with these diseases would aggregate into non-zero h2g for EA. **Thus, the relevant question is: to what extent and by what causal mechanisms is EA heritable in a general, healthy population?**

5.2 | Direct heritability

In the presence of cultural transmission and assortative mating only the direct estimate of h2g retains any causal interpretability, and even there we need to be careful (see [**3.0**]), so let's start with what is known about direct h2g from family-based molecular analyses.

Total direct heritability

(Young et al. 2018) developed and applied Relatedness Disequilibrium Regression (RDR, see [**3.2**]) to Icelandic family data to estimate the *nearly total direct* h2g of EA. "*Total*" refers to the association with all inherited genetic material regardless of frequency, and was enabled by the unique availability of high-quality Identity-By-Descent (IBD) segment measurements. Such segments will capture any variation transmitted along with the segment, including structural variation or other atypical variants. "*Nearly*" refers to the fact that IBD sharing will not capture extremely rare genetic variation that arose after the common ancestor for an IBD segment, estimated to miss ~10% of rare variant h2g in simulations. As rare variation contributes to a minority of trait heritability (see [**4.6**, **4.7**] and [**5.10**] below for EA) these missed ultra rare/recent variants are generally not expected to greatly impact the estimates.

The (nearly) total direct h2g for EA was 0.09 estimated with HE-regression and 0.17 when estimated with REML with wide confidence intervals. Direct h2g estimated using only common variants was 0.17 with REML (the HE-regression estimate was not available), indicative of a minimal contribution to direct heritability from rare variants, though again with wide confidence intervals. As was observed for other traits, estimates from kinship models and prior twin analyses ranged from 0.42-0.49, further evidence of substantial inflation in twin and family models due to confounding from the shared environment. Finally, genetic ancestry components were more strongly associated with EA than any other trait, underscoring a substantial effect of population stratification.

***Components of h2g for Educational Attainment estimated in** (Young et al. 2018)*

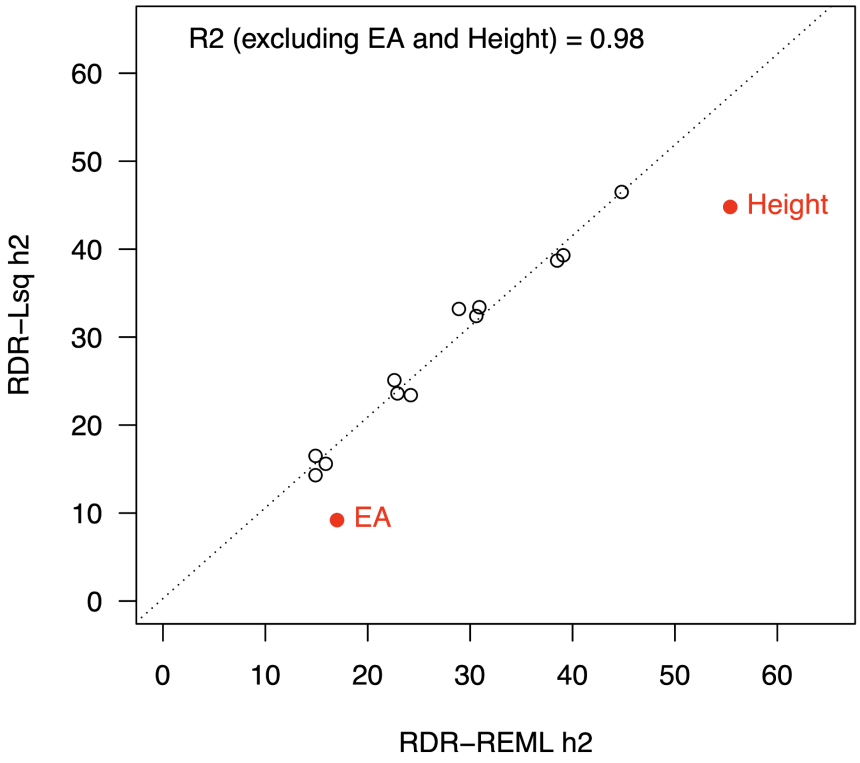
IBD: Identity-By-Descent segments estimating association with most genetically transmitted material; SNP: estimates from common (>1% frequency) variants only. HE: Hasemane-Elston regression / least squares estimator; REML: maximum likelihood estimator; AM: adjustment for assortative mating. Kinship/twin models estimate total trait transmission and are confounded by any shared environment.

IBD RDR direct h2g (HE)	IBD RDR direct h2g (HE) [AM]	IBD RDR direct h2g (REML)	SNP RDR common direct h2g (REML)	SNP common pop h2g (REML)	Kinship (RDR sample)	Kinship (random)	Previous Kinship	Previous Twin [AM]
0.09 (0.14)	0.09	0.17 (0.09)	0.17 (0.04)	0.30 (0.04)	0.52 (0.04)	0.46 (0.02)	0.42 (0.04)	0.49 (0.08)

The large difference in estimates from HE-regression versus REML highlights the potential influence of assortative mating on the RDR estimator, which are known to be differentially biased by AM (see [**3.3**]). Indeed, HE-regression versus REML estimates were nearly identical (R2=0.98) for all traits except for EA and height, the two phenotypes with the largest evidence of assortative mating from mate pair correlations:

Comparison of HE-regression versus REML estimates from RDR analysis of 14 traits.

Estimates for each evaluated trait shown as a single point with REML on x-axis and HE-regression on the y-axis (referred to as Least Squares / Lsq). Height and EA highlighted in red, linear fit to traits excluding height and EA shown with dotted line (R2=0.98).

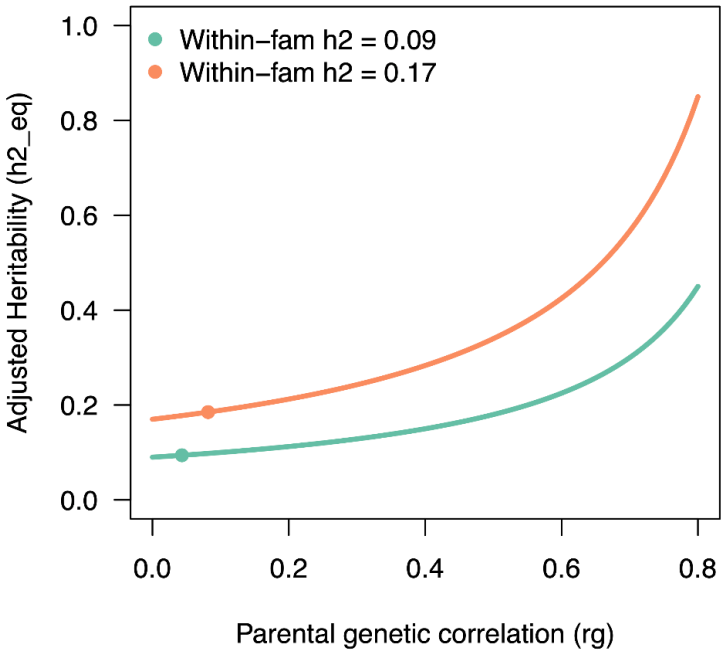


We thus consider corrections to the HE-regression estimate under a variety assortative mating scenarios. Recall that the goal of these corrections is to recover the true association between genetic variation and the trait in the current population, under the assumption that assortative mating has reached equilibrium. In other words, the squared partial correlation between the trait and the genetic value after conditioning on the genetic values in the parents (if we had perfect estimates of genetic values or perfect PGIs).

In the scenario where assortative mating occurs on the observed EA phenotype with a mate pair correlation is 0.42-0.48, the direct h2g remains ~0.09. The fact that the estimate does not change may be surprising given the lengthy prior discussion of AM, but AM biases are minor when either AM or h2g is small (and thus the excess genetic correlation between mates, the cause of AM bias, is also weak). In this case, the genetic correlation between mates is expected to be 0.09*0.48=0.04 and introduce a negligible bias.

Expected assortative mating correction for direct h2g.

Corrected, equilibrium heritability (y-axis) as a function of parental genetic correlation (x-axis) for an estimated within-family direct h2 of 0.09 (green) and 0.17 (orange).



It is, of course, possible that AM is acting on a latent, more heritable, phenotype and the true genetic correlation between mates is higher than what would be expected from the observed phenotypic correlation (see [**3.3**] and [**5.14**] below). Under an extreme latent mating scenario, where assortative mating occurs on an 80% heritable trait with phenotypic correlation of 0.48 the corrected estimate would be 0.15. Alternatively, using a recently proposed method to adjust for assortative mating based on observed population PGI correlations (Young 2023), the estimate that pops out is 0.16 (this correction is imperfect as PGI correlations were derived from population-level effects, not direct effects, and used only common variants, not all variants). Note, all above corrections are made to the HE-regression estimate rather than the REML estimate because only the former follows analytical expectations for bias. **In short, under either phenotypic or latent assortative mating, the corrected (nearly) total direct h2g estimate for EA is 0.09-0.16**.

RDR total direct heritability estimates of Educational Attainment with corrections for assortative mating.

Using a raw RDR estimate of 0.09 each row reports the results from different AM scenarios for: the mate correlation, corresponding genetic mate correlation, corrected estimate. Row 3 assumes assortment on an underlying latent phenotype with 80% heritability. Row 4 uses the method of (Young 2023) based on total PGI correlations. Adjustments for a twin estimate of 0.43 also shown for comparison.

Assortment type	Mate correlation (r)	Mate genetic correlation (rg)	RDR h2 Adjusted for AM	Twin h2 Adjusted for AM
1. None	0.00	-	0.09	0.43
2. Phenotypic (Kemper et al. 2021)	0.42	0.04	0.09	0.56

Assortment type	Mate correlation (r)	Mate genetic correlation (rg)	RDR h2 Adjusted for AM	Twin h2 Adjusted for AM
3. Phenotypic UKB (Horwitz et al. 2023)	0.48	0.05	0.09	0.61
4. 0.48 assortment on 80% heritable latent trait	-	0.38	0.15	0.69
5. PGI-based correction (Young 2023)	-		0.16	1.86

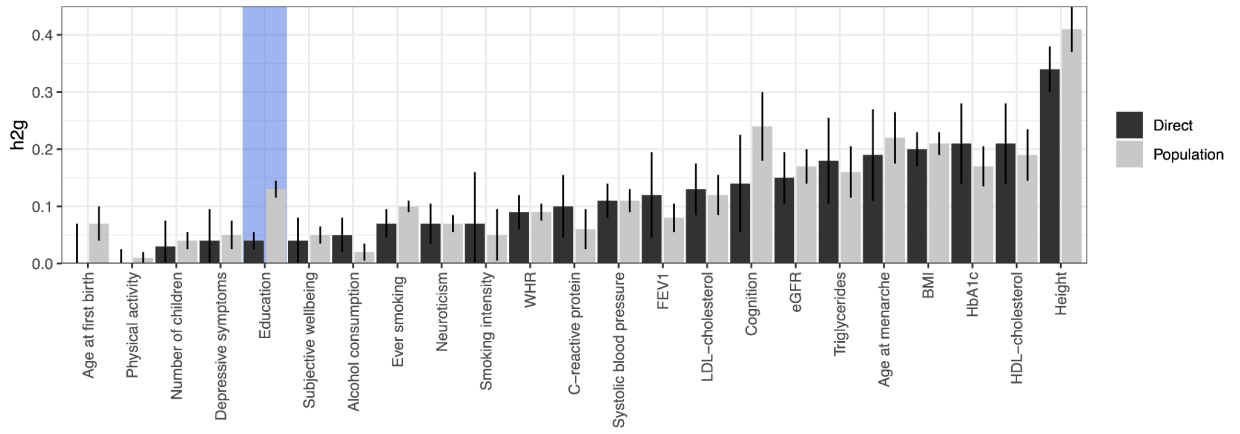
5.3 | Common direct heritability and PGIs

In addition to the RDR approach described above, direct h2g for common variants can be estimated by conducting within-family GWAS (see [**3.2**]) followed by conventional summary-based heritability analyses (e.g. LDSC regression, which is approximately equivalent to HE-regression). Across ~129k individuals, (Howe, Nivard, et al. 2022) estimated direct common SNP h2g of 0.04 (s.e. 0.01) for EA. Unlike variance partitioning / RDR, within-family effect size estimates are not biased by assortative mating and thus no correction is needed (Lee et al. 2018; Brumpton et al. 2020; N. M. Davies et al. 2019).

What does this direct h2g mean practically? For a trait with 40% prevalence (e.g. college attainment) under a completely random environment, an h2g of 0.04 means that having a sibling graduate college increases one's probability to graduate college to 41%; whereas having both parents graduate college increases one's probability to graduate college to 42% (see [**1.1**]). **In short, the direct genetic contribution of common variants is miniscule**.

The direct h2g of 0.04 was contrasted with a population h2g estimate of 0.13 (s.e. 0.01; p=5.3×10^{-26} for difference): a reduction of 76% and one of the largest seen for any trait. Recall that population h2g will include the effect of environment that is non-causally correlated with genotype, particularly for traits undergoing cultural transmission (see [**3.4**]). **In other words, 76% of the apparent population h2g of EA is non-causal environmental confounding**. The direct h2g estimate was also remarkably low compared to the other phenotypes, 4th lowest across the 25 traits tested (with the other three traits all behavioral and vaguely defined: physical activity, age at first birth, and number of children) and far lower than the average common direct h2g of 0.11.

Population and direct common h2g estimates across 25 traits.
Population-level (environmentally confounded) h2g shown in light gray, direct (within-sibship) h2g shown in dark gray. Error bars indicate confidence intervals. EA highlighted in blue. Traits with negative estimates not shown. Data from (Howe, Nivard, et al. 2022).



This cohort was much larger and more representative than the (Young et al. 2018) analysis and exhibited substantially lower population h2g, so the two estimates are not directly comparable. However, in both analyses the population-level h2g was 2-3x inflated relative to the true direct h2g – possibly the largest gene-environment confounding observed for any common trait.

Direct vs. indirect common SNP PGIs

An alternative approach to quantifying direct and indirect genetic effects, proposed by (Kong et al. 2018), is to predict PGIs into parents and children in families and then jointly evaluate their association with the trait of the child. This enables the use of large population GWAS to build highly predictive PGIs at the cost of interpretability, as the estimated parameter no longer corresponds to the *total* variance explained and is highly dependent on how the specific PGI was trained (more discussion in [**3.2**]). Unlike h2g estimators, however, direct effects (but not indirect effects) estimated from within-family PGIs are immune to assortative mating bias (see [**3.3**]), and thus enable triangulation of the estimated direct h2g with different methods.

Within-family PGIs for EA have now been analyzed across multiple cohorts, with representative studies summarized in the table below. The direct variance explained ranged from 2%-5%, with the most recent study using the best PGI to explain 3.2% of the variance in EA directly (Okbay et al. 2022). **These independent PGI-based analyses are consistent with the within-family GWAS estimates of ~4% direct h2g**. The *fraction* of total PGI variance explained by direct effects ranged from 50-60% in earlier studies (Kong et al. 2018; H. Liu 2018) to 26-30% in more recent studies (Young et al. 2022; Okbay et al. 2022), potentially indicating that larger GWAS are picking up more indirect associations (though cohort-specific effects and assortative mating / stratification bias in the indirect effect estimate are difficult to disentangle here).

Recent studies of direct/indirect effect partitioning using within-family PGIs.

For each analysis, the standardized PGI effect and R2 is reported. As each study used slightly different PGI analyses, the fraction of population variance that is direct – which can be compared across studies – is also reported.

Study	EA PGI	Effect	R2	% of pop variance that is direct
(Kong et al. 2018)	Transmitted	0.22	**5.0%**	**50%**
(Kong et al. 2018)	Untransmitted	0.07	2.5%	
(Kong et al. 2018)	Untransmitted, adjusted for parental EA	0.03	0.6%	
(H. Liu 2018)	Direct PGI	0.16	**2.7%**	**63%**
(H. Liu 2018)	Population PGI	0.20	4.3%	
(Willoughby et al. 2021)	Direct PGI	0.19	**3.5%**	**38%**
(Willoughby et al. 2021)	Population PGI	0.30	9.3%	
(Young et al. 2022)	Direct effect	0.14	**2.0%**	**26%**
(Young et al. 2022)	Untransmitted effect	0.14	2.0%	
(Okbay et al. 2022)	Direct PGI	0.18	**3.2%**	**31%**
(Okbay et al. 2022)	Population PGI (family data)	0.33	10.9%	

Incomplete correlation of direct/indirect effects and evidence of stratification

In addition to partitioning the direct/indirect variance of EA, it is of interest to understand the correlation of the direct and population/indirect effect sizes. If direct and population effects are highly correlated, then population-level PGIs used in within-family analyses (as above) can fully capture direct effects and merely misestimate the overall PGI magnitude. **Whereas if direct and population effects are only partially correlated, then the genetic variation causally driving EA in contemporary participants is different from the genetic variation correlated with EA in the population (GWAS/PGI)**, either because different processes are at play for cultural transmission (for example, the mechanisms of mate choice and educational advancement were different in prior generations) or because the population-level estimates are confounded by population stratification (see [**2.9**, **3.4**]).

The genetic correlation between direct and *population* effects was estimated in (Young et al. 2022) at 0.74 (s.e. = 0.09), significantly lower than 1 and indicative of confounding in the population-level estimates. The genetic correlation between direct and *indirect* effects (note, population effects are a weighted average of direct and indirect effects) was estimated at 0.34 (s.e. = 0.22), suggestive of substantially different mechanisms but with very high uncertainty. What could explain this deviation? In simulations with realistic parameters, population structure alone produced a correlation of 0.92, whereas assortative mating *and* cultural transmission produced a correlation of 0.88 – less than 1 but still higher than what was observed in real data. These simulations were intentionally simplistic, but **demonstrated that some combination of stratification *and* AM *and* VCT was present in the population level EA statistics**.

The presence of population stratification was specifically confirmed with additional analyses: adjusting for geographic coordinates or principal components computed from recent relatedness (see [**2.5**]) increased the direct-population correlation up to ~0.79, and a population analysis with more sophisticated control for population structure (BOLT-LMM) produced direct-population correlation of 0.94. **Thus, population-based PGI estimates are inflated by some amount of recent stratification** and this will likely differ depending on how population stratification was accounted for in each study as well as in the target population.

5.4 | Common population heritability (with environmental confounding)

In the previous sections the direct h2g of 0.04 was contrasted with an (environmentally confounded) population h2g of 0.13 estimated in the sibling-oriented study of (Howe, Nivard, et al. 2022). Is the population h2g estimate representative? **Yes, the largest meta-analysis of EA heritability** (Lee et al. 2018) **estimated an average common h2g of 0.15 across >1 million individuals**. This is slightly higher than the 0.13 observed in (Howe, Nivard, et al. 2022) and lower than some of the initial estimates from smaller studies (e.g. 0.22 in (Rietveld et al. 2013)) but broadly consistent with estimates from individual large cohorts (see table below). Bias due to assortative mating (see [**3.3**]) was specifically quantified in (Border, O'Rourke, et al. 2022), producing an AM-corrected h2g of 0.15-0.16 (down from 0.16-0.17) using two approaches. **Thus, the gap between the direct h2g and the population h2g cannot be explained by assortative mating corrections alone and can be attributed to cultural transmission or population stratification**.

Common h2g estimates of Educational Attainment across multiple studies and methods.

Study / Method	# Samples	Estimate
(Rietveld et al. 2013) multi-cohort	126,559	0.22
(Howe, Nivard, et al. 2022) multi-cohort	128,777	0.13
(Lee et al. 2018) multi-cohort	1,060,743	0.15
(Lee et al. 2018) UK Biobank (mostly UK)	442,183	0.14
(Lee et al. 2018) 23andme cohort (mostly US)	365,538	0.14
(Lee et al. 2018) EGCUT (Estonia)	36,631	0.16
(Border, O'Rourke, et al. 2022) UK Biobank HE-reg	332,198	0.17
(Border, O'Rourke, et al. 2022) UK Biobank HE-reg (AM corrected)	332,198	0.16
(Border, O'Rourke, et al. 2022) UK Biobank HE-reg (AM_g corrected)	332,198	0.12
(Border, O'Rourke, et al. 2022) UK Biobank REML	332,198	0.16
(Border, O'Rourke, et al. 2022) UK Biobank REML (AM corrected)	332,198	0.15

Study / Method	# Samples	Estimate
(van Alten et al. 2022) UK Biobank (all)	392,433	0.15
(van Alten et al. 2022) UK Biobank (participation weighted)	160,707	0.18

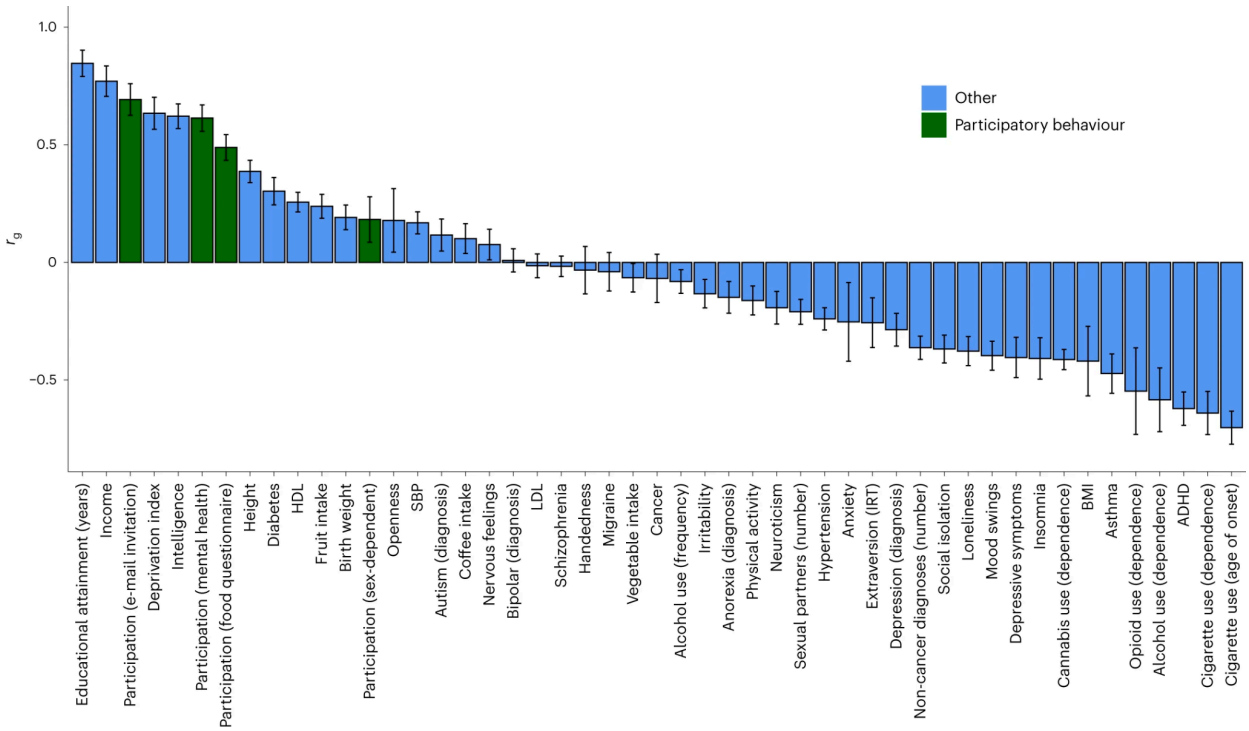
Dominance

Dominance variation, where the effect of multiple copies of an allele deviates from additivity, has a negligible role for common variants across nearly all common traits (see [**4.1**]) and we should expect similar for EA. Indeed, (Okbay et al. 2022) conducted a dominance-GWAS of EA in 2.5M individuals and estimated a total common dominance h2g of 0.00015, which was not significantly different from zero. The GWAS did not identify a single genome-wide significant association, and concluded that "*we can rule out the existence of any common SNPs whose dominance effects explain more than a negligible fraction of the variance in EA*".

Participation bias

GWAS participants have to opt in to the study by definition, and this creates a potential bias if the participation is not random. When participation is correlated with a trait being tested, this can (a) restrict the variance in the study relative to the full population and deflate heritability or estimated relationships across traits (van Alten et al. 2022); (b) induce a collider bias by conditioning on a variable that is influenced by the outcome and lead to distorted estimates of the genetic effects (Young et al. 2022). In the UK Biobank (and likely other biobanks as well) multiple studies have shown that participation is correlated with EA and related traits. (Schoeler et al. 2023) and (van Alten et al. 2022) used representative census data to infer the participation bias between the UK Biobank population and the general population. (van Alten et al. 2022) then re-estimated the h2g of EA after re-weighting the sample to match the population, leading to a slight increase in the population h2g from 0.15 to 0.18. (Schoeler et al. 2023) conducted a GWAS on participation itself and estimated the genetic correlation between the "participation GWAS" and other traits, demonstrating that EA had the highest positive genetic correlation of any trait tested (including income and IQ). Lastly, (Benonisdottir and Kong 2023) used a clever sibling design to identify excess shared genetic variation in participating siblings and derive a participation phenotype. This approach was notably different in that it did not require inferring the relationship between the biobank sample and the general population. The participation phenotype was significantly heritable (population h2g = 0.13, nearly as high as EA itself) and had a substantial genetic correlation with EA of 0.37 (s.e. 0.10). Thus, three different approaches demonstrated that EA is significantly genetically correlated with biobank participation and this can influence genetic correlations between EA and other phenotypes in complex ways.

Genetic correlation between participation in the UK Biobank and other traits.
Figure from (Schoeler et al. 2023).

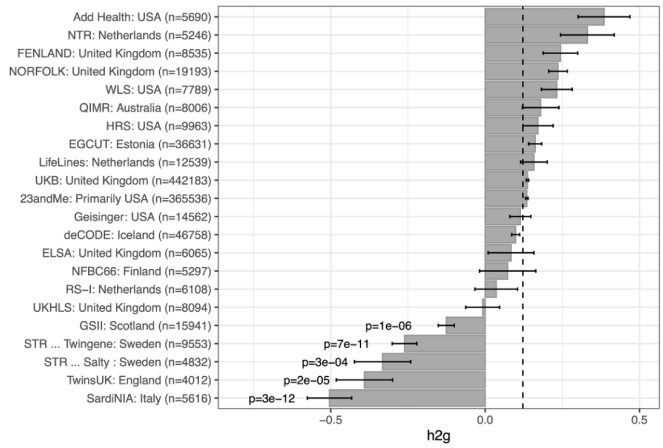


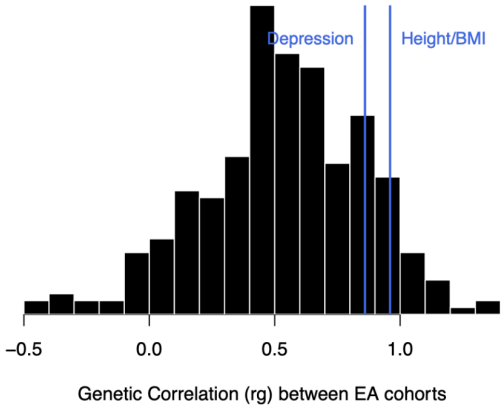
Cohort heterogeneity

Although (Lee et al. 2018) reported a weighted mean estimate of 0.15, there was significant evidence of inter-cohort heterogeneity. First, multiple sub-studies exhibited highly significantly negative estimates of common h2g. While random fluctuations and small sample sizes can lead h2g estimates to be negative purely due to statistical chance, highly significant negative estimates are indicators of either systematic data/processing issues or unusually complex genotype-phenotype relationships (Steinsaltz, Dahl, and Wachter 2020). Cohorts with negative h2g accounted for only 6% of the total sample size and so are more of a cohort-specific curiosity than a global bias. Second, and more systematic, was the low mean genetic correlation observed across cohorts, estimated at 0.72 (s.e. 0.14, p = 0.03 for difference from 1.00). A genetic correlation below 1 is indicative of systematic differences in the effect sizes between pairs of cohorts. For context, height and BMI exhibited cross-cohort genetic correlations of 0.96 and 0.95 respectively (Loic Yengo et al. 2018); depression, a more diffuse psychiatric phenotype, exhibited a cross-cohort genetic correlation of 0.86 across three different cohorts (Howard et al. 2019). In short, and unsurprising given the phenotypic definition, both the h2g and the individual genetic effects differ substantially across studies.

Sub-cohort heterogeneity in h2g and genetic correlation.

(left) cohort-specific h2g estimates for all cohorts with standard error < 0.1, p-values are shown for significant negative estimates after Bonferroni correction. (right) histogram of pairwise cross-cohort genetic correlations for estimates with standard error <0.1. For reference, the estimate for depression and height/BMI from other studies is shown in blue.





The high degree of cohort heterogeneity complicates the interpretation of any individual PGI analysis. Differences in PGI prediction across different populations could reflect true underlying genetic differences, or underrepresentation of the given cohort in the PGI training set, or – for the minority of cohorts with negative heritability – completely nonsensical estimates presumably due to data processing.

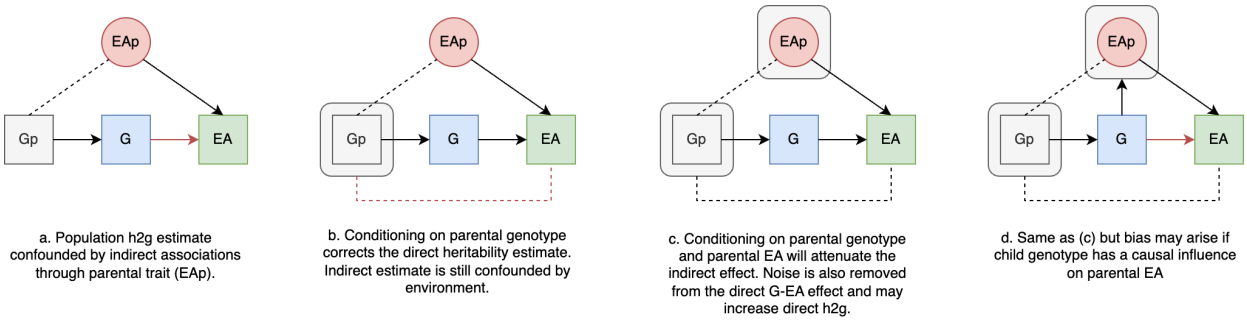
5.5 | Measurable environmental confounding in population PGIs

Within-family environmental conditioning

Differences between (AM corrected) within-family h2g and population-scale h2g are indicators of potential environmental confounding through cultural transmission, which can be further localized by adjusting for specific measured environmental variables (see [**3.2**]). Recall that accounting for random environmental variation should increase h2g (by decreasing the environmental value for the trait), whereas accounting for passive gene-environment confounding should decrease h2g. Moreover, when partitioning direct and indirect effects, environmental factors that decrease the indirect effect lend evidence to cultural transmission along that specific factor (the most logical factor being EA itself in parents).

Scenarios for within-family conditional analyses.

*[Gp]: Parental genotype; [G]: Participant/child genotype; [EA]: Educational Attainment in child; [EAp]: Educational Attainment in parent (potentially confounding); [gray rounded box] indicates conditioning. (**a**) Population-level estimate where direct G-EA relationship is confounded by indirect correlations from parents. Note Gp-EAp relationship may not be causal in the presence of AM (thus shown as a dashed line without arrows). (**b**) Within-family estimate where direct G-EA relationship is properly estimated and indirect association captures all other factors correlated with parental genotype. (**c**) Within-family estimate with additional conditioning on parental phenotype, indirect association will be attenuated if EAp mediates the Gp-EA correlation (i.e. cultural transmission directly through EA). The direct estimate may increase if EAp also has a non-genetic influence on EA (i.e. purely environmental variance). (**d**) Same estimation as (**c**) but G also influences EAp (evocative rGE) which can bias the conditioned effect (likely down).*



Such a conditional analysis was, in fact, conducted in the original direct/indirect analysis of (Kong et al. 2018), where adjusting for parental education attenuated the r^2 of the non-transmitted (i.e. indirect) PGI from 2.5% to 0.6%. In other words, educational attainment in the parents explained the vast majority of the apparent indirect genetic association with educational attainment in the children. The remaining 0.6% was still significantly non-zero, suggesting either assortative mating / stratification or other environmental factors correlated with the EA PGI may still have an effect on the child phenotype.

Several studies have now replicated this within-family conditional analysis for EA. (Willoughby et al. 2021) analyzed a sample of 2,517 genotyped twins and parents with multiple measured traits. In a joint model of parent and offspring EA PGIs, the PGI in offspring explained 2.6% of the variance in child EA and the PGI in the parent explained 4.0% of the variance in child EA (consistent with other PGI analyses in [**5.1**]). Adding either parental EA or parental SES as a factor completely attenuated the parental PGI effect to no longer be significant. Interestingly, adding parental IQ test performance as a covariate in the model reduced the parental PGI effect and variance explained to 1.2% (p=0.004), suggesting that EA itself rather than a latent cognitive feature like IQ was the underlying mediating factor for cultural transmission. Adding parental factors also slightly increased the variance explained by the direct/offspring PGI, consistent with parental EA additionally having a non-genetic environmental influence on child EA (which, when accounted for, refines the direct genetic association).

Variance explained in offspring EA after adjusting for parental features.

Partial r^2 between EA and the offspring PGI and parent PGI in a joint model are reported. Each subsequent row reports adjustment for parental IQ, EA, or SES traits (not PGIs). NS: not statistically significant. Data from (Willoughby et al. 2021).

Feature	Direct/ Offspring PGI	Parent PGI
PGI only	2.6%	4.0%
w/ Parental IQ	2.9%	1.2%
w/ Parental EA	3.6%	*0.2% [NS]*
w/ Parental SES	3.6%	*0.2% [NS]*

Similar findings were observed in an analysis of two US cohorts, the Framingham Heart Study and the Health and Retirement Study, by (H. Liu 2018). **First, parental EA explained far more variance**

in child EA than either parent or child PGIs, underscoring the important cultural role of parental environment in shaping EA in children. Second, the variance explained by the parental EA PGI decreased substantially after adjusting for parental EA in both cohorts, by 2.6x and 4x respectively. Third, the variance explained by the child EA PGI decreased when adjusting for parental EA and decreased further when adjusting for parental EA and parental EA PGIs, indicating that some residual indirect genetic association was present.

Variance explained in child EA from genetic and non-genetic factors.

Results from three cohorts are shown (FHS, HRS wave 1-2, and HRS wave 2-3). Data from (H. Liu 2018).

Feature	FHS	HRS 1-2	HRS 2-3
Parent EA	12.3%	9.6%	18.5%
Parent EA PGI	2.6%	-	3.2%
Parent EA PGI (w/ parental EA)	1.0%	-	0.8%
Child EA PGI	4.0%	4.4%	-
Child EA PGI (w/ parental EA PGI)	2.7%	-	-
Child EA PGI (w/ parental EA)	2.3%	3.2%	-
Child EA PGI (w/ parental EA + parental EA PGI)	1.7%	-	-

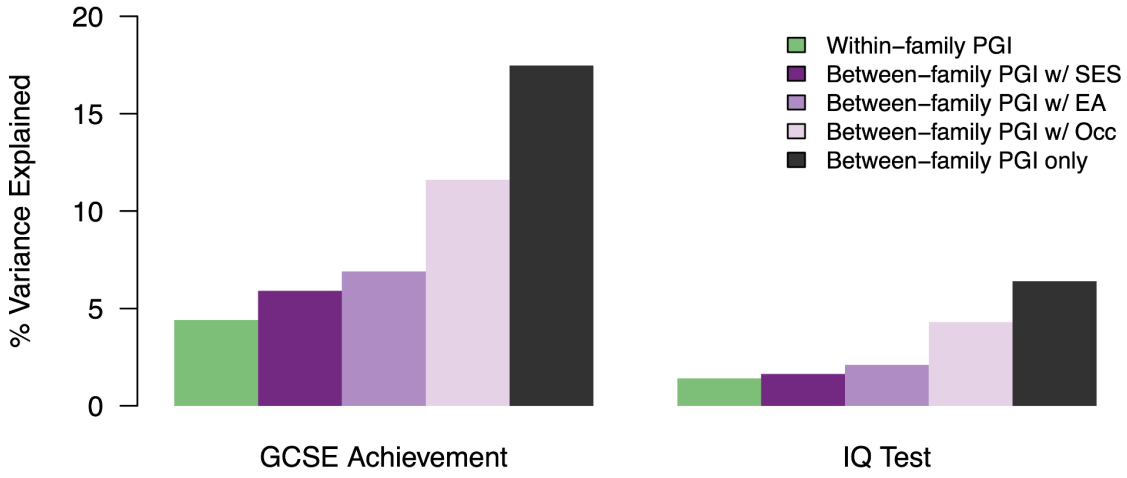
Population-level environmental conditioning

While less accurate, potential environmental confounding can also be evaluated in population studies through conditional analysis, when those environments are measured. If adjusting for primordial factors reduces the predictive effect, then those factors (or something correlated with them) likely mediate the gene-trait correlation (see [**3.2**]).

A hybrid within-family/population approach was taken in (Selzam et al. 2019) using a cohort of ~2,400 dizygotic twins from England and Wales aged 12-21. The General Certificate of Secondary Education (GCSE) exam grades were used as the relevant EA outcome, which is a hybrid of educational attainment (GCSE is one of the "steps" in EA GWAS, see [**5.1**]) and "achievement" (test performance). Consistent with prior results, the within-family PGI explained 4.4% of the variance in achievement and within versus between family differences were "almost exclusively" observed for EA and IQ related phenotypes. The population PGI explained 17% of the variance in achievement, which was attenuated to 5.9% after adjusting for a parental socioeconomic status composite computed from parental education, occupation, and age at first birth, with most of the attenuation coming from parental EA itself. **Thus adjusting for parental environment factors explained the majority of the gap between population and within-family genetic effects.**

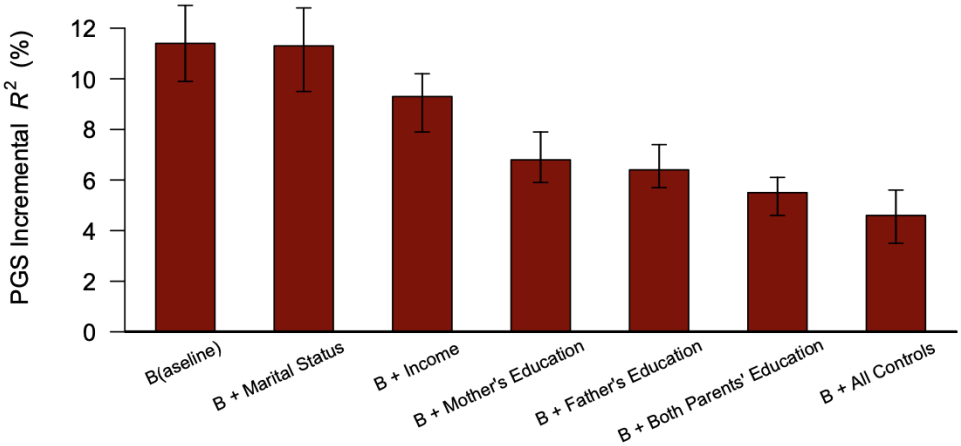
Variance in educational achievement / IQ test explained by EA PGI.

*The variance explained in the General Certificate of Secondary Education (GCSE) test performance (**left**) and IQ test results (**right**) shown for a PGI evaluated by DZ twin difference (green), between families (i.e. in the population) after adjusting for environmental factors (purple), and between families without adjustment (gray). SES was estimated as a composite of parental education, occupation, and age at first birth. Data from (Selzam et al. 2019).*



Using a fully population-based design, (Lee et al. 2018) similarly quantified the change in PGI prediction accuracy after adjusting for basic familial environmental factors: starting from a population-level r^2 of 11.7%, adjusting for parental EA led to a substantial reduction in PGI accuracy (to ~6%), and adjusting for all available factors (marital status, household income, parental EA) further reduced the PGI accuracy to 4.6%. While not directly comparable, this conditioned estimate was again roughly consistent with the independently estimated direct h2g of 4%.

Population PGI accuracy for Educational Attainment after adjusting for environmental factors.
Leftmost bar is the baseline PGI accuracy alone, each subsequent bar adds a covariate for a measured environment. Note: marital status and household income may be downstream of genetic effects. Figure from (Lee et al. 2018).



Finally, (Abdellaoui, Dolan, et al. 2022) estimated conditional common SNP h2g after adjusting for geographic covariates in the UK Biobank. Whereas non-behavioral phenotypes had marginal changes to their h2g after adjusting for birthplace or place of origin (see [**4.3**]), EA was one of the traits most strongly affected by geographic mediation. Starting from a baseline of 0.14, h2g was reduced by 15% (to 0.12) after including birth address, and by 32% (down to 0.09) after including both birth and current address. Yet again a significant portion of population heritability is actually mediated by very crude environmental factors.

Heritability of EA before/after conditioning on birth address, current address, or both.
Raw estimate corresponds to no adjustment. Each estimate is followed by the % of heritability relative to the raw estimate. Results shown for the MSOA analysis, which produced larger deviations. Data from (Abdellaoui, Dolan, et al. 2022).

Raw	Birth Address		Current Address		Both	
h2	h2	%	h2	%	h2	%
0.14	0.12	85%	0.10	74%	0.09	68%

Summary

In sum, multiple studies and study designs confirm that the vast majority of indirect EA h2g can be mediated by parental EA itself or composites of parental EA and socioeconomic status. In some studies, the indirect PGI association was completely attenuated (Willoughby et al. 2021), consistent with simple cultural transmission of EA itself. In other studies, ~25% of the indirect association remained, indicative of a small amount of "latent" cultural transmission on other traits not captured by parental EA (for example, socioeconomic status), or assortative mating / stratification biasing the indirect PGIs. Finally, a recent review and meta-analysis across many different within-family studies found that >90% of the variance explained by indirect effects was attenuated after adjusting for parental EA or SES (B. Wang et al. 2021).

Similar patterns were observed in population-level analyses, where accounting for parental variables attenuated the variance explained by the population PGI by 60-65%, with EA/SES composites generally leading to more attenuation than EA alone. In several instances the adjusted population PGI accuracy approached the expected direct effect h2g. A practical implication of these findings is that proper adjustment for the parental environment may enable more accurate identification of direct effects from population-level data (without families) by blocking much of the environmental confounding (this was, in fact, hypothesized but not done in (Lee et al. 2018)).

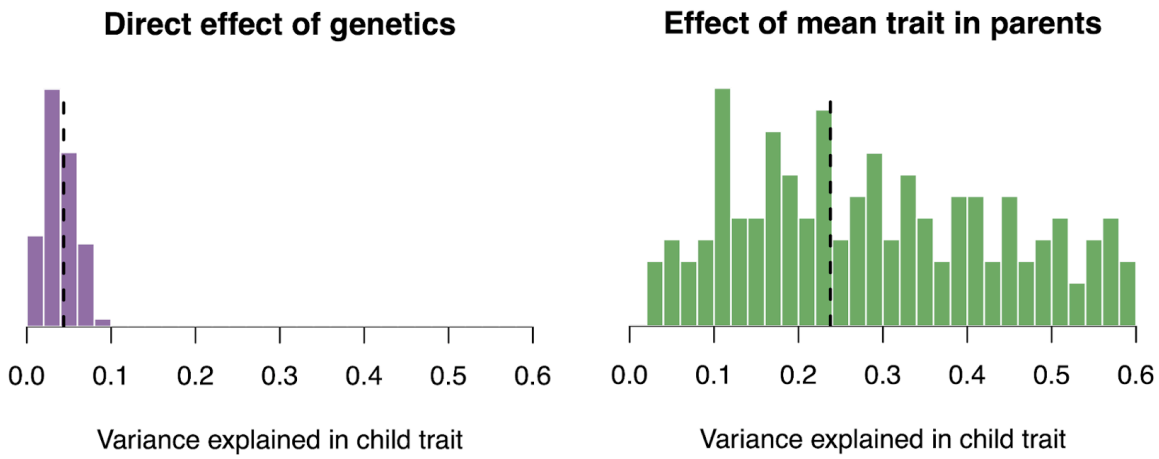
5.6 | Interpreting h2g parameters under a cultural transmission model

While both (Howe, Nivard, et al. 2022; Young et al. 2018) demonstrated a clear and substantial gap between the population-level and direct h2g estimate, the mechanism for this gap has not been quantified. Such mechanistic parameters can be estimated under a model of assortative mating and cultural transmission on EA itself, consistent with some of the observations in [**5.5**]. Knowing that the phenotypic assortment on EA is ~0.48 and the estimated direct and population h2g (0.04 and 0.13 respectively), one can then identify corresponding direct h2g and cultural transmission values that would produce the observed estimates (including potential bias due to RDR/HE-regression estimation).

The figure below shows the results of such a parameter search using HE-regression RDR to estimate direct h2g (see [**3.2**]) and HE-regression to estimate population h2g (see [**2.2**]) in simulations (unpublished). The single best fit true direct h2g was 0.04, with a range of 0.01-0.08 (consistent with the above assortative mating adjustments). **The best fit cultural transmission (defined as the variance in the child trait explained by the mean parent trait) was 0.23, with 90% of parameters >0.10 (but a very wide range)**.

Genetic and cultural parameters fitting the observed common h2g.

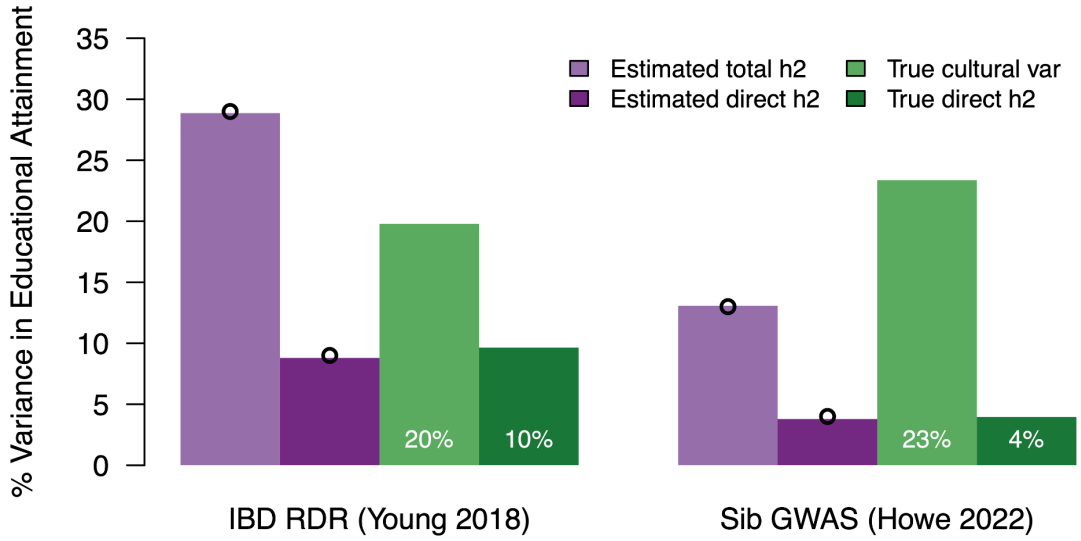
Histogram of genetic and cultural parameters that yield estimates within two standard errors of (Howe, Nivard, et al. 2022): 0.04 direct and 0.13 total h2g. Both are reported in terms of variance explained.



Conducting a similar exercise is more challenging for the (Young et al. 2018) RDR estimates because of the very wide standard errors. For completeness, simply taking the point estimates of direct h2g of 0.09 and total h2g of 0.30, the single best fit parameter model was 0.10 direct h2g and 0.20 cultural transmission. Both results qualitatively support a small fraction of trait variance (4-10%) explained by direct genetic effects, a larger fraction of variance (20-24%) explained by cultural transmission that is correlated with EA genetic values, and a *much* larger fraction of variance explained by environmental factors or through cultural transmission that is *uncorrelated* with EA genetic values.

Matching cultural parameters to two empirical estimates of total and direct h2g.

Using the population/total and direct (i.e. within-family) estimates of h2g for Educational Attainment from RDR (Young et al. 2018) and sib-GWAS (Howe, Nivard, et al. 2022) and a mate correlation of 0.48 (Horwitz et al. 2023) simulations with VCT were fit to identify parameters that produced matching variance partitions. The empirical estimates from data are shown in black dots, the simulation-based estimates are shown in purple bars, the corresponding VCT (% of child trait variance that is explained by mean parental trait) and true direct equilibrium h2g are shown in green bars.



It is difficult to compare these estimates with epidemiological results due to differences in ascertainment and phenotype normalization across studies, the wide credible intervals on the parameter fits, and the fact that the cultural transmission model is very simplistic. However, the estimated cultural variances are at least facially consistent with the average correlation (i.e. square root of the variance) of 0.43 between parental and child schooling across the globe, and 0.46 in the USA, which has held steady for several decades (Hertz et al. 2008). Studies of genetic cohorts have also reported broadly similar parent-child correlations for EA of 0.35-0.43 (H. Liu 2018).

In short, under a phenotypic cultural transmission model, direct genetic variants account for less of the variance in EA than cultural transmission and *much* less than environmental variance – consistent with sociological observations.

5.7 | Gene-Environment interactions / Scarr-Rowe

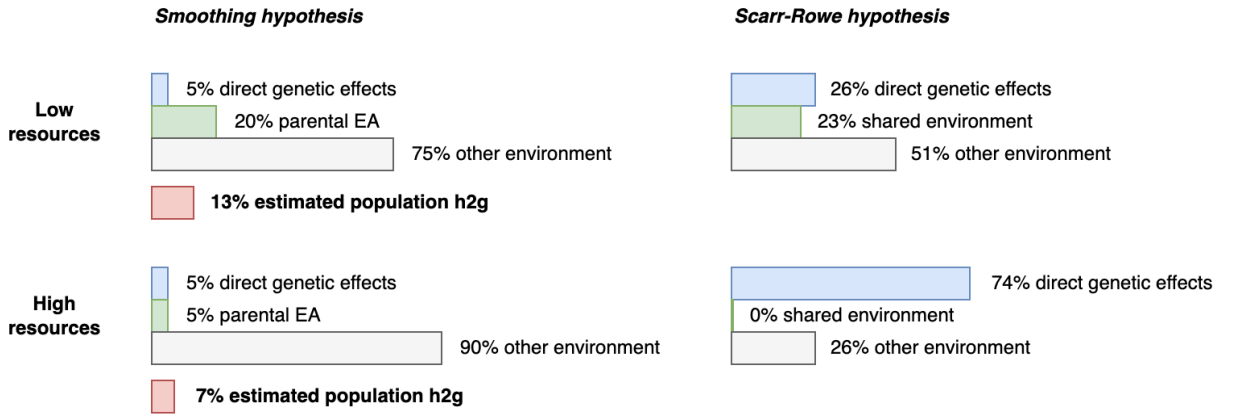
Hypothesis

If the majority of population-scale EA h2g is confounded by cultural transmission from parents, one could expect substantially different h2g estimates in different environments (i.e. GxE interactions, see [**1.2**]) due to differences in cultural patterns. If, for example, the influence of parental education on offspring EA is less important in high resource environments and individual aptitudes (which are primarily non-genetic, see [**4.1**]) are more important, then indirect effect correlations will be weakened and population h2g will *decrease* with higher SES. In the movie *Parasite*, the patriarch of a struggling family observes that "*rich people … have no creases on them"*, to which his wife replies: "*It all gets ironed out. Money is an iron. Those creases all get smoothed out by money*". In this example, wealth/resources "smooth out" the advantages of familial/dynastic environments and decrease the environmentally confounded population h2g.

The smoothing example inverts a classic GxE hypothesis from twin studies known as Scarr-Rowe (Scarr-Salapatek 1971; Rowe, Jacobson, and Van den Oord 1999), which proposes that natural aptitudes become more relevant than environmental effects in high resource settings (or, alternatively, that high resource environments enable individuals to *actualize* more of their natural potential (Bronfenbrenner and Ceci 1994)). The fundamental difference is that the Scarr-Rowe hypothesis presumes that natural aptitudes are highly and directly heritable, and expects heritability to increase with SES as environmental contributions decrease. Whereas the smoothing hypothesis presumes that population h2g is largely driven by environmental confounding. Interestingly, if population h2g and twin/family h2 methods are biased in different ways but observe consistent changes in shared environment, the two study designs could yield estimates consistent with both hypotheses. It's also worth noting that quantifying the generalizability of the Scarr-Rowe effect in family/twin studies remains an active area of study (Turkheimer and Horn 2014) and it is simply one GxSES hypothesis out of many.

Schematic of two GxSES heritability hypotheses.

(left) A hypothetical "smoothing" model where parental EA has a large influence on the child trait in low resource environments but not high resource environments, leading to a higher estimate of population h2g in the former due to environmental confounding. (right) results from twin-based analysis of (Rowe, Jacobson, and Van den Oord 1999) showing substantial changes in estimates of shared environment, but with the majority of trait variance assigned to direct genetic effects.



Beyond understanding current mechanisms, reconciling these models is important for forecasting the expected change in h2g as environments change over time. The Scarr-Rowe effect predicts that heritability will increase as a society becomes more resource rich (a presumption geneticists very much want to believe, if only out of career self-preservation). The smoothing hypothesis predicts that population h2g will decrease as society becomes more resource rich, approaching the (much smaller) direct h2g estimate.

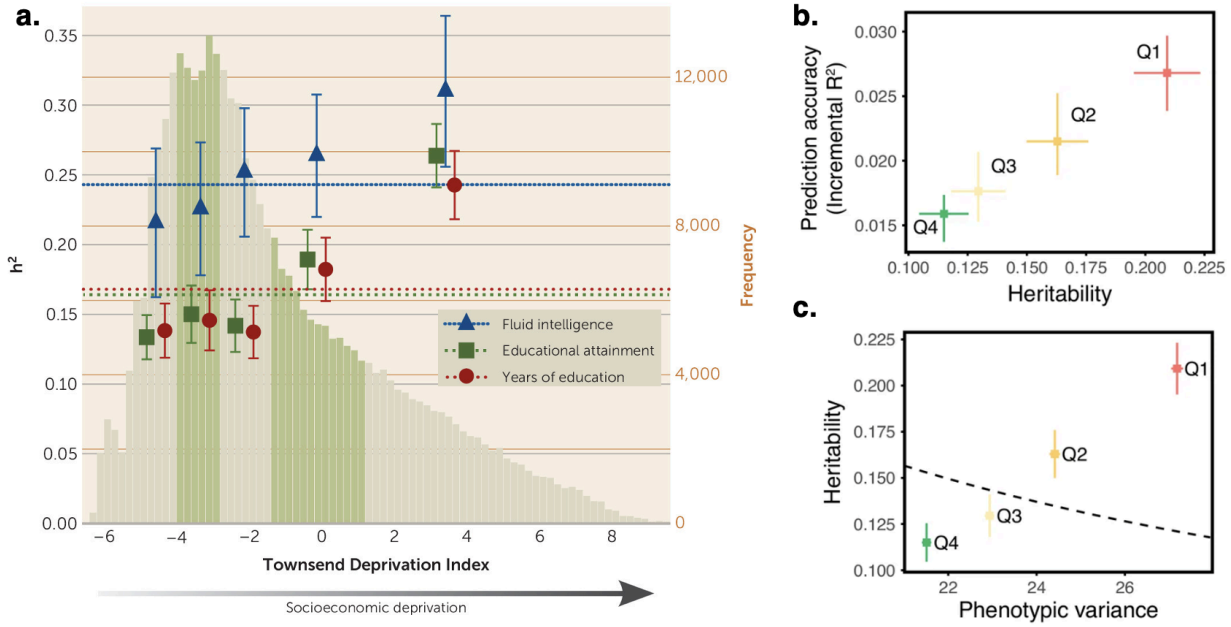
Evidence of interactions between genetics and socioeconomic environment

Two recent studies in the UK Biobank observed significant decreases in population h2g with resource-increasing environments (Mostafavi et al. 2020; Rask-Andersen et al. 2021), consistent with the smoothing hypothesis. In both analyses, resources/SES were quantified using the

Townsend Deprivation Index (a composite of unemployment, car ownership, home ownership, and household size) and h2g estimated in different TDI strata. (Mostafavi et al. 2020) used years of education and observed both population h2g and PGI r2 to be significantly higher for the highest TDI (lowest SES) quartile (h2g = ~21%) compared to the lowest TDI (highest SES) quartile (h2g = ~11%). (Rask-Andersen et al. 2021) observed the same with college attainment (in addition to years of education): in the highest TDI quintile (26% of participants graduating college) the population h2g of EA was 26%, whereas in the lowest TDI quintile (36% of participants graduating college) the population h2g of EA was 13%. In a population PGI analysis, a highly significant GxE interaction was observed between the population EA PGI and TDI (p = $1x10^{-10}$). Notably, the genetic correlation across groups was not significantly different from 1.0, indicating the same pattern of genetic variation but differences in overall magnitude.

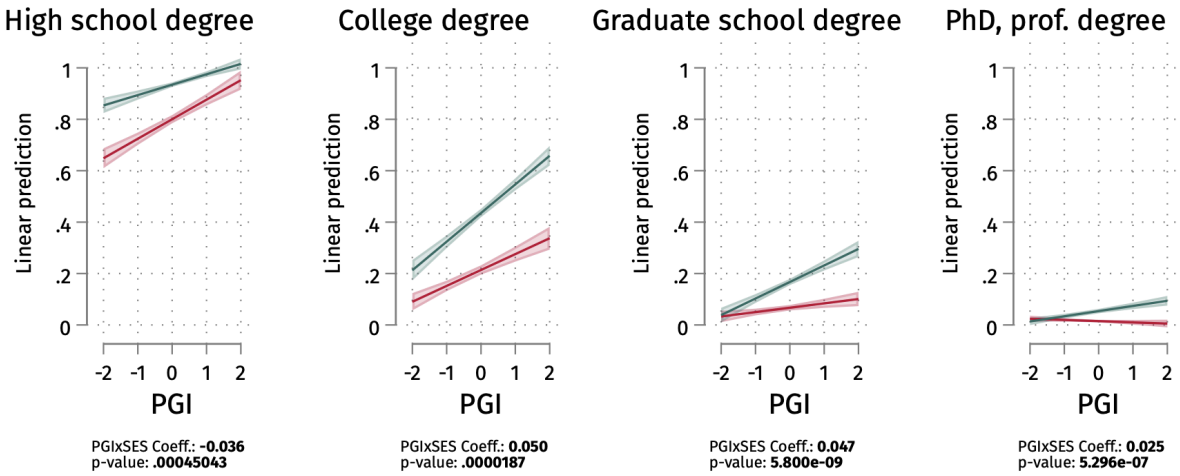
(Mostafavi et al. 2020) hypothesized that the GxE effect could potentially be explained by changes in the environment alone: if environmental variance is lower in higher TDI environments but genetic variance remains the same, then h2g (a ratio of the two) would increase. Strikingly, the opposite relationship was observed: phenotypic variance actually increased slightly in the high TDI environments, implying that either genetic variance alone or both genetic variance and environmental variance had increased. The authors proposed an "amplification" model where genetic effect sizes (and thus overall genetic variance) are magnified in high TDI environments; a model that had earlier been considered for IQ (Tucker-Drob, Briley, and Harden 2013). As noted by (Rask-Andersen et al. 2021), this is the exact opposite to what would be expected from the Scarr-Rowe effect. **Notably, these findings forecast that h2g and r2 will decrease as societies become more resource rich**.

Population h2g and prediction accuracy of EA by Townsend Deprivation Index in the UK Biobank. *(**a**) Population h2g as a function of TDI quintiles for EA (green) and EduYears (red). Figure from (Rask-Andersen et al. 2021). (**b**) PGI prediction accuracy versus population h2g of EduYears for quartiles of TDI (Q1 = highest TDI/lowest SES, Q4 = lowest TDI). Figure from (Mostafavi et al. 2020).*



Recent work by (Ghirardi and Bernardi 2023) continued to explore the GxSES interaction for individual EA "steps" in multiple longitudinal cohorts. Notably, while there was no significant interaction between the EA PGI and SES for overall years of education, there were highly significant – and different – interactions for individual EA milestones. In the largest of the three cohorts, for example, the effect of the PGI is significantly weaker for high-SES families, with individuals in the low/high PGI groups achieving ~90%/~100% graduation compared to ~70% /90% (respectively) for the low-SES families. In contrast, the same interaction is negative when looking at graduate school degrees: for high-SES families, individuals in low/high PGI groups achieve ~5%/~30% graduate degree attainment, compared to ~5%/~10% for low-SES families. Similar effects were seen for other college degree stages and across the three cohorts evaluated.

Variation in GxSES interaction across educational attainment steps.
From left to right: interaction between EA PGI (x-axis) and high-SES (green) versus low-SES (red) for each EA step. For early steps the population PGI effect is lower with high-SES. Whereas for later steps the population PGI effect is higher with high-SES. Figure from (Ghirardi and Bernardi 2023).



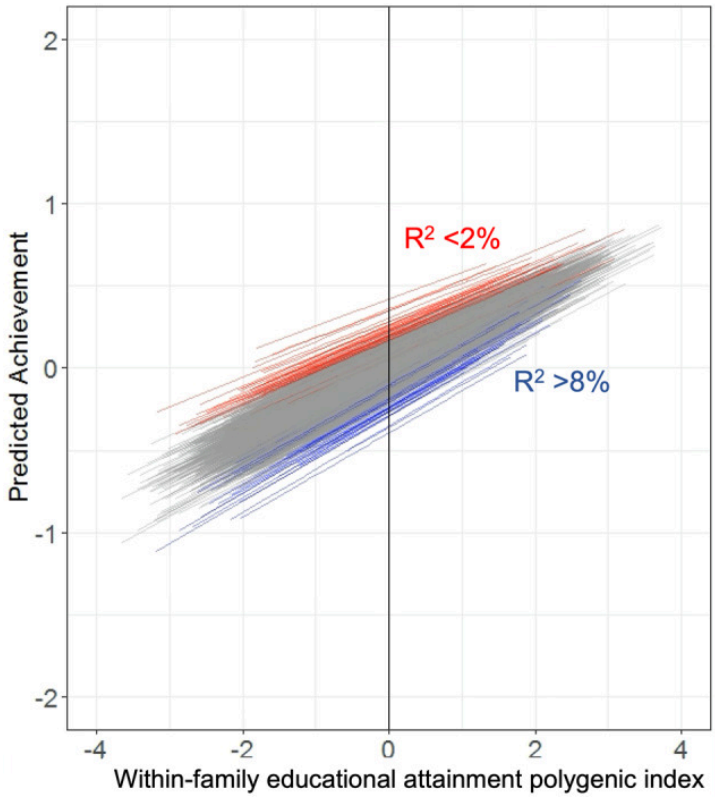
To explain these complex results, the authors propose a "compensatory advantage model (CAM)". Under the CAM, individuals in high resource environments get more second chances to succeed, and are thus able to better overcome initial failures. For example, students who initially struggle in school can be supplemented with private tutoring to maintain their progress. This is facially consistent with the observation that phenotypic variance in low TDI (high resource) environments is lower because high resource students are less likely to suffer dramatic losses in educational attainment. On the other hand, for more selective EA steps like college or graduate school, the authors argue that high-SES families appear to be maximizing slight genetic advantages into more substantial attainment gains. The authors generally present these results in terms of "genetic endowments", as is typical in the field. But recalling that the PGI is actually largely capturing *familial/dynastic* educational attainment (or stratification) and not direct genetic effects, these findings instead suggest that family connections matter less for high-SES individuals in high school but provide an "extra boost" for high-SES individuals to attain a college and graduate degree. Interestingly, a recent large-scale (non-genetic) analysis of selective universities in the US found that high-income families had a significant advantage in admissions

to Ivy League colleges (compared to applicants with comparable test scores), and that Ivy status then had a strong causal effect on admission into an elite graduate school (Chetty, Deming, and Friedman 2023). **In short, the direction of the GxSES interaction may be dependent on the selectiveness of the educational outcome being considered, consistent with non-genetic studies of college admissions**.

Finally, a recent study in a large Norwegian cohort conducted a within-family EA PGI-school interaction analysis (Cheesman et al. 2022). The mean within-family PGI explained 5% of the variance in educational *achievement* (i.e. grades) but interacted significantly with school performance. In the highest achieving schools, the PGI explained ~2% of the variance in individual achievement, whereas in the lowest achieving schools the PGI explained 8% of the variance in individual achievement. This interaction reflects a highly significant increase in predictive ability (and, by extension, direct h2g) in lower quality/achievement schools. Interestingly, including school-level SES factors as covariates did not significantly alter the interaction, indicating that these influences are either weak or are implicitly adjusted for by the within-family design. While these findings present clear evidence of GxE even at the level of direct genetic effects, they again go in the opposite direction of the Scarr-Rowe model.

Interaction between EA-PGI and school achievement.

2.5% of schools with the weakest (strongest) PGI effect shown in red (blue). The PGI effect is weaker in schools with higher mean achievement. Figure from (Cheesman et al. 2022).



Taken together, these results demonstrate a highly complex structure of GxSES on both direct and population-level genetic variation. For overall years of education, population h2g (including indirect effects) appears to be “amplified” in low-SES settings (or “smoothed” in high-SES settings). For individual steps in EA, the relationship is initially consistent with high-SES smoothing

for high-school graduation, followed by high-SES amplification for college and post-graduate attainment. For direct genetic variation in within-family analyses, higher school quality again has a "smoothing" effect on the population PGI whereas SES does not matter (or is implicitly factored out). Since no single study conducted the full battery of population and within-family interaction analyses across EA steps, these discordant findings have not been fully reconciled.

A word of caution on interpreting statistical interactions

While the above studies showed highly significant evidence of *statistical* interactions, the mechanistic interpretation is more complicated (See [**1.2**] and (Domingue et al. 2020)). First, in the case of the UK Biobank analyses, the TDI/SES factors were based on the most recent census data and thus may in part reflect factors that are downstream of the EA PGI rather than predating it. TDI has a very low molecular h2g (more on this later) so we may *expect* the genetic confounding to be low, but it's not clear how low. Second, for the studies that conducted a formal interaction test, class imbalance between groups (e.g. a lower baseline of graduates in the low-SES group) can lead to apparent statistical interactions. (Ghirardi and Bernardi 2023) conducted extensive sensitivity analyses to evaluate the possibility of artifacts, but these can be very difficult to rule out. Likewise, (Cheesman et al. 2022) used school grade composites as the outcome, which can be susceptible to artifacts from data harmonization. Lastly, the PGI analyses all used population-based scores so the usual caveat applies that it is unclear what these scores actually measure outside of the training population (see [**3.2**]).

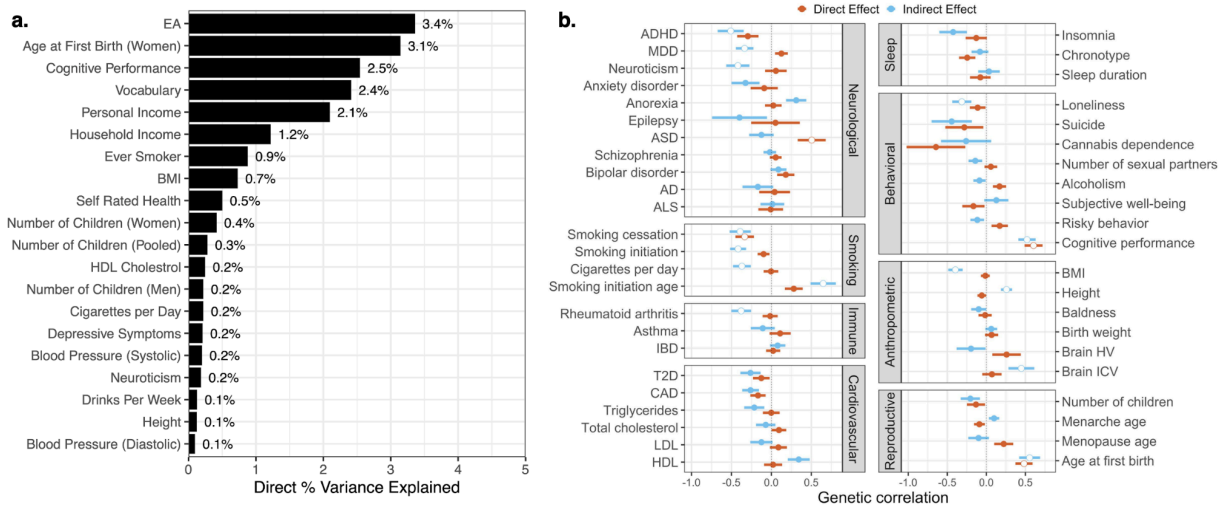
5.8 | Direct common effects on other phenotypes

Beyond the direct effects of genetics on EA itself, we may be interested in the direct effect of EA genetics on other traits. For interventions, we may want to know how much changing an EA PGI in an individual would change a second trait (with the environment and social structure held constant)? For understanding disease architecture, we may want to know how correlated the effect-sizes acting on EA in an individual are with the effect sizes acting on the second trait. These parameters can be approximated in two ways: (1) by evaluating the EA PGI within-families for its association with another trait: this a parameter that quantifies the predictive accuracy and is specific to the sample and PGI; (2) by estimating the genetic correlation between the direct effects on EA and the direct effects on the second trait: this is a population parameter that quantifies the overall correlation of effect sizes. Note that (1) is an approximation that does not account for environmental heterogeneity (see [**3.4**]), and (2) is not a causal estimate at all. Neither estimate is guaranteed to operate through EA itself, as variants that influence EA can also directly influence the secondary trait (or act on EA via the secondary trait).

Using the PGI approach, (Okbay et al. 2022) showed that the population PGI effect of EA on other traits was attenuated at a similar level as the PGI effect on EA itself (i.e. down to ~35% of the population effect). What remained was generally very little: the EA PGI explained ~3% of the variance in age at first birth (a correlate of socioeconomic status), ~2.5% of cognitive performance and vocabulary, 1-2% of income, and <1% for any health-related traits. Using the genetic correlation approach, separate analyses by (Howe, Nivard, et al. 2022; Wu et al. 2021; Young et

al. 2022) likewise found that genetic correlations with EA were greatly attenuated when using direct/within-family effects. Notably, population-level genetic correlations with height, BMI, smoking, brain volume, and psychological traits were all attenuated to zero. **Just as most of the association of genetics with EA is due to environmental confounding, so is most of the *apparent* genetic correlation of EA with other phenotypes**. This of course does not mean that Educational Attainment itself is not causal for health outcomes, but that the small amount of genetic variation influencing EA is mostly directly uncorrelated with the (typically larger) amount of genetic variation influencing health traits. Indeed, causal within-family estimates of the effect of actual educational attainment on other traits generally track with the *population*-level correlations, as the environmental confounding on EA and on non-EA traits effectively cancels out (Howe et al. 2023).

Within-family prediction and genetic correlations between EA and other traits.
*(**left**) Variance explained by EA PGI in within-family analysis. Data from (Okbay et al. 2022). (**right**) Genetic correlations with direct (orange) and indirect (blue) effects. Error bars indicate standard error, white dots indicate significant correlations at 5% FDR. Figure from (Wu et al. 2021).*

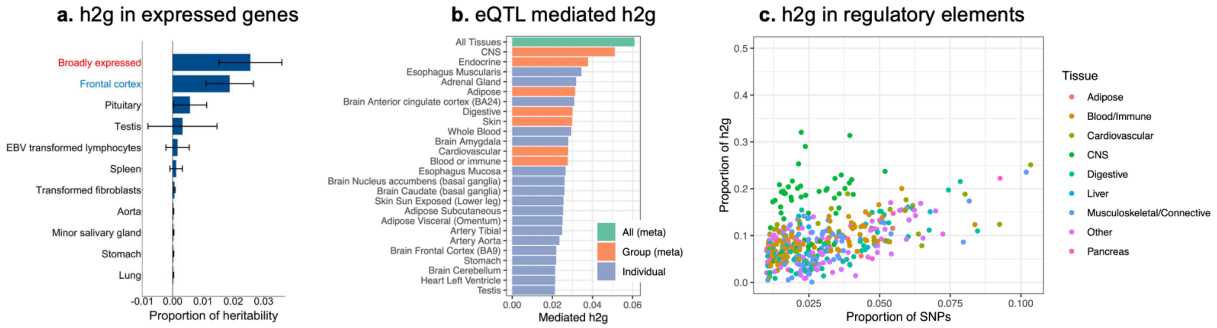


5.9 | Functional interpretation of common variant h2g

While we have focused on heritability, a primary goal of genetic analyses is to identify individual biological mechanisms. For EA this is complicated by extensive environmental interactions even after isolating the variants acting directly in within-family analyses. A variant may have an apparent direct effect because it impacts skin pigment, which is in turn associated with societal discrimination, and has nothing to do with neurological/psychological factors EA GWAS intends to identify (Burt 2022). One proposed solution for disentangling such biologically spurious (but statistically real) direct effects is to evaluate their local "activity" (D. Morris, Ritchie, and Young 2023): if we could distinguish variants that are active in the brain from those that are active in skin or muscle we can focus on the "right" mechanisms. Setting aside the implication that brain-related mechanisms are actually free of discrimination, can this approach work in principle? Recall that the h2g of common traits is generally non-coding and broadly enriched in regulatory elements (see [**4.1**]). While the mapping between variants and their target genes is a field of study

in and of itself, we can consider "activity" in three ways: (1) the variant is *near* a gene that's only expressed in a specific tissue (Finucane et al. 2018)); (2) the variant is actually associated with the expression of such a specifically expressed gene (Yao et al. 2020); (3) the variant is in a regulatory that's only active/open in a specific tissue. We can then evaluate the extent to which EA heritability is localized to such regions using "functional partitioning" (see [**2.8**]), which does not require knowing the individual associations.

Functional enrichment of EA h2g for gene expression and regulatory activity.
(a) Proportion of h2g in genes expressed in different contexts (Figure from (Lee et al. 2018)). (b) Expression-mediated h2g (data from (Yao et al. 2020)) by eQTLs in different tissues and tissue groups. (c) h2g in regulatory elements from different tissues (data from (Finucane et al. 2018)).



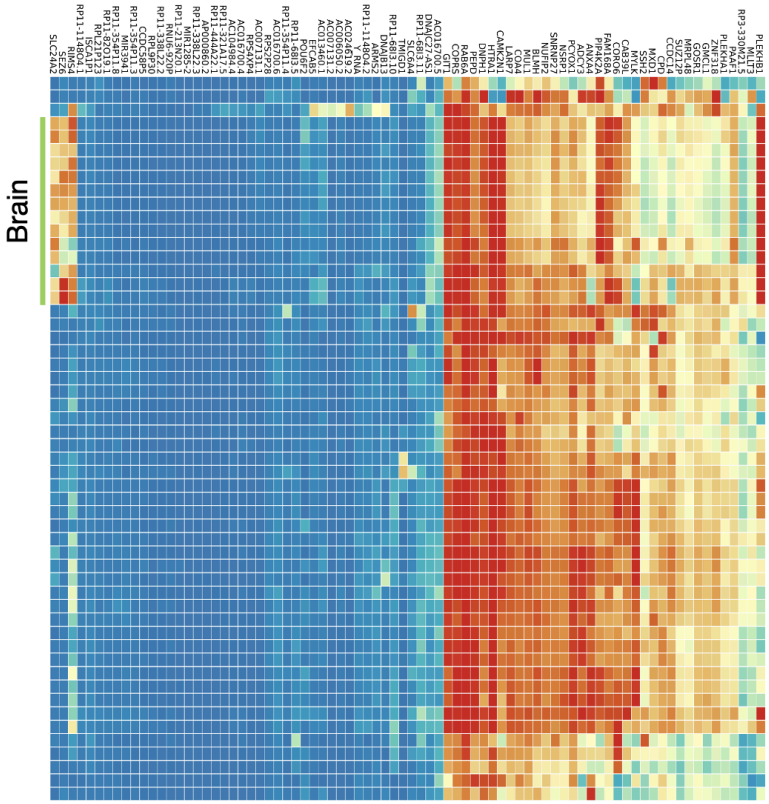
The results from these analyses are highlighted in the figure above. In all instances, genes/elements expressed in the brain are indeed significantly enriched for EA h2g – meaning they contain more of the trait-correlated variation than would be expected by chance. **However, the majority of h2g still resides in broadly expressed or uncategorized genes/elements simply because these are far more abundant than genes/elements expressed in the brain**. This pattern was observed for all data types evaluated. (Lee et al. 2018) estimated the proportion of EA h2g that could be partitioned to specifically expressed genes: broadly expressed genes accounted for ~2.5% of h2g, whereas genes expressed in the frontal cortex accounted for ~2% of h2g, naturally the remaining 95% was in genes active in other tissues or not in genes. (Yao et al. 2020) estimated the proportion of EA h2g that was *statistically mediated* by variants associated with gene expression in specific tissues. Variants active in a cross-tissue meta-analysis mediated ~6% of the h2g, variants active in the central nervous system (including the brain) mediated ~4% of the h2g, and variants active in the frontal cortex mediated 3% of the h2g. Again, >90% of the trait h2g was not mediated by genes that could be easily categorized as active in a specific tissue/group. Finally, (Finucane et al. 2018) looked at tissue-specific regulatory elements, typically the most enriched functional class for common traits. Elements expressed in CNS/brain tissues contained ~30% of the EA h2g, meaning ~70% was localized to other functional regions. While broadly expressed elements were not considered here, other tissues also explained large fractions of EA h2g: ~25% in elements active in the cardiovascular system or in muscle/connective tissues (precisely the problematic scenario where a mechanism may be acting on EA through some component of appearance or discrimination).

It may seem surprising that the functional partitioning of EA is so non-specific, but this is visually clear even at the level of individual genes. To further illustrate this, let's look at the results from a cognitive function GWAS conducted by (Williams et al. 2023) (we'll use cognitive function

because it's expected to be less diffuse than EA, and because they generated a nice looking figure). The study identified a number of associated loci and then investigated the tissue-specific expression of the 90 genes that were nearby. In total, 2/90 genes were exclusively active in the brain, ~2/90 genes were much more active in the brain but still active in other tissues, and the remaining ~85/90 genes were either broadly inactive or broadly active. The vast majority of identified genes were either broadly expressed or not expressed at all.

Gene expression heatmap for 90 genes identified in a cognitive function GWAS.

Each column is a cognitive function GWAS gene and each row is a tissue (from the GTEx consortium). Brain tissues are the rows highlighted in green; red is high expression and blue is low.



The low specificity of functional enrichment is not unique to EA, in fact it is a major and often remarked upon challenge for complex trait analysis in general (Boyle, Li, and Pritchard 2017; Connally et al. 2022; Mostafavi et al. 2023). However, the inability to localize signals to their active systems is particularly important for EA because of the diffuse nature of environmental confounding and the importance of understanding the mechanism for intervention. **Ultimately there are no shortcuts, the mechanism for each of the tens of thousands of EA variants will need to be mapped through the full biological network before we can know whether the variant acts through relevant or irrelevant mechanisms**.

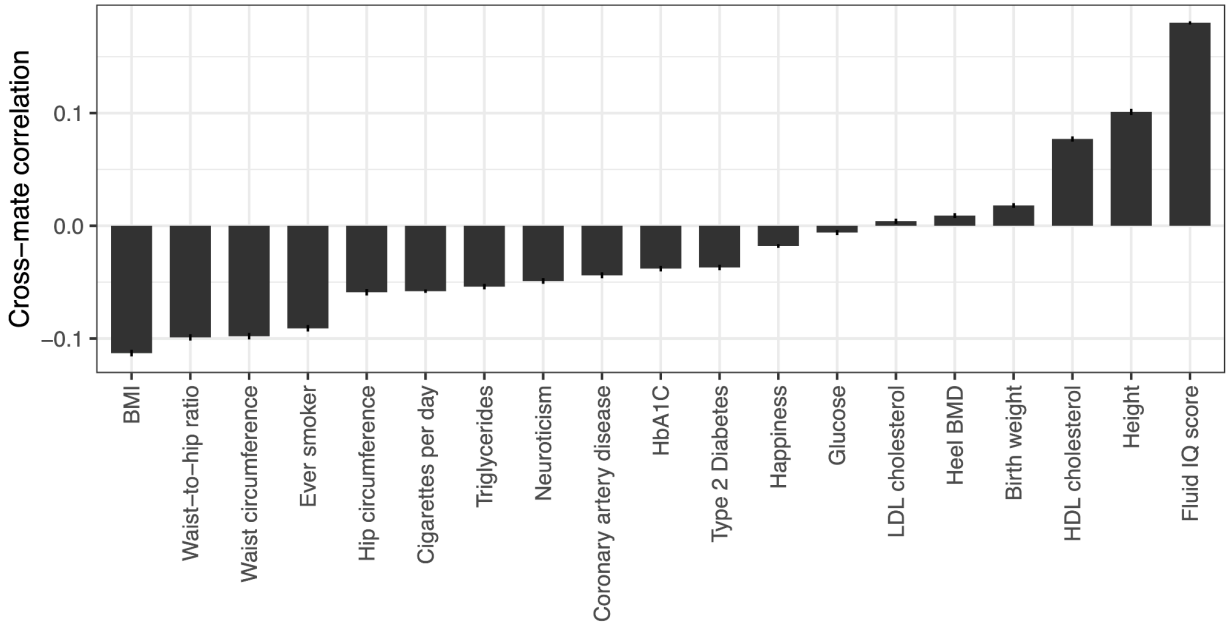
Interpretation in light of cross-trait assortative mating

An important caveat regarding the significant EA h2g enrichment in brain/CNS regions is the challenges in interpretation due to the confounding forces of cross-trait assortative mating (see [**1.2**]). Under cross-trait AM, variants that are causally associated with a spousal trait become

non-causally associated with the primary trait in offspring. For a trait that exhibits high spousal correlation with other heritable traits, this would induce excess population h2g enrichment in non-causal regions. Indeed, EA is just such a trait, with (Border, Athanasiadis, et al. 2022) recently demonstrating widespread and substantial cross-mate correlation with IQ scores, height, and cardiometabolic traits (see figure below). Given the particularly high correlation with IQ scores, it is very likely that the above brain related enrichments are overstated (in addition to enrichments for other functional categories).

Cross-mate phenotypic correlations with EA.

All statistically significant correlations are reported. Data from (Border, Athanasiadis, et al. 2022).



5.10 | Rare variant heritability and gene-level analyses

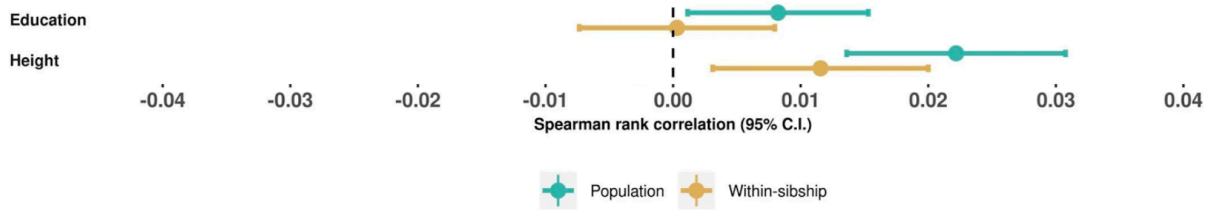
Theory

Traits under weak selection/neutrality are expected to be primarily associated with common variation (see [**4.4**]), thus selection parameters provide a forecast of the expected rare variant contribution. Is EA under weak or strong selection? Precisely quantifying *polygenic* selection remains challenging due to the confounding effects of population stratification (more on this later), which are particularly strong for EA. To mitigate this, (Howe, Nivard, et al. 2022) correlated within-family effect estimates, which are expected to be free of confounding (though see the last paragraph of [**4.2**]), with rare-variant statistics (SDS) that quantify "recent" selection in the past 2,000-3,000 years (Field et al. 2016). **The correlation with EA was squarely at the null, indicating no detectable selection** in this very large sample. Notably, the population-level estimator showed a nominally non-zero effect, further evidence of bias due to population stratification in the conventional GWAS. Height was used as a positive control, as it exhibits a strong North/South European gradient and a plausible relationship to fitness. As expected, height

exhibited significant correlation with the SDS statistics and was the only trait in the analysis that showed evidence of recent selection. This finding of no/weak selection on EA was consistent with prior analyses based on the frequency/heritability relationship using common variants alone (Schoech et al. 2019). Under this relationship <10% of the total trait h2g was expected to be assigned to rare variants which, incidentally, was slightly *weaker* than the average analyzed trait.

Estimates of selection for EA and height.

Correlation with the SDS recent selection score shown for both traits using population (green) and within-family (yellow) statistics; the latter expected to be free of confounding by population structure. Only height showed significant evidence of selection.



Results from >300,000 sequenced exomes

(C.-Y. Chen et al. 2023) conducted the first large-scale rare variant study of EA, as well as two other cognitive phenotypes (verbal/numeric reasoning and reaction time), in ~300,000 European ancestry sequenced exomes. They estimated genome-wide exome burden heritability (see [**2.4**] for methods, [**4.6**] for other results) across a range of variant classes and frequency definitions. **All rare burden h2g estimates were <1%**, with the largest estimate coming from the least restrictive variant threshold (consistent with weak selection where rarer/more pathogenic variants do not explain substantially more heritability). This estimate places a very low ceiling on the *total* contribution of rare coding burdens in individual genes.

Burden heritability regression results for EA from ~300,000 exomes.

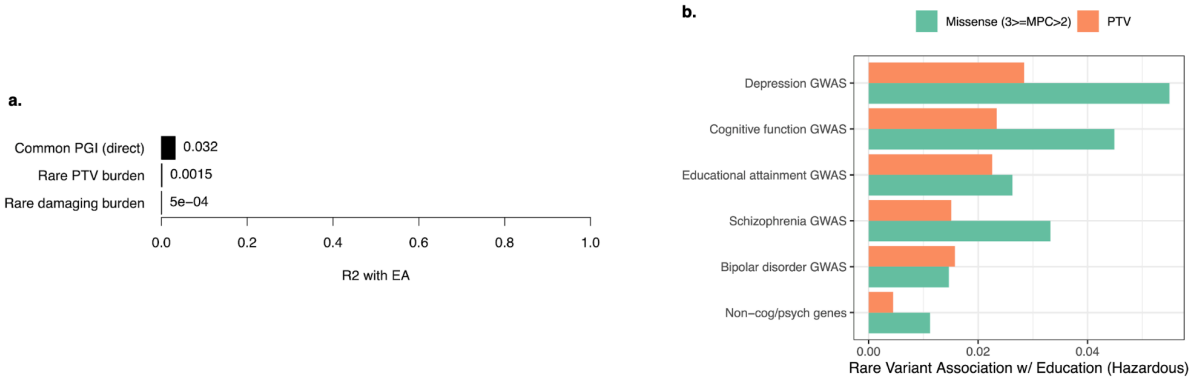
Each row shows a burden h2g estimate for a given variant class. Data from (C.-Y. Chen et al. 2023).

Frequency cut-off	Variant category	Burden heritability	SE
0.0001	PTV	-0.0002	0.00027
0.0001	missense	0.0011	0.00024
0.001	PTV	0.0004	0.00026
0.001	missense	0.0009	0.00025
0.01	PTV	0.0008	0.00024
0.01	missense	0.0025	0.00038

(C.-Y. Chen et al. 2023) subsequently aggregated carrier status of all rare pathogenic variants in constrained genes into a single score, akin to a uni-directional rare variant PGI, and tested it for

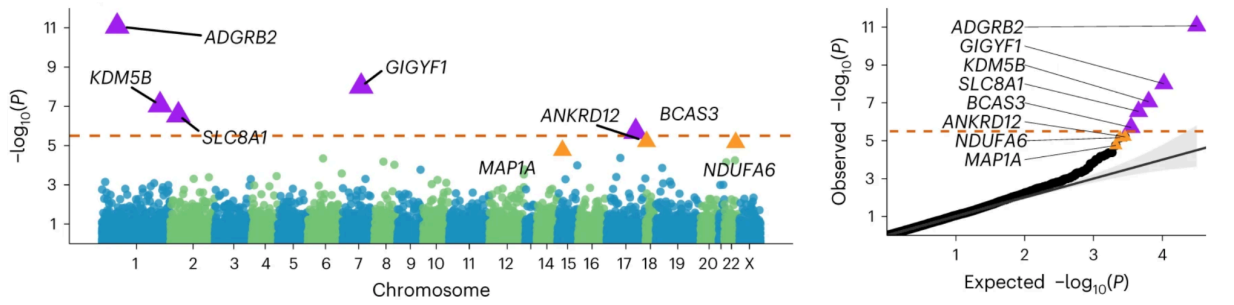
association with EA. The effect of a score built from protein truncating variants was -0.095 (R2=0.0015) and the effect of a score built from damaging missense variants was -0.053 (R2=0.0005). **The genome-wide rare variant burden thus also explained very little of the variance in EA**. Next, the study evaluated whether genes from common GWAS were also enriched for trait-associated rare variant burden – evidence of converging mechanisms between rare and common causal variants. Surprisingly, the strongest enrichment was from genes identified in GWAS of depression, then cognitive function, and then EA. The rare variant architecture of EA may thus be genetically closer to the common architecture of cognitive/psychiatric traits than to EA itself.

Prediction accuracy (R2) of common versus rare polygenic scores.
*(**a**) Predictive accuracy of common within-family EA PGI (Okbay et al. 2022) vs. rare protein truncating variant (PTV) and damaging missense burden from (C.-Y. Chen et al. 2023). (**b**) Enrichment of rare burden in genes near common GWAS associations for a variety of GWAS. Rare PTV enrichment shown in orange, rare damaging missense enrichment shown in green. Data from (C.-Y. Chen et al. 2023).*



Finally, the rare variant burden in each gene was individually tested for association with EA, producing six significant associations after multiple test correction. For context, similar burden analyses of UK Biobank exomes identified 55 genes for standing height, 20-30 for blood cell counts, and 15-20 for fat mass (Backman et al. 2021). Notably, all six associations were deleterious and 4/6 had previously been associated with developmental or psychiatric disorders. **Thus, to the extent that rare variant effects appear to matter for EA, it is through deleterious effects often at established syndromic genes**. Surprisingly, even these large-effect genes were often also associated with a diverse number of non-cognitive phenotypes, including taking pain medication, blood biomarkers, bone/fat density, lung function, cancer, and lipid levels. These widespread effects again highlight the challenge of inferring the precise mechanistic path from genetic associations.

Rare exome-wide association study of EA in ~300,000 individuals identifies five hazardous genes.
Statistical significance (y-axis) versus physical position (x-axis) of each gene tested. Purple triangles indicate associations significant after stringent Bonferroni correction. Figure from (C.-Y. Chen et al. 2023)

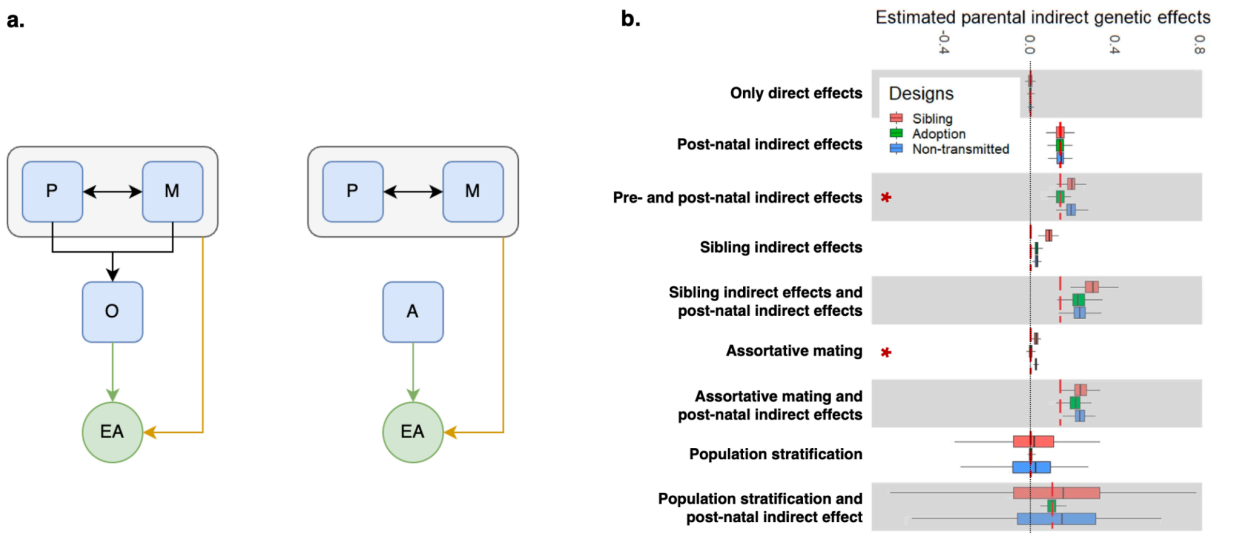


5.11 | A word on adoption studies

The adoption design provides an alternative approach to distinguish direct and indirect genetic effects. In principle, adoption severs the genetic correlation between children and their adoptive parents, leaving only the direct genetic effect of the offspring genotype and the uncorrelated effect of the parental environment. For molecular studies, this means h2g/PGI in adoptees are estimators of the direct genetic effects. Additionally, by comparing estimates in adoptees to population-level estimates, one can infer *indirect* genetic effects under two specific scenarios: (1) if there are indirect effects via cultural transmission but no assortative mating, these will be estimated accurately in the adoption design (the population PGI correlates with indirect + direct, the adoptee PGI only correlates with direct, so the difference is indirect); (2) if there is assortative mating but no indirect effect via cultural transmission, the indirect effect will be accurately estimated at zero (both the population PGI and the adoptee PGIs will be biased upwards by assortative mating and this will cancel out in the difference). **In other words, if an indirect effect is observed in the adoption design, then some amount of cultural transmission must be present**. These properties of the adoption design were demonstrated in simulations by (Demange et al. 2022) and shown in the figure below.

The adoption design and estimates of indirect effects in simulations.

(a) *The adoption design breaks the genetic (but not environmental) relationship between parents and offspring and eliminates correlations due to assortative mating. P: Paternal, M: Maternal, O: Offspring, A: Adopted offspring, EA: Educational Attainment phenotype. Genotypes shown in blue, direct effects in green, indirect/environmental effects in orange. (**b**) Estimates of parental (post-natal) indirect genetic effects under different simulation scenarios. The adoption design is uniquely unbiased (shown with red star) in the presence of prenatal indirect effects or assortative mating. Figure from (Demange et al. 2022).*



In practice, adoption is a highly non-random process, which imposes additional complexities on the data. These complexities have been extensively discussed in the sociology/psychology literature but I will briefly review them here to aid the interpretation of molecular data:

- Adoptive environments are systematically different from the environments in matched non-adoptive families. For example, (McGue et al. 2007) conducted environmental surveys as part of an adoption study in the US and found that the adoptive parent had significantly higher education (63% college grades versus 44% in non-adoptive families and 26% in non-adoptive non-participants), SES, and occupation. Based on the GxE findings above [**5.7**], this improved environment could be expected to decrease the h2g in adoptees (in addition to increasing their mean phenotype).
- At the same time, adoption also often operates through selective placement, whereby adoptive parents choose offspring that come from families more similar to their own (for example, in the level of education). Selective placement induces a correlation between the phenotype in the birth and adoptive parents such that the adopted offspring is no longer raised in a statistically independent environment (Kendler et al. 2015). This correlation is sometimes incorrectly interpreted as "heritability" when comparing adopted offspring to their birth parents.
- As shown in simulations above, adoption designs do not estimate the effects of the prenatal/maternal environment (and corresponding indirect effects). Notably, (McGue et al. 2007) also found 3x higher drug dependence in their matched non-adoptive families, which is likely to influence the prenatal environment and be unaccounted for in the adoptive design.
- Being adopted is itself correlated with genetic variation. (Cheesman, Hunjan, et al. 2020) estimated the common SNP h2g of being adopted at 0.059 (s.e. 0.004) in the UK Biobank, indicative of some small genetic differences between adopted and birth offspring. While this h2g is very small, it is comparable to the weak direct h2g of EA itself, and may thus be a strong relative confounder.
- Genetic variation associated with being adopted is negatively genetically correlated with educational attainment (rg = -0.52 s.e. 0.065), as well as age at first birth, depression, and

positively genetically correlated with obesity – all factors highly associated with SES (Cheesman, Hunjan, et al. 2020). Adopted offspring will thus have systematically different genetic values for certain traits/PGIs.

- To state the obvious, adopted offspring may simply be treated differently by their parents, family, teachers, peers, etc. "evoking" different environments.

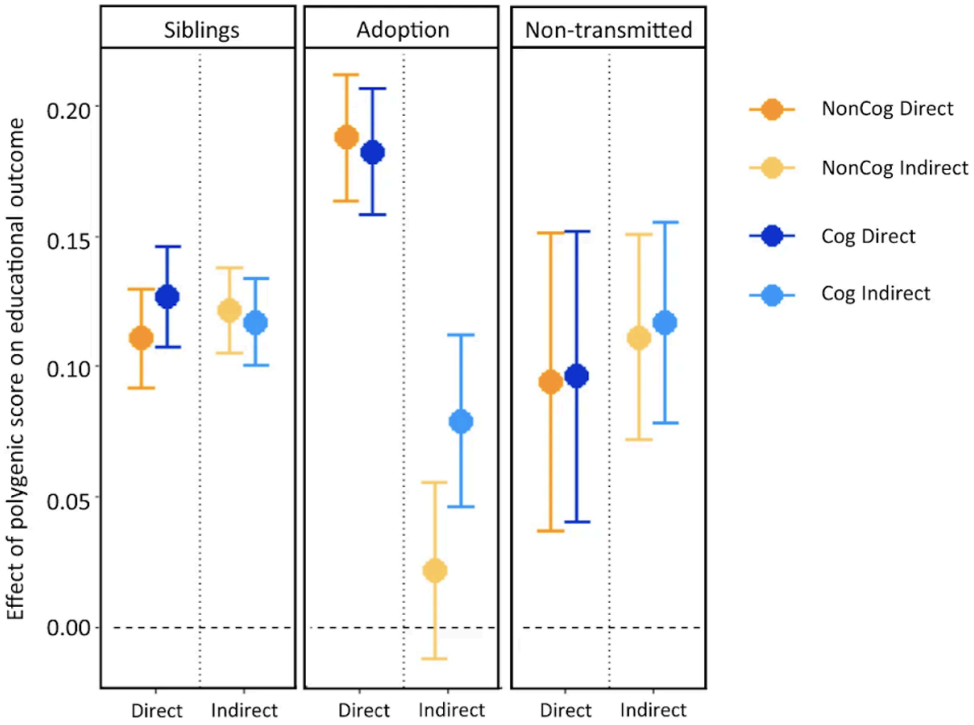
In short, while the adoption design eliminates certain biases, it also introduces new biases: no measurement of prenatal effects, systematically higher EA environments and lower EA variance, systematically lower EA and EA related genetic values, and complex structure due to selective placement.

With that in mind, what insights can we glean from molecular analyses of adoption studies? First, (Cheesman, Hunjan, et al. 2020) compared non-adopted to adopted individuals in the UK Biobank, and found that EA PGI accuracy (R^2) decreased from 7.4% to 3.7%. Because adoption breaks the correlation with parental indirect effects, this provides orthogonal evidence that the population PGI is inflated by indirect effects and that the direct effects are weak (though may, to some extent, also be a consequence of GxE with the adoptive environment; see above).

Second, (Demange et al. 2022) conducted a similar analysis in the UK Biobank but partitioned the EA PGI into its cognitive and non-cognitive components and compared across designs (figure below). The "cognitive" EA PGI showed significant indirect effects (meaning, that the population PGI effect was again higher than the effect in adopted offspring) whereas the non-cognitive PGI did not. This was in contrast to sibling and trio-based designs showing substantial indirect effects for both PGIs. One interpretation of this difference is that non-cognitive indirect effects (which are more strongly genetically correlated with neighborhood deprivation (Demange et al. 2021)) occur prenatally, and are thus not captured in the adoption design. Alternatively, GxE in the adoptive families could be attenuating the indirect non-cognitive effects, or assortative mating in the sibling/trio families could be inflating the indirect non-cognitive effects. **Thus the adoption analysis provides orthogonal evidence for cultural/indirect transmission on cognitive function that cannot be explained by assortative mating alone**.

Direct and indirect PGI estimates from three different family designs.

Analyses employed an EA PGI divided into "cognitive" (blue) and "noncognitive" (yellow) components and tested for association with EA.



Finally, a recent study of adopted offspring with genotyped parents employed an adoption process that was less susceptible to selective placement (J. Beauchamp et al. 2023). Adoptive parent PGIs explained 7.3% of the variance in adopted offspring EA, again confirming the presence of indirect associations. The study additionally employed a variance decomposition analysis to estimate the total variation attributable to genetic and non-genetic components. The variance attributable to total genetic variation was non-significant but with a very wide standard error. The variance attributable to the family environment was statistically significant and ranged from 0.25-0.28, with the rest assigned to other environmental factors. A more complex generalized model was also fit, yielding very similar family environment estimates and larger but only nominally significant estimates of additive genetic variance. **While still highly uncertain, these estimates were strikingly consistent with the cultural transmission model estimates in [5.6].**

Variance decomposition from family-based models in adoptees.

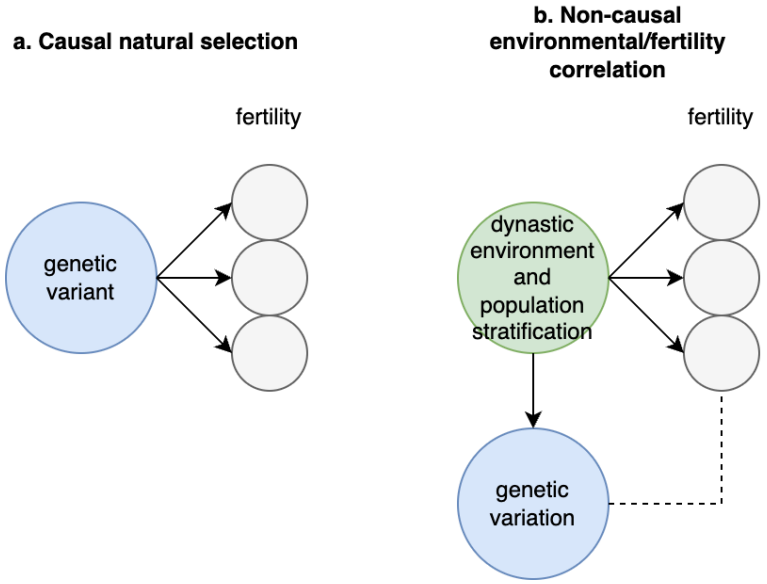
Standard errors shown in parenthesis. Data from (J. Beauchamp et al. 2023).

Trait	Additive Genetic Variance	Family Environment Variance	Remaining Environment Variance
EA	-0.07 (0.30)	0.28 (0.11)	0.79 (0.22)
College	0.07 (0.32)	0.25 (0.10)	0.68 (0.26)

5.13 | A word on “natural selection” using EA PGIs

Several studies have employed EA PGIs to evaluate the association between PGI and number of offspring, which they refer to as "natural selection" (J. P. Beauchamp 2016; Kong et al. 2017; Hugh-Jones and Abdellaoui 2022). Classically, natural selection is defined as genetic variation that *causally* leads to increased/reduced fertility. Selection, together with heritability, then *directly* drives the phenotypic response in subsequent generations, for example via the Breeder's Equation. Classical natural selection is also notoriously slow and, in humans, weak (more on this in later sections) **In these studies, however, the definition is flipped on its head: a PGI that is largely *indirectly* correlated with *environmental* variation is being associated with fertility**. In essence, an environmental correlate (the PGI) is being tested for association with another environmental correlate (number of offspring), and then wrapped in causal language.

Contrasting causal natural selection versus environmental/fertility correlations.
(a) The classical conception of selection where genetic variation increases fertility/fecundity. (b) An alternative non-causal model where dynastic and stratification effects are correlated with fertility and also correlated with genetics, inducing a confounded correlation between the two.



This potential contradiction is, in fact, alluded to in (J. P. Beauchamp 2016), arguing that "*the association between the score of EA and EA is not likely to be driven by the effects of culture, the environment, or population stratification, and is likely to reflect the true causal effects of multiple genetic variants*". We now know that this claim is incorrect and the PGI is heavily confounded by cultural/environmental factors and at least some amount of stratification (arguably this was already apparent in within-family analyses in the cited work of (Okbay et al. 2016)). These studies nevertheless go on to make strong causal claims about ongoing human evolution and the potential effect of genetic variation on inequality and societal structure.

Let's pause and ask: what are we actually trying to estimate? If EA has non-zero h2g and people with lower EA have more kids, then EA-associated genetic variation will also be correlated with the number of offspring. Since we know that EA has non-zero h2g, this effect is expected and does not require genetic analysis, one simply needs to look at birth rates by EA status in the census. Given that the direct common h2g of EA is just 4%, we already know that the magnitude

of any such effect is also likely to be very small. The question that molecular genetics *can* shed light on is: how small and does it deviate from expectation? It is possible that the *direct* effects on EA are weakly associated with fertility or not at all and the apparent associations are entirely explained by the familial environment. Indeed, this was quantified by within-family analysis in (Okbay et al. 2022) and the direct effect of the EA PGI explained just 0.3% of the variance in the number of children born (see [**5.8**]). **The *causal* common variant effect of EA on fertility is thus essentially negligible.** More generally, the direct h2g for "number of children born" was estimated by (Howe, Nivard, et al. 2022) in siblings at 0.03 with a confidence interval spanning zero. **The causal contribution of *all* common variation to fertility (including mechanisms other than EA) is also very low to non-existent.**

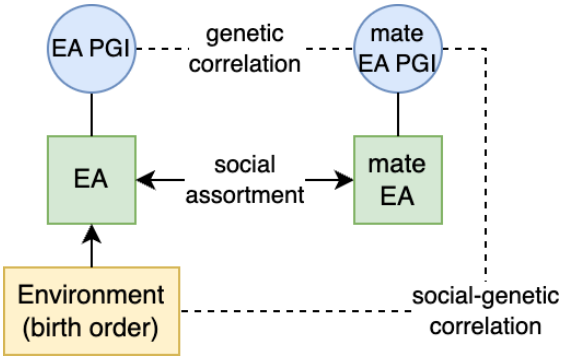
5.14 | A word on latent assortment

A lingering question regarding assortative mating on EA is the possibility of "latent" assortment that is stronger than the observed phenotypic assortment. If partners are pairing up based on more heritable genetic factors that are strongly correlated with EA (e.g. other behavioral traits) or are pairing up based on the latent genetic value (e.g. based on sibling/family matching) then spousal genetic correlations will be higher than expected. In this case, the within-family h2g estimates (e.g. RDR) will be more strongly biased downward and population-based estimates will be more strongly biased upward (see [**3.3**]). Indeed, there is some evidence of latent assortative mating, with (Okbay et al. 2022) estimating a significantly higher than expected PGI correlation in mates, which was only partially attenuated by adjusting for EA itself, cognitive function, and principal components. So there are two potential explanations: either individuals are pairing up based on latent, heritable factors, or residual population stratification (which was documented in the population PGI in (Young et al. 2022)) is inflating the genetic correlation.

Recent work by (Abdellaoui, Borcan, et al. 2022) sought to estimate the extent of genetic assortment by leveraging an environmental shock. If EA can be changed while controlling for genetics and produces a corresponding change in spousal correlation, that is evidence of phenotypic assortment. Additionally, if the genetic correlation between mates is completely explained by EA itself, that is evidence against latent/genetic assortment. The environmental shock (Abdellaoui, Borcan, et al. 2022) exploited was birth order: later born children tend to have fewer resources and slightly lower EA after controlling for family size and year of birth. As later born children are not systematically genetically different from first-borns, this provides an environmental shock that is free of genetic confounding.

Schematic of Socio-Genetic Assortative Mating.

Individuals pair up based on EA (green), which induces correlations in their PGIs (blue) and "socio-genetic" correlations between scores and PGIs.

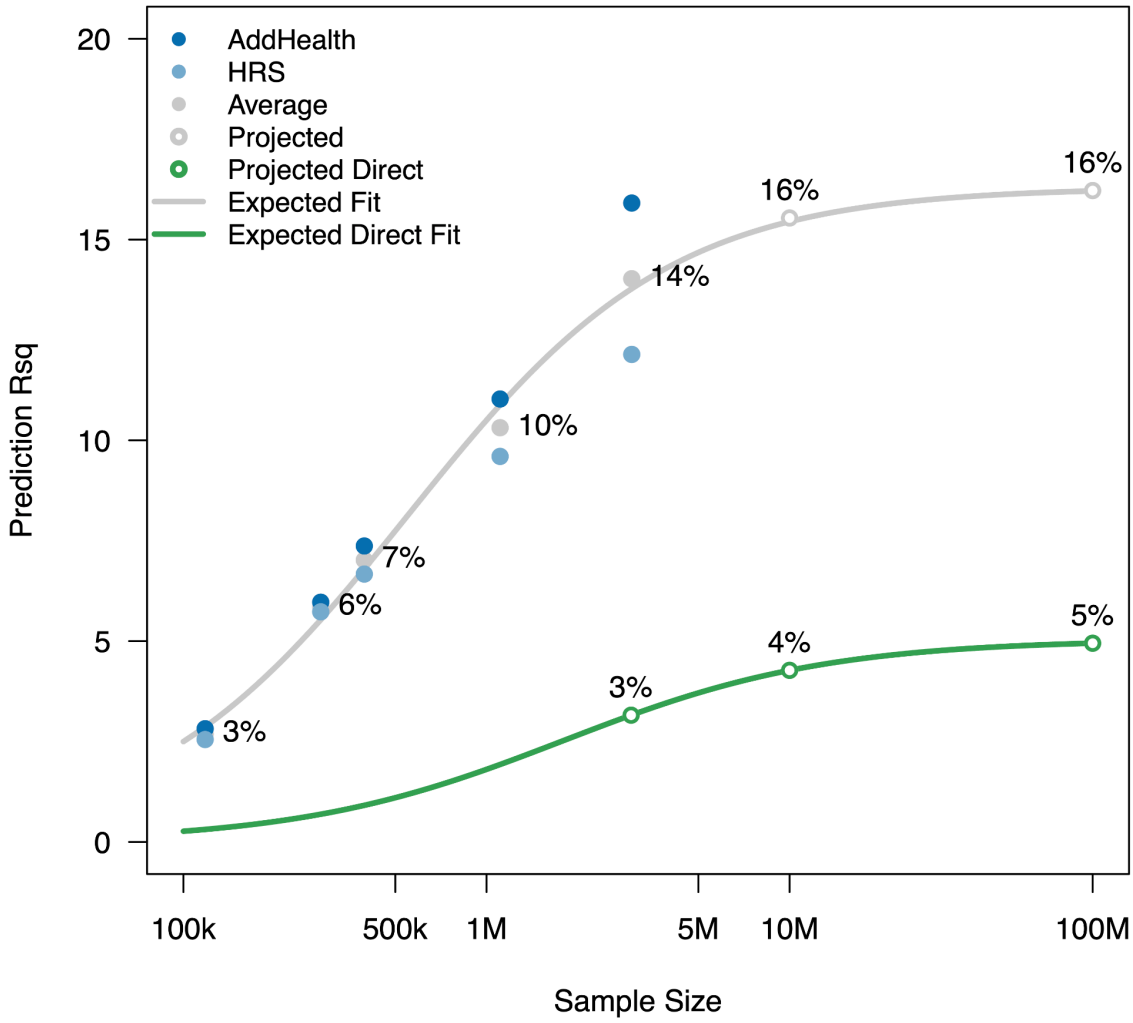


As expected, birth order was (a) correlated with EA, (b) correlated with spousal EA, and, as a direct consequence, (c) correlated with the spousal EA PGI (which the authors call "socio-genetic assortative mating" or SGAM). This demonstrates that purely environmental factors contribute to phenotypic assortment on EA. Furthermore, after conditioning on EA and income variables, the association between spousal PGIs was no longer significant: decreasing from 0.057 (s.e. 0.01) to 0.011 (s.e. 0.01), as was the association between birth order and spousal PGI. **This demonstrates that the genetic correlations between mates can be completely explained by the EA phenotype itself in the UK**. Notably, this was not the case in a separate analysis in a Norwegian cohort, suggesting that the amount of latent assortment can differ by cohort. As these quantities were estimated in population-level analyses, the *causal/direct* effect of the PGI on assortment is unknown, but this study provides evidence of negligible overall latent assortment in the UK.

5.15 | A word on EA PGI accuracy

While h2g is an unbiased estimator of the maximum achievable prediction r2, some of the above analyses involved PGIs trained in a given sample which may have incomplete prediction accuracy. Since the relationship between h2g, r2, and sample size is well established (see [2.1]), one can use labeled data to fit these parameters and then project how the PGI will behave with additional training data. (Okbay et al. 2022) evaluated PGI r2 as a function of down-sampled training size in two target cohorts (the HRS and AddHealth). The best fitting parameters from these analyses are an h2g of 0.16 and an effective number of variants of 90,000 (estimated by minimizing the residual sum of squares to the average PGI r2 between HRS and AddHealth). This is in line with the mean h2g of 0.15 observed above and ~60,000 effective variants observed in prior studies (Yang, Weedon, et al. 2011). With these parameters, we can extrapolate from the current prediction accuracy to that of larger studies. In (Okbay et al. 2022) the mean prediction r2 was 0.14 (with ~3.5 million training samples), which would be expected to reach an asymptote of 0.16 with ~10 million training samples. Thus the latest PGI achieves 88% of the maximum possible accuracy and is unlikely to be superseded for some time. Likewise, if we assume that the direct h2g is 0.05, then direct/within-family r2 with 3.5 million training samples is expected to be ~3% (which is very close to the within-family prediction actually observed in (Okbay et al. 2022)), reaching 4% with 10 million individuals. Emerging methods may also enable "correcting" PGI estimates for this small amount of outstanding uncertainty (van Kippersluis et al. 2023).

Extrapolation of EA PGI prediction accuracy versus GWAS sample size.
Extrapolated fit for the population PGI shown in gray, and for a "direct effect" PGI shown in green. Previously reported estimates shown with colored dots, average of previously reported estimates shown with gray dots. Unfilled circles represent extrapolations for specific sample sizes.



5.16 | A few words on scientific value and responsibility

Preface

[🔥While the previous sections aimed to provide a review and interpretation of the genetic findings, the question inevitably comes up: what is the value of this research? Should it even be conducted at all? The field does not shy away from this debate: this concern was raised (and left unanswered) in the coverage of the very first large EA GWAS (Flint and Munafò 2013) and continues to be raised with each subsequent study (Meyer et al. 2023; Burt 2022). Of course, the research continues actively and in my opinion the discussion has fallen into a set of tired patterns (often mirroring the broader, and even more tired "cancel culture" fights). Here, I will try to put the

above results into a broader context and then present a more actionable perspective. It goes without saying that this section is opinionated.]

Before diving in, it is worth noting that much of the early history of behavioral and psychiatric genetics research used genetically motivated approaches to **undo** decades or centuries of harmful misconceptions about the brain. Genetically informed studies demonstrated that child autism was not caused by cold/aloof parents ("refrigerator mothers", see: (Kanner 1943)) but by a genetic predisposition; that addiction and compulsion were not simply indicators of poor self control or lack of will; that psychiatric conditions were not demonic possession or inhuman "madness"; and so on (though, it should be noted, that genetically informed research also contributed to calls for forced sterilization of the mentally ill). In many cases, evidence was triangulated across many different study designs and cohorts to synthesize a deeper understanding of a mysterious phenotype (as an example, see the extensive, decades-long investigation into the genetics of stuttering (Yairi, Ambrose, and Cox 1996)). **These are all examples of how causal rather than correlative reasoning, enabled by genetic analyses, led to both an improved understanding of the world around us and also less suffering**. We should also keep in mind that behavioral geneticists have skin in the game too. They get harassed by angry readers who misinterpret GWAS to imply genetic determinism even when no such determinism is claimed. They are called to task for, often, minor stylistic choices in their work in ways that other fields do not. And they are also often more responsive to these concerns than other fields: writing a detailed **FAQ** and Supplementary Material for each major paper, providing extensive discussion of the history of eugenics and Nazism in **talks** and in **perspective** reports, etc. In fact, the few times you hear *any geneticists* acknowledge these sordid origins of the field in a scientific presentation, most likely it's a talk by a *behavioral geneticist*.

Premise

Coming back to the premise. Distinguishing correlations from causes is a fundamental goal of science. Anyone can notice co-occurrences, but the scientific process empowers us to gain a mechanistic understanding of their relationship or know that one is not identifiable. As Richard Lewontin put it: "*The analysis of causes in human genetics is meant to provide us with the basic knowledge we require for correct schemes of environmental modification and intervention*" (R. C. Lewontin 2006). Understanding causes helps us operate more accurately in the world. Genetics can be particularly powerful as a causal inference tool. But genetics can also be *dangerous* if it is smuggling in correlations under the guise of causality. **Thus, the key question in judging the value of this research is whether it has provided us with basic knowledge of causes.**

So ... what did we learn?

Let us review the **basic knowledge of causes** gained from the past decade of research into the genetics of educational attainment.

The direct effect of genetics on EA is extremely small, perhaps the smallest of any well-defined trait rigorously evaluated to date. The population level estimate is heavily confounded by cultural factors and stratification, to the extent that 50-75% of the predictive genetic variation is not causal

when properly evaluated within families. Depending on the study, these cultural factors are either largely or entirely explained by educational attainment or socioeconomic status in the parents or relatives. **In other words, we've learned that people who advance academically then create environments for their kids to do the same, and this relationship is almost entirely non-genetic.**

Because the population PGI captures a combination of genetics, passive environment, and stratification many studies have racked up provocative (but largely uninterpretable) correlations with environments. Assortative mating occurs on educational attainment and so a tiny bit of genetic variation will be correlated among partners. Environmental factors (such as birth order) are correlated with educational attainment, and so a tiny bit of genetic variation will be correlated with those environmental factors in spouses. Birth rates differ by education status and so a tiny bit of genetic variation will be correlated with birth rates. Migration patterns differ by education status and so a tiny bit of genetic variation will be correlated with migration patterns. These correlations mirror their non-genetic counterparts and so are not surprising. Estimates of *causal* effect sizes – the innovation that a genetically-informed study could bring – require careful study designs and so are hardly ever bothered with.

For rare coding variants, the heritability is likewise tiny, explaining far less than 1% of the trait even before restricting to directly causal estimates. The few genes that are implicated seem facially plausible, often identifying previously known developmental delay genes in the general population. While there is some convergence of rare and common variation, the most enriched common phenotypes are non-EA traits – depression and cognitive function – further underscoring the unclear nature of common variant mechanisms on EA. Rare variant analysis thus provides a convenient means of identifying large influences on developmental delay at the individual level, but has little impact on the population-level variance of EA.

What's left? The rare non-coding genome has yet to be interrogated. For height and BMI, this explained <25% of the total h2, mostly concentrated in coding regions (see [**4.7**]). Assuming the same proportion for direct EA h2g, we could expect to explain an additional ~1% of EA variance with rare non-coding variation. It is thus likely that rare non-coding variants will contribute a negligible amount to overall trait variance and, as with coding variation, primarily through developmental delay genes.

Can we use this knowledge *causally*?

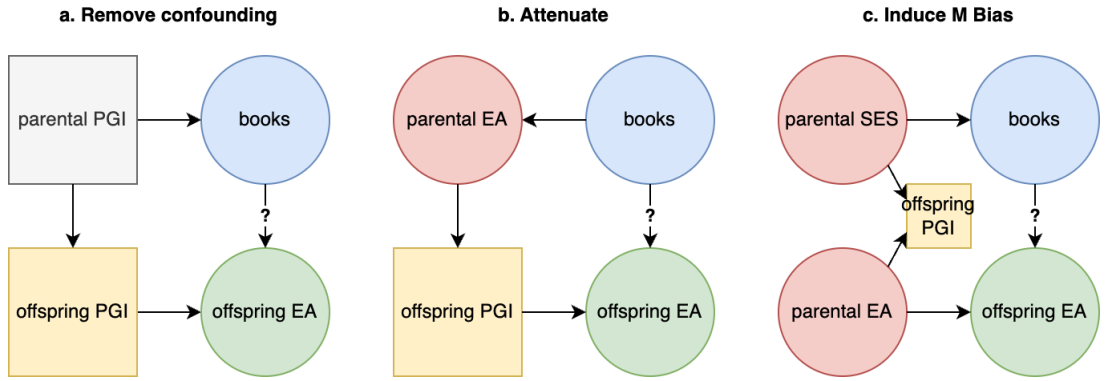
As summarized in (Lee et al. 2018), the EA GWAS and PGI results had several intended applications including: (1) causal instruments to study the relationship between educational attainment, other traits, and environments; (2) controls for genetic confounding in population-level studies; (3) an atlas of causal biological mechanisms. Environmental confounding presents a problem for all three cases:

(1) The population PGI is **not usable as a causal genetic instrument** because it captures the passive influences of non-genetic factors. *In the population*, the PGI is dominated by correlations with the familial environment and population stratification on top of a small amount of direct genetic influence. **Any association with the PGI is simply telling us that**

***some* factor (genetic or environmental) related to education is *somehow* correlated with the outcome, a finding that is true a priori for nearly any outcome**. The ample evidence of population stratification in the PGI, which remains to be fully quantified, may preclude even this trivial interpretation. Depending on the balance of indirect associations and stratification, a PGI correlation may actually capture **no** directly causal variation, particularly under environmental shifts (see cross-generation example in [**3.5**]). *Within families*, the problem is reversed: a PGI constructed from a population GWAS underestimates the direct effect due to incomplete correlation between direct and indirect effects in the population it was trained in (see [**5.3**]). An accurate causal effect-size – the key component of a genetic instrument – is thus undefined either within or between families.

(2) The population PGI is **not usable as a control for genetic confounding** and can induce both loss of power and upwards bias. When testing for an association between different environmental factors we often want to control for confounding from unmodeled genetic variation. The classic example is the availability of books in the home either being a causal influence on offspring EA (through increased reading) or confounded by correlation with parental (and thus offspring) genetics (Hart, Little, and van Bergen 2021). We may attempt to disentangle this relationship by including an offspring PGI as a covariate. However, the offspring PGI captures both a small amount of offspring genetic effects and a large amount of parental environmental variance and is thus **susceptible to many of the classical causal inference confounds**. If books in the home improve parental EA (and offspring EA), which in turn affects the offspring PGI through assortative mating, then adjusting for the offspring PGI will attenuate the true causal effect of books in the home. Even more complex biases arise in the presence of multiple environmental confounders (see M-Bias in the figure below) or under study ascertainment, where conditioning on the wrong covariates can significantly reduce power (Mefford and Witte 2012).

Consequences of adjusting for a PGI under different scenarios.
*(**a**) What we hope to accomplish by including a PGI covariate to remove confounding. What we may actually be doing is attenuating the true total effect (**b**) or inducing bias (**c**) when parental environments (red) influence the offspring PGI (yellow) through assortative mating.*



(3) In addition to being confounded in the overall magnitude, **the individual effects, loci, and genes from EA GWAS are also significantly confounded** relative to the direct effects, as evidenced by the low genetic correlation between population and direct effects on EA. Cross-trait assortative mating induces widespread associations at variants that are not causal for EA either directly or "indirectly". Indeed, these variants could be causally associated with height, BMI, smoking or other factors that appear correlated in spousal pairs. **This confounding precludes any clear biological insights from individual variants or loci**. As a "backdoor" into the genetic mechanism of intelligence, these population-level associations are uninterpretable and susceptible to confounding from non-cognitive factors in potentially dangerous ways.

In short, for a causal interpretation, all of the effects need to be re-estimated in family-based GWAS. Basing the family-based analysis on the population analysis can induce bias due to population stratification (Zaidi and Mathieson 2020), so the population level estimates cannot be used at all.

Can we use this knowledge *non-causally*?

If we set aside the pursuit of causes, the picture looks a bit brighter:

- **In randomized trials adjusting for the PGI can improve statistical power** to identify a treatment effect by accounting for a blob of random genetic and environmental variation. In this case, randomization guarantees that there is no confounding and a causal understanding of the covariate is no longer needed. The FDA now recommends adjusting for baseline prognostic covariates in clinical trials (Center for Drug Evaluation and Research 2023), so this kind of application is quite practical. PGI adjustment would be expected to account for ~5% of the variance in EA after including basic covariates like household education and income and may thus modestly reduce the cost of running an RCT (Meyer et al. 2023).

- In some cases it is not necessary to distinguish between genetic and environmental causes, and *any* correlation of education is useful **as a hypothesis generating tool**. This is particularly the case in data where other measures of educational attainment are unavailable. For example, (Antaki et al. 2022) investigated the association between an EA PGI and symptom severity and case status for Autism Spectrum Disorder (ASD). They found surprising compensatory patterns of association that may point to a new ASD subtype. While these associations cannot be interpreted causally (and are almost certainly not strictly causal), they can point to subsequent studies or, eventually, randomized trials that do attempt to disentangle causal influences related to EA.

- The EA PGI *may* be useful **if we simply want to predict at any cost**, but there are still a lot of unknowns. Because of the extensive environmental confounding, the EA PGI is likely to be more sensitive to environment, geography, and time than typical genetic scores. For example, (Kong et al. 2018) observed that the PGI was significantly less accurate in parents than in the offspring, presumably due to temporally shifting environments. To

what extent the PGI can be a useful *prospective* predictive tool remains to be quantified with more longitudinal data, though we know the common population h2g is the upper bound.

- The approach of using EA as a **convenient proxy phenotype** has been reasonably effective in studying large-effect rare variants. For example, the subset of the UK Biobank that provided information on EA is substantially larger than that which completed cognitive function surveys, thus the former may provide more statistical power to discover associations at the cost of environmental confounding. Unlike for PGIs or common variants, rare variant interpretation and experimental follow up is also more straightforward. However, the extent to which EA continues to be a useful proxy for developmental delay (DD) phenotypes remains to be seen, especially as studies of DD itself increase in size.

- Finally, EA studies have pinpointed fundamental flaws in genetic analyses and, often, provided the first methods to estimate them: biases due to cultural transmission and assortative mating, subtle population stratification (and how to estimate it), cross-trait assortment, and selection/participation biases are all stronger or strongest on EA. It is difficult to motivate and fund the development of methods for problems that don't actually show up in the data, and so EA has often served as an impetus to better understand confounding. One does wonder though, if the same knowledge could have been achieved with an environmentally confounded but much less controversial trait like height.

Where are we and how did we get here?

The leap of faith for GWAS was the assumption that environmental confounding could be controlled by restricting to genetically unrelated individuals with any remaining population stratification controlled by adjusting for genetic ancestry components, thus enabling the aggregation of massive cohorts. The first EA GWAS study was largely framed around this sample-size / convenience trade-off: "*One commonly proposed solution is to gather better measures of the phenotypes in more environmentally homogenous samples. Our findings demonstrate the feasibility of a complementary approach: identify a phenotype that, although more distal from genetic influences, is available in a much larger sample*" (Rietveld et al. 2013). **For the majority of non-behavioral traits, this approach has been surprisingly successful (see [4.2]), but for Educational Attainment it was a spectacular failure in ways that seem obvious in hindsight**: it is a phenotype that is heavily influenced by parental environment, geography, and assortative mating – the perfect circumstances for environment to leak into genetics. **A field that is highly critical of genetic confounding in observational studies was blindsided by environmental confounding in genetic studies**. Moreover, a major component of environmental confounding could have been addressed by simply adjusting for parental educational status.

What happened next? In the five years since RDR was used to demonstrate major confounding from indirect effects (Young et al. 2018), no larger RDR analyses have been conducted, no attempt to replicate the findings in other cohorts, and no effort to quantify the precise mechanisms of the confounding. Confounded population PGIs continue to be actively employed

to make causal claims, some going so far as to argue that a causal analysis is unnecessary because genetics has a "*unique causal status*" (Robert Plomin and von Stumm 2022). Sometimes a caveat is added that indirect effects may include "*genetic nurture or assortative mating or cultural transmission or stratification"*, like the chef telling you the meal you just ate may have been "*a juicy steak or a slice of stale bread or a wet sock*". A recent consensus report (Meyer et al. 2023) dedicated an entire section and multiple figures itemizing the heritability estimates for EA, leading with an environmentally confounded twin estimate, while making no effort to actually explain these sources of confounding ("*to avoid additional complexity*"). The report also hastened to add that the predictive accuracy of the direct effect PGI is likely to increase without ever mentioning robust estimates of very low direct h2g from sibling GWAS (even though such speculative claims are criticized later in the same report). The true impact of many major biases still remains unknown: study participation, cross-trait assortative mating, recent population structure, etc. After the first EA GWAS in 2013, (Flint and Munafò 2013) noted "*It seems that a genetic association has been observed for "something," but exactly what will require considerably more work*". **A decade and several million participants later, we still don't have an answer**.

It may seem harsh to declare any scientific project that generated many manuscripts a failure but EA studies have, over time, come to acknowledge this fact as well. Here's a brief timeline, moving from denial, to bargaining, to acceptance:

Study	**Discussion Point**
(Okbay et al. 2016)	"these results indicate that the score captures true polygenic signal but **do not allow us to draw firm conclusions about the extent to which the score is biased due to population stratification**"
(J. P. Beauchamp 2016)	[*included as an example of the contemporaneous interpretation of EA PGIs*]: "As shown in Okbay et al. [2016], **the association between the score of EA and EA is not likely to be driven by the effects of culture, the environment, or population stratification, and is likely to reflect the true causal effects of multiple genetic variants**. … Thus, although it is not possible to rule out with certainty that my results are (at least partly) confounded by stratification, stratification is unlikely to be an important concern."
(Lee et al. 2018)	"our within-family analyses suggest that **GWAS estimates may overstate the causal effect sizes**: if EA-increasing genotypes are associated with parental EA-increasing genotypes, which are in turn associated with rearing environments that promote EA, then failure to control for rearing environment will bias GWAS estimates. **If this hypothesis is correct, some of the predictive power of the polygenic score reflects environmental amplification of the genetic effects**. Without controls for this bias, it is therefore inappropriate to interpret the polygenic score for EA as a measure of genetic endowment."
(Okbay et al. 2022)	"The population effect captures the sum of the direct effect, indirect effects from relatives (e.g., genetic influences on parents' education, socioeconomic status and behavior), **other gene–environment correlation (i.e., correlation between genotypes and environmental exposure, with population stratification being one possible cause)** and a contribution from the genetic component of the phenotype that would be uncorrelated with the PGI under random mating but becomes correlated with the PGI due to the LD between causal alleles induced by assortative mating"
SSGAC FAQ for (Okbay et al. 2022)	"**Our finding implies that a substantial part of the predictive power of the polygenic index is due to some mix of assortative mating and gene-environment correlation**. For this and other reasons, we believe it is misleading to use phrases such as "innate ability" or "genetic endowments" to describe what is measured by polygenic indexes based on our GWAS estimates. These phrases incorrectly imply that the polygenic index is entirely capturing direct effects, and they further ignore the potentially important role that environmental factors play in mediating direct effects."

(Young et al. 2022)	"We examined the degree to which GWAS estimates reflect direct effects by estimating the genome-wide correlation between direct and population effects, **finding that population effects and direct effects are not highly correlated (<0.9) for EA and cognitive ability**. **We found evidence that this is in part due to recent structure in the population** that is captured by PCs of the IBD relatedness matrix, but not by PCs computed from common variants. Our simulation results suggest that a combination of vertical transmission and AM may also contribute to the low correlation between direct and population effects."
(Meyer et al. 2023)	"The educational attainment PGI that can account for the highest percent of the total variance (or the PGI with the highest R2) so far has in fact accounted for approximately 15 percent of the total variation among individuals in education attainment, with only about a third of that, or 5 percentage points, associated with causal effects. (These are the effects that can be detected within sibling pairs and therefore are plausibly causal.) **The remaining approximately 10 percentage points are due to an unspecified mix of environmental confounds**, including population stratification, various types of gene-environment correlation (including "genetic nurture"), and assortative mating."

What do the critics get wrong?

Because this debate has been going on for some time, it's worth pointing out areas where criticism of EA studies has veered into the unhelpful or outright erroneous:

- **Attempting to partition "valid" versus "invalid" phenotypes and populations**. It is tempting to isolate EA (and other, typically behavioral, phenotypes) as being an *a priori* invalid/sensitive/stigmatized trait that should not be studied. Such categorization into levels of concern has even recently been attempted by the behavioral genetics community itself (Meyer et al. 2023). Such efforts run into immediate challenges of taxonomy: is schizophrenia a sensitive trait that shouldn't be studied (is obesity)? And of practicality: is it okay to study the genetics of EA to refute established stigma/stereotypes but not to support them (and, if so, how does one know before the study has been initiated)? Double standards are also inevitable. While it is generally appreciated that reporting genetic differences by race is "sensitive", the same sensitivities are, for some reason, not applied to analyses of group differences by geography, income, or profession. So, for example, a study reporting lower EA PGIs in coal mining towns is a cover article in one of the most prestigious journals in the field (Abdellaoui et al. 2019), whereas the same study stratified on race would have received special scrutiny at the same journal ("Why Nature Is Updating Its Advice to Authors on Reporting Race or Ethnicity" 2023); in this case special scrutiny for *both* studies would have been appropriate, but the double standard is clearly already in place. What happens when you have vague and arbitrary standards? They get ignored.

- **Claims that EA is irrelevant to the study of public health**. The *environmental* influence of EA on health outcomes can be substantial, and understanding how these factors get entangled with genetics is extremely important. Conditioning on measured EA in a genetic analysis of some other trait, for example, could induce erroneous associations between genetic variants correlated with EA via collider bias. Understanding these confounds is critical to properly conducting and making sense of studies of other traits in heterogeneous environments (i.e. all studies). This, of course, does not imply that *any* study of EA is a public health study, some topics are obviously just sociological questions

of general interest (more on this later). Second, EA does show (very weak) direct effects on other traits observed in within-family analyses, and with further study these may point to useful health policy interventions even if they do not explain meaningful variance in the trait (recall: heritability is not related to malleability). In principle, rigorous genetic analyses could short-list the most confident EA-trait relationship, which could then be promoted into targeted randomized trials to actually estimate a causal effect. Likewise, rare genes associated with EA may serve as targets for further research into identifying and alleviating severe developmental delays.

- **Claims EA (or other behavioral traits) have no genetic contribution at all**. Qualitatively, even in the complete absence of EA GWAS, genetic variation (particularly rare coding variants) is known to be associated with developmental delays and this will in turn lead to challenges with educational attainment. Quantitatively, several analyses have shown statistically significant within-family genetic effects on EA. While a general interpretation of within-family/direct effects has challenges, there is little doubt that these effects are *causal* in some form or context. Claims that genetic variation contributes *nothing* to the EA phenotype is not supported by the data nor basic intuition. This extends to related spurious claims that EA GWAS findings are simply overfitting, do not replicate, or *solely* identify stratification. These arguments are so readily refuted that they do damage to other valid criticism.

Why it matters

There are important reasons to be talking about this work *right now*. The published studies are sufficiently large, and done in multiple ways and across multiple cohorts, that we can reason with accuracy about the sources of confounding. The primary GWAS efforts are essentially complete and the natural next step will be to extend these studies to other populations, where both the challenges of environmental confounding and the potential harm due to public misinterpretation are heightened. These issues extend well beyond EA:

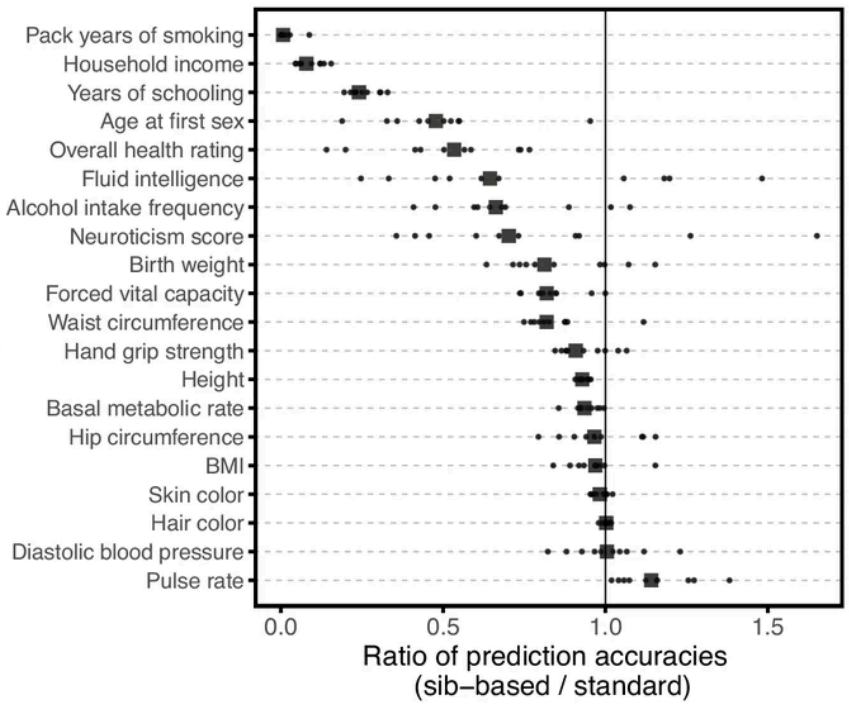
- **Eroding public trust**: As cliche as it may sound, when people participate in genomic studies they are donating biological data with the explicit trust that the data will be used responsibly. The UK Biobank, for example, was established as a resource to “improve the prevention, diagnosis and treatment of illness, and the promotion of health throughout society”. EA research is certainly a component of health understanding and promotion (see above) but it also easily pushes into the realm of broad sociology: studies claiming that second-born children tend to marry a spouse with “bad genes”, that certain geographic regions or professions have lower EA , or that individuals with lower EA genetics have more children and increase social inequality, etc. Regardless of what you think of the value of these sociological questions, the underlying analyses have moved beyond the remit of a public health biobank. They erode the public’s trust that their data and funding is being used as promised. **Over time, this makes it more difficult to recruit underrepresented populations and it risks drawing general public skepticism of *all* areas of genetic research.**

- **Driving health-oriented cohorts to clamp down on secondary use**: Funding agencies and consortia have begun responding to these boundary-pushing analyses by simply defining sociological phenotypes to be off limits for genetic analyses. Industry collaborators, who hold much more genetic data than academic institutions, have followed suit and started withdrawing from collaborations. Imposing hard limits on entire classes of phenotypes like this *also* does damage to the public health effort (rather than, say, requiring clear definitions and the use of rigorous methods). Worse, the response from behavioral geneticists has mostly been to **petulantly complain** that these studies should open back up, or threaten to **find other cohorts** to continue doing the same research, without any self-reflection for how to actually address the underlying concerns. This mutual escalation is a recipe for more restrictions and fewer open cohorts.

- **Vague and purposeless science**: As a general scientific principle, it is important to have clearly defined parameters and estimators. Muddled parameter definitions make it difficult to evaluate the performance of new methods against old ones. The inability to rigorously evaluate methods, in turn, leads to a lack of consensus on how to properly conduct analyses and either a deluge of shoddy analytical work and a simultaneous exit of good researchers. Muddled estimators make it difficult to communicate to the public what it is we are doing and why it matters, and can encourage gross misconceptions that are difficult to undo. This is how fields become insular and, eventually, irrelevant.

- **EA is only the beginning**: While the focus on this section has been on EA, the most well studied behavioral trait, it is just one of many environmentally confounded measurements that are being incorporated into genetic analyses. (Mostafavi et al. 2020) observed large differences in within-family versus between-family prediction for *many* measurements in the UK Biobank, including controversial and culturally loaded phenotypes like income, sexual behavior, intelligence, neuroticism, and smoking/drinking. Notably, smoking/drinking phenotypes may be even more confounded than EA and are of undeniable relevance to public health. The challenges with environmental confounding identified in EA studies are going to keep reappearing in studies of more conventional phenotypes under cultural transmission.

Traits with substantial difference between within-sib and population-based prediction accuracy.
Within-sib prediction accuracy is proportional to the direct heritability and "standard"/population accuracy is proportional to the population heritability. Training cohort size was specified to match statistical power for the two study designs. Figure from (Mostafavi et al. 2020).



What to do about it

Future studies of culturally complex phenotypes can make a number of design decisions to better focus on the analysis of causes:

- **Instead of trying to define sensitive phenotypes and groups, define the causal parameters**. For reasons outlined above, deriving guidelines for which traits are/aren't sensitive or stigmatizing has not worked and is not going to work. Instead, the field should focus on defining and estimating robust causal parameters. Quantifying (1) the difference between direct and population-scale h2g, (2) the correlation between direct genetic effects and indirect associations, and (3) the influence of recent population stratification provides a data-driven rubric for identifying *environmentally confounded* traits. **In this respect, EA is *sensitive* not because a committee put it into a special bucket but because assortative mating, cultural transmission, geographic structure are major confounds *observable in the data***. Studies that use genetic variation but do not control for cultural transmission (or cannot demonstrate that it is absent) should be clear that they are estimating **an unknown component of environmental confounding** – these are no longer genetic analyses and any interpretation should be treated with great skepticism. Novel correlations that emerge from these studies should be presented as hypothesis generation, not discovery.

- **Actually estimate and interpret the causal parameters**. Accurate estimates of direct h2g are woefully lacking for the majority of behavioral phenotypes, and thus the basic work of estimating these parameters needs to be done. **At present, the majority of behavioral phenotypes are unknowably environmentally confounded**. Methods like RDR can infer the relevant causal parameters from just tens of thousands of genotyped families or

siblings and should be routinely applied. As WGS data becomes available, the RDR approach can also be extended to rare variant burden. For traits where the genetic correlation between direct and indirect effects is less than 1.0 (such as EA), confounding due to population stratification needs to be rigorously ruled out. This could be investigated using precise estimates of birth place and environment or using genetic ancestry inferred from rare variants. Finally, for confounded traits, the *specific* contributions of cultural transmission versus assortative mating need to be delineated either analytically or through simulations. It is not sufficient to simply enumerate the potential confounders in the Discussion section and leave it up to the reader to interpret their contribution, as is the current trend. A parameter that is reported as some combination of environmental correlation, assortative mating, and population structure is meaningless.

- **Get serious about environmental confounding**. For population GWAS of culturally transmitted phenotypes where within-family data is unavailable, it should be standard protocol to adjust for parental environmental factors, just as it is standard protocol for GWAS to adjust for genetic ancestry principal components. Indeed, such a "Familial Control Design" (Hart, Little, and van Bergen 2021) has been advocated to partially address genetic confounding in studies of exposures, and should likewise be employed to evaluate environmental confounding in studies of genetics. More generally, environmental measurements have been very poorly collected (e.g. using family size and education as stand-ins for socioeconomic status) and a renewed focus on collecting high-quality environmental data is also needed.

- **Environmental correlations alone are not special**. If the population PGI for a trait is environmentally confounded, then correlations between that PGI and other environmental factors (income, migration, family size, etc) are trivially expected. Using confounded genetic variation to correlate two environmental factors does not make the resulting correlation "genetic" in any meaningful way (and, in fact, the correlation could be explained entirely by indirect factors or by cultural structure in prior generations). In cases where an underlying environmental correlation was already known (e.g. education and family size), the study investigators and reviewers should ask themselves whether the study is really contributing anything novel at all by bringing non-causal genetics into the mix.

- **Address the many outstanding estimation challenges**. As detailed in [**3.6**], a variety of estimation challenges still remain for culturally structured traits, particularly related to cohort ascertainment/selection and latent/cross-trait assortative mating. The influence of these confounders remain largely unknown and make many results impossible to interpret.

- **Stop pretending sociology is public health**. For studies that venture outside obvious and direct public health questions, the connection to health needs to be made clearly and credibly in the manuscript or the patient population needs to be consented for non-health research. A trait simply being *correlated* with health outcomes is not sufficient justification to study sociological aspects of that trait under the auspices of public health research.

The direct public health relevance should be clearly indicated so that other investigators can explain to concerned participants why the study was conducted.

- **Lead with relevant parameters instead of irrelevant ones**. It is common to start GWAS/PGI papers with a reference to large twin study estimates even though these estimates are completely irrelevant. Twin models theoretically capture the contribution of *all* genetic variation rather than the molecular variation being tested in the study, and they are practically known to be inflated by environmental confounding. Moreover, relevant metrics – typically common or rare h2g – can be estimated from the data itself and have often already been derived in prior studies. Thus the relevant molecular parameters should be reported, rather than impressive-sounding but irrelevant and confounded parameters from family studies. For environmentally confounded phenotypes, it is also typical to start with impressive population level h2g (or PGI r2) estimates and then eventually close with the much smaller causal within-family estimates. This gets the importance of results backwards and misleads readers into prioritizing confounded results. One would ordinarily not start a paper by reporting the results prior to QC first and then showing what remains after proper data cleaning, and the same holds for "environmental QC" for environmentally confounded traits.

5.17 | Further reading

Commentary/review:

- (Roseman, n.d.): Lay article on The Bell Curve and the history of hereditarian theories for behavioral traits.
- (Meyer et al. 2023): Comprehensive though staid perspective on the history, present state, and future opportunities in behavioral genetics with an extensive focus on EA.
- (T. T. Morris et al. 2022): Comprehensive review of methods to infer causal relationships in behavioral genetics .
- (Coop and Przeworski 2022b): Perspective and warning for the interpretation of EA PGI results.
- (Turkheimer, Pettersson, and Horn 2014): A review of classical genetic analyses of personality and proposal to evaluate biometric/genetic correlations against a phenotypic null rather than against a null of zero.

Key studies:

- (Rietveld et al. 2013), (Okbay et al. 2016), (Lee et al. 2018), (Okbay et al. 2022): The four landmark EA GWAS studies.
- (Young et al. 2018): RDR quantification of total direct h2g of EA in Iceland.
- (Mostafavi et al. 2020): Analysis and consideration of PGI effects in different environments.
- (Abdellaoui, Dolan, et al. 2022): Geographically conditioned heritability estimates for EA and related traits.
- (C.-Y. Chen et al. 2023): The first large-scale rare variant analysis of EA, in the UK Biobank.

The heritability of IQ test performance I: What does IQ measure?

In contrast to Educational Attainment (see [**5.0**]), the definition and measurement of IQ is more complicated both technically and conceptually. It is sufficiently complicated, in fact, that this section will first focus entirely on outlining specific theories and models of the IQ test and how well those models correspond to empirical observations. If we want to understand the genetic influences on a measurement we first need to understand the measurement. But let's step back: **Why even talk about IQ tests at all rather than stop at EA?**

First, the field of IQ research has been struggling for over a century to define the parameter they are estimating and has increasingly used crude heritability results as appeals to biological "reality" and self-justification. Molecular heritability and GWAS associations for EA have recently been marshaled as "independent" evidence of the supposed biological reality of IQ, with claims that "everything hangs together nicely" (S. Ritchie 2016). But as we have now seen, essentially *every* phenotype no matter how meaningless, has some non-zero heritability, typically explained by thousands of genetic variants of miniscule effect (see [**4.1**]). Moreover, it is precisely the behavioral traits most closely related to education, cognition, and socioeconomics that tend to exhibit the most confounding and stratification – i.e. are arguably the least genetic "reality" (see [**4.2**, **4.3**]). **The work of molecular geneticists is thus routinely used to prop-up IQ theories even as molecular genetic analyses of EA and IQ (as we will see) have revealed numerous sources of bias and environmental confounding**. From its very inception, EA GWAS was understood as a "backdoor" into the genetics of IQ; as intelligence researchers are increasingly coming in through the front door, molecular geneticists need to understand how their work serves that cause.

Second, IQ research has been highly focused on models that attempt to simplify the complexity of cognitive function into a single score or factor. This practice of data summarization may be convenient, but it is a major barrier for trying to make sense of what trait is actually being estimated and how that trait is influenced by genetic variation. It would be absurd to study cancer

by taking all neoplasia-related diagnoses across individuals and reducing them to a "general cancer factor" (in fact, most cancer research takes the exact opposite approach and is highly focused on understanding types, sub-types, and so on) and yet this is exactly what has been done in the the largest GWAS of IQ (or "intelligence") to date (Savage et al. 2018). **While this section takes no position on whether IQ is "worth studying", it does intend to seriously interrogate *what* IQ is studying, with the aim of improving precision, especially of work carried out by geneticists**. In my opinion, people can study whatever they want, but they have a responsibility to be precise in describing what that is (and is not).

6.0 | Summary

- An IQ test score is a weighted average of scores across tests of memory, vocabulary, numeric reasoning, and general knowledge. **A consistent observation from IQ test data is that individuals who do poorly on one test tend to do poorly on multiple tests – producing a correlation across scores known as the "positive manifold"**. Motivated by these correlations, IQ is often summarized with a "general factor" (or *g*) score, which is simply a different re-weighted average of IQ subtest scores.
- Much research has gone into developing theories of IQ test correlation and the positive manifold. **Theories are critical to understanding what the test is measuring, how to design accurate/unbiased tests, how to use tests to understand interventions, and how to draw broader conclusions about the mind**. Common theories that can explain the positive manifold include:
    - Bonds/sampling theory: Cognition is formed by a very large number of processes, with each IQ subtest sampling some subset of processes. The positive manifold is merely a statistical artifact of the incidental overlap between the processes across subtests.
    - Dynamic mutualism: Cognition is formed by the "mutualist" interaction between multiple underlying processes where development of one process leads to growth in other processes. These relationships induce a positive manifold over time even though no general factor exists as a causal entity.
    - *g*/Factor theory: Cognition is formed by the general factor itself (akin to a "mental energy"), which drives performance across all subtests in addition to some independent test-specific abilities. *g* theory has been expanded to include multiple factors or factor hierarchies.
    - Process Overlap Theory: A synthesis of sampling and factor theories where subtests sample from processes that are either domain-specific (with three named domains) or domain-general. The positive manifold is an emergent property of the domain general process overlap but is not itself a causal entity.
- Five paradoxical findings regarding the measurement of IQ and g:
    - The general factor weights (or "loadings") of subtests are nearly perfectly correlated with the culturally-specificity of each subtest (e.g. higher for vocabulary, lower for numeric memory) (Kan et al. 2013). **Thus a *g* score is merely an IQ score re-weighted by acculturation**.
    - **The positive manifold increases with *lower* IQ**, meaning that low IQ individuals tend to do poorly on all tests whereas higher IQ individuals tend to do well on only

some tests. Paradoxically, **the positive manifold also *increases* as children develop and decreases as adults decline**. These **paradoxical** observations are incompatible with a single *g*-factor process across all individuals and likely necessitate a dynamic model.

- Multiple longitudinal studies have found that **IQ is not associated with an increased rate of cognitive or academic growth** in young age through adolescence (Larsen and Little 2023), nor with faster acquisition of job skills in adults (Schmidt et al. 1988), nor with the rate of cognitive decline in the elderly (Gow et al. 2011). This yields a **third paradox**: if *g* is a measurement of "general processing speed", why is it not associated with faster learning (nor with slower cognitive decline)?
- **Socioeconomic status (SES) is significantly associated with IQ gains**: on average, children in low SES families started at a 6 IQ point deficit at age 2, and had a 15-17 IQ point deficit by age 16 (von Stumm and Plomin 2015). **The effect of SES on academic achievement remained significant even when adjusting for future IQ measurements**, indicating that SES can drive an environmental feedback loop between IQ and schooling. This yields a **fourth paradox**: if g is causal and largely independent of the shared environment, as is often claimed, why does the shared environment (SES) correlate with IQ gains while IQ does not?
- **The Flynn Effect: IQ has increased an average of ~2 points per decade, with the largest gains in teenagers** (Wongupparaj et al. 2023). The gains were not homogenous: increasing scores were observed on the more g loaded subtests in lower IQ individuals and decreasing scores were observed on less g loaded subtests in higher IQ individuals (Colom et al. 2023). **The heterogenous increase in IQ suggests substantial, culturally induced changes acting on different processes**. This yields a **fifth paradox** for g, as the underlying construct itself appears to be changing rapidly over time or else implies that the average individual born in the 19th century was severely mentally handicapped.
- Test-retest reliability of a general factor in the UK Biobank was high (r = 0.82) for a 30 day gap (Fawns-Ritchie and Deary 2020). **Test ranking generally stabilizes in adolescence (r>0.7)** (Tucker-Drob and Briley 2014) with moderate correlations (r = 0.45) observed from age 11 to age 90 after removing outliers (Deary, Pattie, and Starr 2013).
- There is meta-analytic evidence that **IQ test results can be substantially impacted by motivation** and the stronger the motivation the larger the effect (though studies have generally been limited and small) (Duckworth et al. 2011).

- Multiple lines of evidence – longitudinal measurements, cross-sectional model fitting, neurological, and interventional – refute a simple general factor theory of intelligence:
  - **Dynamic / mutualist models have been supported by cross-sectional and longitudinal studies**, where performance in one cognitive domain is associated with improvement in other domains (Kievit, Hofman, and Nation 2019). Network models also often provide a better fit to IQ subtest data in cross-sectional studies (Kan et al. 2020). A recent large-scale genetic analysis revealed higher-order negative relationships between subtests, and a substantially different relationship between familial correlations and *g* loadings from that of a conventional factor model (Knyspel and Plomin 2024).

    - **Neurological measurements exhibit highly complex structure and do not support a single "neuro g" factor**: structural data does not form a unidimensional latent factor mapping to IQ (Kievit et al. 2012) nor do structural correlations from different test batteries strongly overlap (Haier et al. 2009); network models generally fit the relationship between connectivity data and IQ tests best (Anderson and Barbey 2023; Soreq et al. 2021); and studies of focal brain injuries generally show local rather than general effects (Protzko and Colom 2021).
    - **One of very few theory-motivated experimental studies found unexpectedly large gains from mutualistic models**: participants who trained on a diverse set of tasks had *more* substantial gains on a different specific task than participants who trained only on that task (Stine-Morrow et al. 2024). This preliminary finding highlights how experimental studies could be used to probe cognitive theories and produce surprising results.
- In sum: **IQ scores clearly do not behave as a single latent process and are best seen as a bundle of processes with multiple sources of within-/between- individual and temporal heterogeneity**. G-factor scores do not mitigate these issues and may in fact exacerbate them, as they are simply a reweighting of subtests to favor those with higher cultural specificity. While IQ scores may be a convenient data summarization technique, they also quickly become obsolete due to the Flynn Effect, are critically confounded by SES, and do not capture the process we are often most interested in: cognitive growth and decline. **There is no reason to think that IQ scores are fundamentally more *real* or *biological* than Educational Attainment, they are simply an index of a different mix of processes which remains just as poorly understood**.

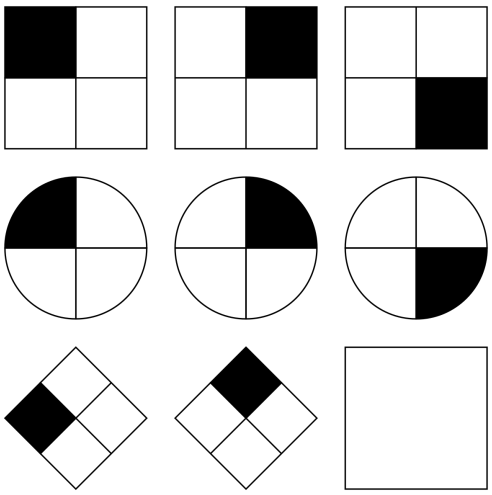
6.1 | Premise: What are IQ tests and what are they good for?

What is an IQ test trying to measure? A common definition is simply "*rapid and accurate problem solving*" (Jung and Chohan 2019). How does one measure *rapid and accurate problem solving*? We can give people some problems to solve and see how well they do in a fixed amount of time. Then we aggregate their scores and rank them against some reference population (the "norm") to arrive at a final "IQ score". Here are some example IQ test problems involving visual, numeric, and vocabulary problem solving:

Some example IQ test questions

(a) Raven's Progressive Matrices

*(b) Verbal-Numeric Reasoning / Fluid Intelligence examples from the the **UK Biobank***



Question	Responses
11 12 13 14 15 16 17 18	Select from:
Divide the sixth number to the right of twelve by three. Is the answer?	- 5 - 6 - 7 - 8 - Do not know - Prefer not to answer
Relaxed means the opposite of?	Select from: - Calm - Anxious - Cool - Worried - Tense - Do not know - Prefer not to answer

It's important to keep in mind that people probably don't think of intelligence this way. We generally think of intelligence as the ability to reason through complex problems and efficiently understand, retain, and synthesize novel information – not the ability to quickly identify word matches or draw lines through numbers. In fact, due to the short-term and structured nature of IQ tests, long term knowledge building and retention is not actually evaluated at all. Yet, when you read the word "intelligence" in the journal Intelligence, for example, odds are that it is referring to some transformation of an IQ score.

Setting aside the distinction between intelligence and IQ, is this IQ test at least accurate? Here we run into a fundamental challenge that the field has been grappling with since its inception: *construct validity*. When our instrument is a ruler, a thermometer, or a blood pressure cuff, we know the underlying *construct* being measured and can quantify accuracy; for example by comparing the absolute measurements from different tools in different contexts or by directly relating it to the underlying quantity (pressure in your veins - pressure on the cuff). Also, conceptually, we know the construct would exist even if we didn't have a tool to measure it. But when our tool is some aggregate of various tests, the underlying construct is unknown and may not "exist" at all. We can run the same person through the test multiple times and compare their scores (aka test-retest "reliability") but a biased instrument can still be highly "reliable", like a thermometer that's always off by 100 degrees. Likewise, an unbiased instrument can appear to be highly "unreliable" if the underlying construct is truly changing over time.

In the absence of construct validity, the uses for IQ fall into several classes:

1. A clinical instrument to identify outlier individuals for intervention. In the same way that one might define "general health" by averaging across a battery of health metrics – BMI, blood pressure, cholesterol, etc – it can be useful to have an index of cognitive health that crudely aggregates multiple different test measures. Even if such an index does not represent a single underlying construct, it could be a useful tool for identifying outliers: younger people with developmental delays or older people with cognitive decline, for example. One would then seek to understand what caused an individual to be an outlier (including pedestrian explanations like

having a biased instrument). A key operational question is thus whether aggregate IQ is more effective at finding etiologically meaningful outliers than other measures (educational attainment, for example), or even the subtest components of IQ itself.

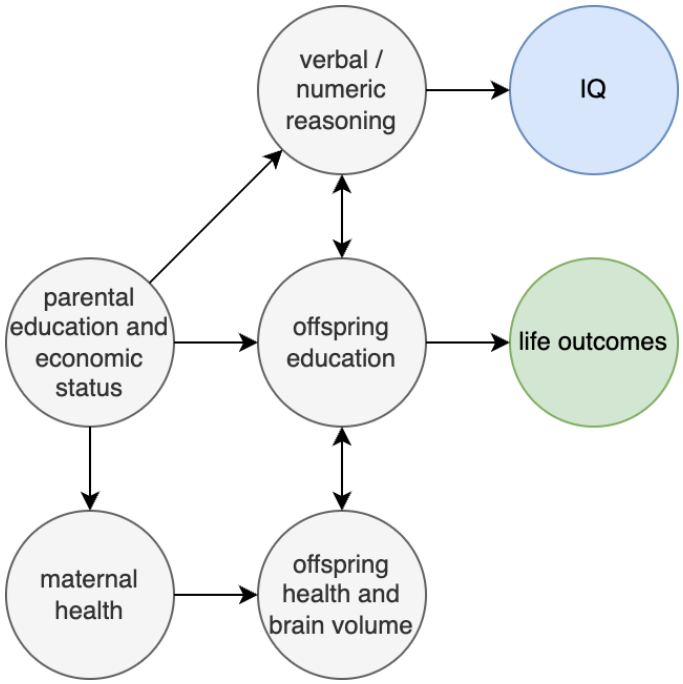
2. As an instrumental predictor of *changes* in cognitive ability. Related to identifying outliers in current cognitive ability, one may also be interested in identifying outliers in potential cognitive growth: students who learn more quickly or more slowly than average, or elderly who experience faster/slower than average cognitive decline. These individuals could then be matched into environments/interventions that optimize their cognitive development. If the underlying construct being tested by IQ is some measure of brain processing speed or "cognitive reserve", then we may expect it to also index faster growth or slower decline. However, as we will see, IQ is a surprisingly *poor* predictor of cognitive growth or decline.

3. A means of developing a theoretical understanding of the mind and moving towards construct validity. One may be able to develop useful constructs for how the mind operates by defining and then refining causal theories for the spectrum of individual variation. IQ tests, subtests, and items provide us with measurable data points from which to test our theories or generate new hypotheses. For this purpose, a useful IQ test is one that is interpretable and can falsify or distinguish between our theories. A theoretical understanding could then lead to better IQ tests as we converge on measuring the thing we actually want to measure.

4. As a number that correlates with a lot of other numbers. IQ tests correlate with school grades (which are themselves often test based), and grades correlate with many aspects of life, and so there is no shortage of correlations with IQ to discover. Unfortunately, these discoveries almost never go beyond correlative observations, which, as we have seen with other traits, can be confounded in both trivial and nontrivial ways. If some third factor (say, education) influences IQ and our outcome of interest, then the correlation with IQ is non-causal and perhaps even misleading. A simple hypothetical example is shown in the causal diagram below: the relationships between brain volume, IQ, and life outcomes are driven by education and socioeconomic status. Intervening on the non-causal factors (brain volume or IQ test taking) would be ineffective, whereas intervening on the causal factors (e.g. an intervention that improves education but not brain volume) could appear to have no immediate effect. Without a valid construct and a causal model, such correlations have very little utility.

A simple non-causal model relating IQ, learning, and life outcomes

In this model, parental education influences maternal and offspring health as well as offspring education (see [**]), which in turn have reciprocal relationships with brain processes and life outcomes. IQ is merely an index of those brain processes whereas the points of causal intervention are on parental education/economic status and offspring education.



To be fair, many concepts in psychology have poor construct validity: What does it mean to be depressed? What are the causal processes underlying substance addiction? What is the precise etiological distinction between schizophrenia and bipolar disorder? Etc. The difference is that these constructs have a clear *operational* purpose and urgency: people are suffering from a disorder and need help, we come up with the best diagnostic groupings we can, and then work on screening and interventions to ease their suffering, revising as needed. And the same is true of the instrumental use of IQ to identify outliers who may be suffering from neurological disorders (use #1 above): you work with the best instrument you can construct. **But IQ research draws appropriate criticism when it seeks to generalize from the operational use of low IQ as a screening tool, to claims that the IQ instrument is *itself* a causal process in the general healthy population**.

And this kind of generalization happens *all* the time, especially as IQ researchers venture into other domains such as genetics. As an example, here is how the (G. Davies et al. 2018) GWAS of cognitive function motivates the topic: "*General cognitive function is peerless among human psychological traits in terms of its empirical support and importance for life outcomes. Individuals who have **higher** cognitive function in childhood and adolescence tend to stay longer in education, gain higher educational qualifications, progress to more professional and better-paid jobs, live healthier lives, and live longer. Individual differences in general cognitive function show phenotypic and genetic stability across most of the life course.*" It's debatable whether general cognitive function is more important for life outcomes than other psychological traits like autism, major depression, schizophrenia, or bipolar disorder. But the fact that it is predictive of "professional and better-paid jobs" should certainly be irrelevant to its "peerless" status as a psychological trait. **Moreover, the entire focus is on "higher cognitive function" even though this is where IQ is operationally useless**. As another example, here's how (R. Plomin and Deary

2015) introduce intelligence: *"it is central to systems approaches to brain structure and function" ... "and to the conceptualisation of how diverse cognitive abilities decline with age" ... "intelligence is one of the best predictors of key outcomes such as education and occupational status" ... "People with **higher** intelligence tend to have better mental and physical health and fewer illnesses throughout the life course, and longer lives"*. Again we see a shift from principled research questions (brain structure and function) or clinically-relevant outcomes (cognitive decline) to questionable correlations among "higher intelligence" individuals (occupational status, fewer illnesses, etc). **The ease with which terminology drifts from "IQ scores" to "general cognitive function" and the research focus drifts from low IQ to high IQ highlights the importance of working from clear definitions and an underlying causal model**.

PS. On correlation, variance, and adjectives: The following sections will inevitably discuss a large number of correlations. There is a silly ongoing debate as to whether correlations should be presented in their raw form (r) or in their squared form (r^2), with the latter also corresponding to "variance explained". I say this debate is silly because nearly all of the correlations discussed are positive and so a reader can easily convert one estimate into the other. The primary advantage of r^2 is that it is *additive*, so two independent predictors with an r^2 of 0.2 and 0.3 respectively will have a combined r^2 of 0.5; whereas two independent predictors with an r of 0.2 and 0.3 respectively will have a combined r of 0.36. An even sillier debate is over when to consider a correlation to be high, strong, weak, modest, etc. In the following text, I will refer to r^2 from 0.5-1.0 (r of 0.7-1.0) as "high" (in that the predictor explains the majority of the variance in the dependent variable), r^2 from 0.1-0.5 (r of 0.3-0.7) as "moderate" and r^2 <0.1 ($r < 0.3$) as "low". Readers are welcome to create their own adjective scales.

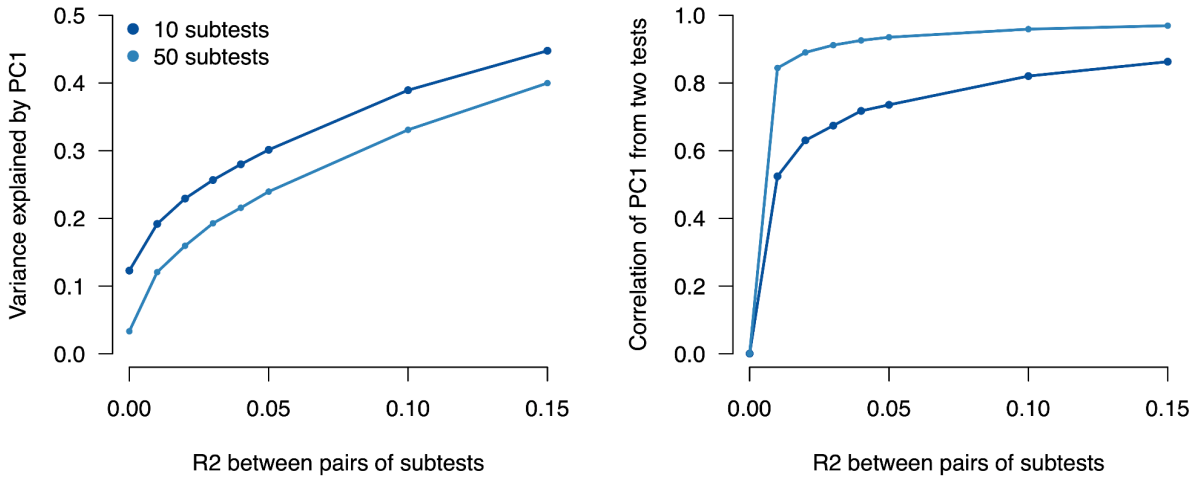
6.2 | The positive manifold

A consistent observation from IQ test results is that people who tend to do poorly on one test also tend to do poorly on others, including a correlation across subtest scores. This correlation across tests is referred to as a "positive manifold" and, while observed across many tests, tends to be modest in absolute terms. In the UK Biobank, for example, correlations between cognitive subtests ranged from 0.07 to 0.50, meaning performance on one test explained 1%-25% of the variance in performance on another test (Williams et al. 2023). When a dimensionality reduction technique such as factor analysis is applied to summarize measurements from multiple subtests, the factor that explains the most variance is often termed the "general factor" or "g". **Just as an IQ score is simply an aggregate of subtest scores, a "g" score is simply a different weighted aggregate of subtest scores, where the weights are defined by the "factor loadings"**.

In practice the general factor typically explains a moderate amount of the variance across all tests (25-45% in the literature and 29% in the UK Biobank across eight cognitive tests). This is an expected consequence of low positive correlations across tests. For example, ten random tests that have squared correlations of ~0.05 will produce a single factor that explains ~30% of the total variance (figure below; left). Moreover, if subtests are weakly correlated across two different tests (for example, two different IQ tests), then factors computed from the two tests will also be highly correlated (figure below; right), and thus "replicate" statistically.

Weak subtest correlations can induce a strong and replicating leading factor.

Subtests are sampled from a multivariate normal with increasing squared correlation (x-axis) and a single factor (PC1) is computed. ***(left)*** *The variance explained by the top factor. (**right**) The correlation across individuals between factors estimated from two separate tests, often interpreted as "replication". [**code**]*



While these correlations and factor variances are moderate, it is worth noting that they are consistently more than would be expected by chance and therefore an interesting phenomenon (at least statistically). Moreover, individual subtests correlate in ways that are not always intuitive or trivial. One could imagine an alternative universe where individuals that are very good at drawing a trail connecting a sequence of numbers (e.g. the Trail Making Test) would be really bad at verbal reasoning questions because they spent all their time learning to draw trails. But in the UK Biobank, the performance on these two tasks had a correlation of ~0.4. Perhaps that tells us something interesting about the function of the brain?

At the same time, it's good to remember that positive correlations are, to some extent, a consequence of test construction. First, even though intelligence is viewed as "fast and accurate problem solving", IQ tests typically evaluate a narrow category of problems: memory, vocabulary, shape rotation and completion, etc. They do not test the ability to work through set-backs on a complex project, resolve conflicts, explain difficult concepts to others, help someone through a trauma, etc. While these examples are undoubtedly real problems (of potentially more importance than the ability to rotate shapes, if anything) they are difficult to evaluate in a standardized setting and so are not included in IQ tests. It's entirely possible this type of problem solving draws on other components of intelligence, and would substantially reduce the positive manifold if they were actually tested. Indeed, **when tests are designed to capture "practical intelligence" they find negative correlations with general intelligence**, as in a study by (Sternberg et al. 2001) contrasting knowledge of herbal medicine with conventional academic tests in a Kenyan village. Second, the problems that do make it into IQ tests tend to match the type of early education and schooling received by children in high income environments: pairing up words and similes, arranging shapes, drawing letters, navigating mazes, etc. are all common components of an expensive preschool curriculum in Western society. **It is, in fact, very unusual for a person to practice only one of these tasks in isolation**. Schooling, in turn, is correlated with many downstream outcomes (both for causal and confounded reasons) and so an IQ test that

taps schooling-related skills will appear to be highly predictive. Just as a "positive manifold" of healthy physiological measurements could be explained by good diet and exercise, good performance on one IQ subtest may simply be an indicator of good early education, which then translates into good performance on many tasks. The positive manifold may thus be entirely consistent with the non-causal diagram of IQ illustrated above.

6.3 | Theories of the positive manifold

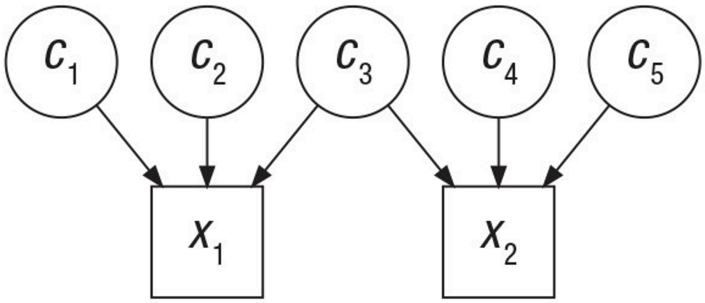
Hopefully it has become clear that the positive manifold can be explained by many causal processes and a combination of theory and data is needed to disentangle them. What theories can explain the observed positive manifold of subtest results? **In particular, what theories would be consistent with observations from molecular heritability: large-scale polygenicity, cultural effects on education, and substantial differences in heritability by environment**? Let's look at three core model theories that capture a broad range of hypotheses and differ substantially in their implications.

Thomson's sampling theory

Thomsons' sampling theory or "bonds" model of intelligence (Thomson 1916) most simply aligns with the highly polygenic architecture of common traits previously observed (see [**4.1**]). It also serves as a useful illustration of how the true construct can be substantially different from the observed factors. In this model, each subtest samples from a handful of specialized skills or processes (or "bonds"), of which there can be very many. The partial overlap in sampled processes in each test produces moderate positive correlation, which then accumulates into the positive manifold across subtests. Maybe the Trail Making Test samples from processes related to visual planning and numeric memory, while the Fluid IQ Test samples from numeric memory and vocabulary: individuals with high numeric memory will tend to exhibit higher scores on both tests and induce a positive correlation. In this model, **the common factor is purely a statistical "artifact" of the sampling processes**; it summarizes the data but tells us nothing meaningful about how it was generated.

Sampling theory

c's are underlying (unobserved) processes and x's are the observed tests. Figure from (Savi et al. 2019).

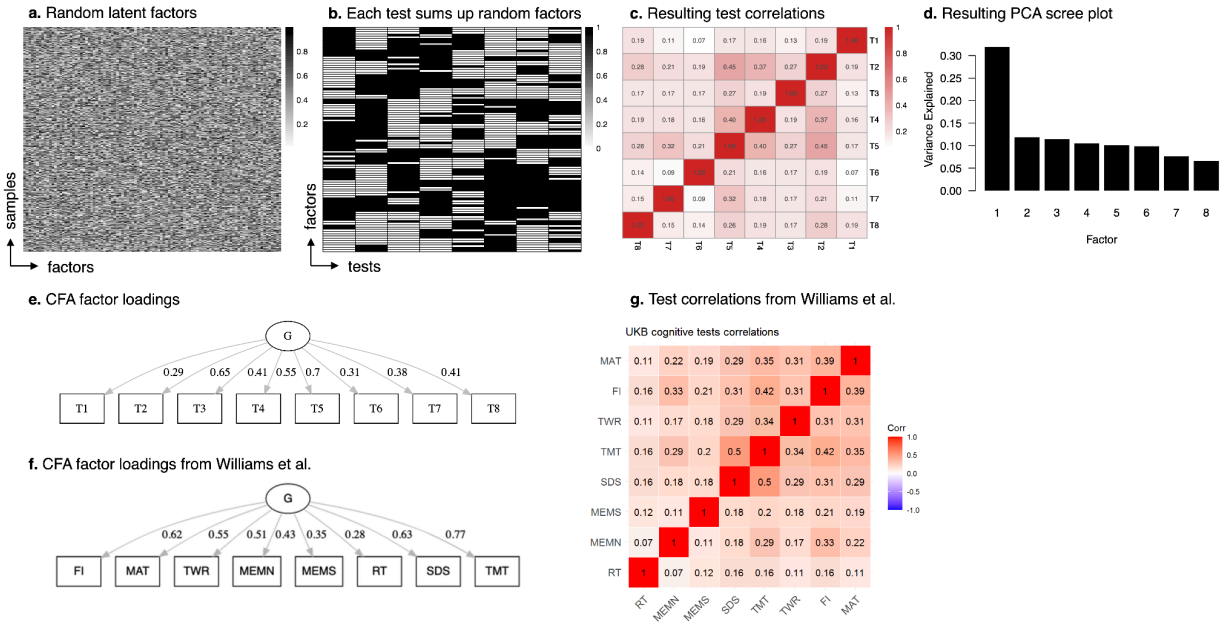


While it seems like this model is so complex it must be incompatible with the positive manifold we observe in real data, it has been shown mathematically that sampling theory can in fact reproduce the patterns observed in real test data (Bartholomew, Deary, and Lawn 2009). The intuition is that slight overlaps in the processes tapped by each test can produce weak correlations that are sufficient to generate a positive manifold and a general factor.

To illustrate this, let's simulate under sampling theory with 100 completely random underlying processes and eight observed tests, where each test samples half of these processes and sums them up to get the final test score (with some additional normally distributed measurement error applied on top). As shown in the figure below, this highly complicated model starting from completely random processes indeed produces realistic test correlations, a positive manifold, a common factor explaining >30% of the total variance, realistic factor loadings, and a confirmatory factor analysis that passes established checks for goodness of fit (KMO = 0.87, CFI/TLI > 0.95, and RMSEA < 0.05 for those interested). **The point being: good model fit is not sufficient evidence that that model is true, and a good fitting model can in fact be very far from the true model.** An important consequence of sampling theory is that if the underlying "processes" are actually known (for example, from a genetic study), they are expected to be uncorrelated and conditioning them out of the tests should make the positive manifold vanish – **i.e. the processes should "explain" the manifold**. Thus sampling theory produces interesting and testable hypotheses.

Sampling theory produces test correlations indistinguishable from a single common factor model

*Simulated data under the sampling theory model: (a) 100 random processes; (b) 8 tests that randomly sample half the processes; (c) the resulting test correlation matrix; (d) the variance explained by the top factor; (e) the factor loadings from a confirmatory factor analysis (FCA). Real data from the UK Biobank produced comparable estimates of (f) factor loading relationships and (g) test correlations (figures from (Williams et al. 2023)). [**code**]*

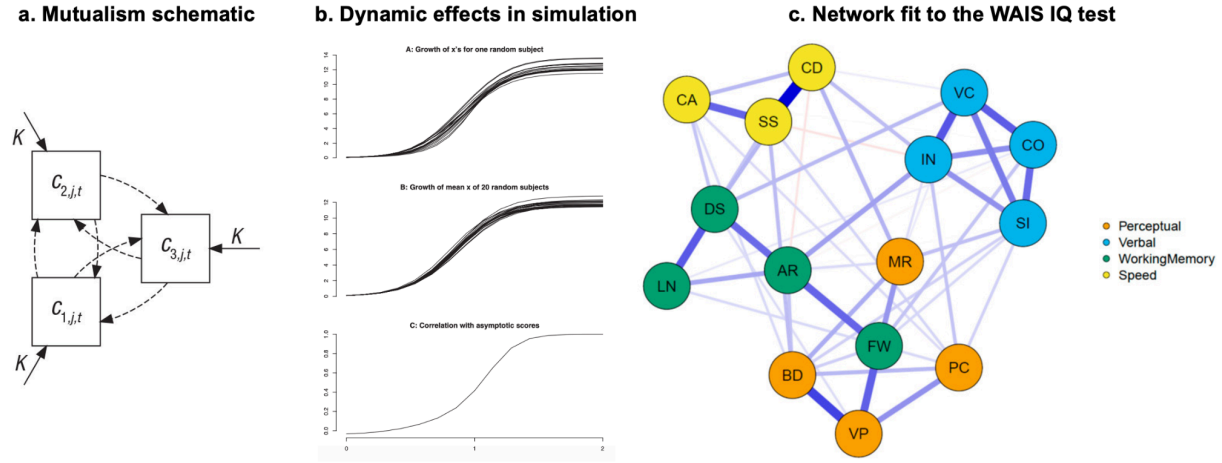


Van Der Maas' mutualism theory

Next, let's consider Van Der Maas' "mutualism" theory (van der Maas et al. 2006), and the broader class of network models (Borsboom et al. 2021), which introduce dynamic interactions. Under mutualism, multiple underlying skills or processes have mutually causal relationships that reinforce and propagate their effects. **Individuals who exhibit aptitude (or practice or environmental/genetic stimulation) in one process, may then propagate those aptitudes into other areas, while deficiencies in one area can hold back the development in others – leading to a rise in overall correlations across aptitudes**. As with sampling theory, mutualism can be shown mathematically to produce the covariances seen in real IQ tests and, over time, the positive manifold and general factor (see figure [b] below). Unlike sampling theory, a general factor is not a statistical artifact but it is also not a causal mechanism: it is merely an "index" of the general state of the underlying system or network. What's the difference? Mutualism provides an analogy to ecology: an ecologist studying why certain lakes form a flourishing ecosystem and others do not could collect measurements and compute a "general factor of lake health", but this factor (or even it's latent construct) is not actually causing the observations; the true causal processes are the interactions between plants, wildlife, and environments in the ecosystem (which can be modeled as a network that *is* causal). **The model also inherently allows for a mutualistic relationship with external genetic or environmental inputs**, for example allowing individuals to "match" into relevant environments (e.g. highly analytical professions) that, in turn, strengthen related underlying processes. A related environmental matching model was previously proposed by (Dickens and Flynn 2001) as a potential explanation for increases in the familial similarity of IQ with age and broader societal trends of increasing IQ (see [**6.4**]).

Mutualism / network theory

*(**a**) Simplified schematic of mutualist theory: c's (measured in individual j at time t) are underlying processes in a network and Ks are external (e.g. genetic/environmental) influences. Figure from (Savi et al. 2019). (**b**) Simulations under mutualism with a dynamic change in multiple tasks in one individual (top) the mean across tasks in multiple individuals (middle) and the positive manifold (bottom). Figure from (van der Maas et al. 2006). (**c**) Confirmatory network model analysis in real WAIS IQ test data. Figure from (Kan et al. 2020).*



Mutualism is typically represented with “network” models. In a network model (panel [**c**] above), the nodes reflect individual subtests (or even individual items on the subtests) and the edges are estimates of the *conditional* associations between nodes: the relationship that remains after conditioning on all other nodes in the model (Borsboom et al. 2021). In simple terms, two nodes will have a non-zero edge only if their correlation cannot be explained by correlations with other nodes. Likewise, nodes that explain the correlations between many other nodes will exhibit many edges and may be interpreted as “hubs”. It’s important to note that this is still a modeling abstraction that comes with many assumptions and is intended to parsimoniously *represent* the data rather than guarantee the inference of true structure. The model can further be expanded to more complex network structures with heterogeneous clusters of processes that are partially rather than fully connected, as well as non-linear/phase transitions as feedback loops build up and dissipate (e.g. children progression through stages of cognitive development) (Van Der Maas et al. 2017).

Mutualism is fundamentally unique in that it is a dynamic model that can incorporate time, and this leads to several interesting predictions. The positive manifold is expected to increase over development, as feedback loops increase and propagate across the network. Initially, interventions on individual processes should spread through the network and increase the dominant factor; but once the network has reached a “steady state”, such interventions will have little immediate effect, as they will be countered by established feedback loops. **Mutualism also leads to a different understanding for the positive manifold from that of other theories: it is an *index* of the state of the system like a speedometer, rather than a causal mechanism like an engine**. Likewise, tests that are highly correlated with the leading factor can either be indexing “core” processes that have many influences on the network, or “peripheral” processes that are influenced by many other processes. Two processes with equivalent factor loadings can thus have two completely different interpretations, and the first-order correlations between tests can even be masking negative partial relationships (Knyspel and Plomin 2024). The same holds for individuals with equivalent factor values: one individual can have a high leading factor because a *single* process was extensively trained and propagated through the network, whereas another individual can have a high leading factor because *all* of their processes were moderately trained. Finally, and in contrast with sampling theory, **accurately estimating/conditioning on the underlying “processes” under mutualism would not make the positive manifold disappear, because the feedback loops induce real correlations across processes**. Thus, mutualism is distinct from sampling theory in its relationship to the positive manifold.

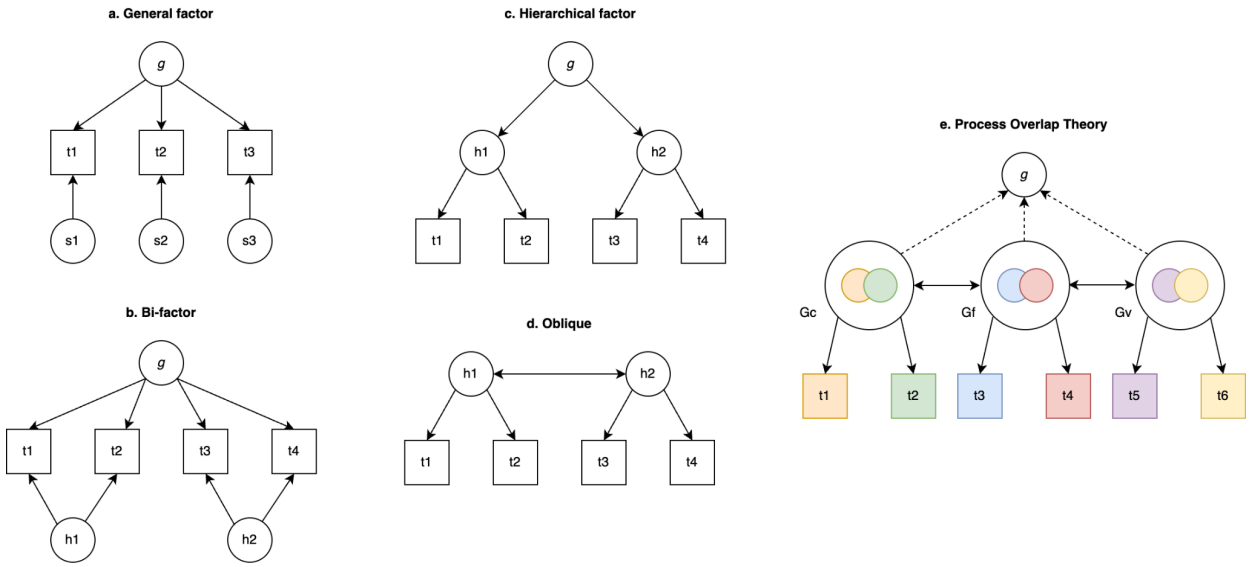
Spearman’s general intelligence (g) and factor theories

Lastly, we can imagine that the statistical factor that results from the positive manifold is itself the underlying *cause* of the positive manifold: i.e. **the data is the model**. This was, in fact, the theory outlined by Spearman when he first observed the positive manifold and developed factor analysis (C. Spearman 1904): postulating that test performance was driven by a single “general” factor (*g)* as well as a number of test-specific factors or abilities. While Spearman specifically avoided the ill-defined term “intelligence” (C. E. Spearman 1927)), he envisioned *g* as a measure of “*general mental energy*” that had an influence on essentially all mental tasks. This is

sometimes referred to as the "reflective" model of *g*, where *g* is an index of the causal mechanism and the tests are a reflection of the mechanism.

Factor theories and latent variable models

*(**a**) Spearman's model: all tasks [t] are influenced by a general factor (g) and task-specific factors (s). (**b**) Bi-factor model: all tasks [t] are influenced by a general factor (g) and partially shared factors (h). (**c**) Hierarchical model: tasks [t] are influenced by group factors (h) which are in turn influenced by a general factor (g) (includes Cattell–Horn–Carroll and g-VPR theories). (**d**) Oblique model: tasks are influenced by group factors (h) but no general factor exists. (**e**) Process overlap theory: tasks sample from overlapping processes that reside within one of three specific domains, with a non-causal g emerging due to the inter-process overlap/correlation. Circles represent "latent" unobserved variables and squares represent observed/measured variables.*



Spearman also hypothesized that the task-specific abilities should be entirely uncorrelated after accounting for *g*, which would be consistent with *g* indexing the only core process. In practice this is rarely the case and subtests often remain significantly correlated even after conditioning out the estimate of *g*. **Thus, the basic single general factor theory of intelligence was invalidated almost immediately.** To accommodate the residual correlations, the general factor model has since been expanded to include secondary factors (e.g. fluid and crystalized intelligence), factor hierarchies (general, broad, and narrow) and so on. Such higher-order factor models continue to be widely used in the analysis and interpretation of IQ test data: see (Savi et al. 2019) for a succinct summary of recent developments and (Beaujean and Benson 2019) for a more detailed early history. A fundamental challenge with factor models is that, in being so closely linked to statistical fitting of data, they often do not make predictions beyond the goodness of fit itself. If *g* is a "real" causal process, how much variance should it explain across a given test battery? How should we expect it to change over time? As a function of ability? Or training/education? Or brain injury? The theory of *g* gives us very few insights into these questions. **Still, *g* has the appearance of being a simple, intuitive explanation and so remains the dominant view of intelligence in the popular imagination**.

Finally, **Process Overlap Theory (POT) presents a hybrid of factor, sampling, and network models**: individual tasks "sample" from a set of processes which are grouped into three main

co-active "domains" with some processes being "domain-specific" and some "domain-general" (Kovacs and Conway 2016). Like sampling theory, IQ subtests are aggregates of multiple underlying processes and the general factor is an emergent property of sampling. Like factor theory, these processes are grouped into latent components (including conventional components like crystalized, fluid, and visual domains). And like mutualism, the latent domains can influence each other interactively over time. POT makes a specific prediction about cognitive development: domain-general processes put a "bottleneck" on overall task ability, such that lower IQ individuals would be expected to perform poorly on all tests / have higher test correlations, as is observed in real data (see [**6.4b**]); additionally, more complex tasks are expected to sample from multiple processes and thus be more "g loaded" (whether this matches the data is debatable, see [**6.4a**]). POT also makes a number of neurological predictions about the involvement of various brain regions in certain domains. Although it is generally recognized as a synthesis, there remains some debate over the extent to which POT is fundamentally different or a reframing of sampling theory (Deary, Cox, and Ritchie 2016; Kan, van der Maas, and Kievit 2016).

A brief word on the "replicability" of *g*

A point that often comes up in the intelligence literature is the "replicable" nature of *g/general intelligence*. Here is a representative example from (Deary, Spinath, and Bates 2006): "*This general cognitive factor is sometimes referred to as just g, or 'general intelligence'. It was discovered by Charles Spearman in 1904* ***and is one of the most replicated findings in psychology***". This statement is not entirely correct: what replicates is the positive manifold – the correlation between tests – whereas the "general cognitive factor" is just one natural *consequence* of the positive manifold and data summarization. Replicating an estimate is the bare minimum we should expect from responsible research: it merely tells us that what we observed was not a statistical fluke. **We should not be fooled into thinking that statistical replication is evidence of construct validity or reality**. We can imagine, for example, measuring parts of the body in some population and using factor analysis to derive a "general size" factor that explains a large fraction of the total variance across measurements. This observation of a "general size" factor would likely replicate and load consistently on the same limbs (loading highly on the size of arms and legs and less on, say, the size of the nose), but this would tell us nothing about whether "general size" is a single causal process through which the body develops. The structure of IQ tests is indeed highly replicable, but the resulting general factor is just one of many theories that could explain that structure.

A word on why theory matters

At this point we might be tempted to ask why theory and modeling even matters. If the positive manifold is seen so consistently, why not simply estimate it with a general factor and treat it as the ground truth? Isn't the debate over the underlying theory purely philosophical? **In fact, developing an accurate theory has substantial practical implications at all levels: conceptual, inferential, and interventional.**

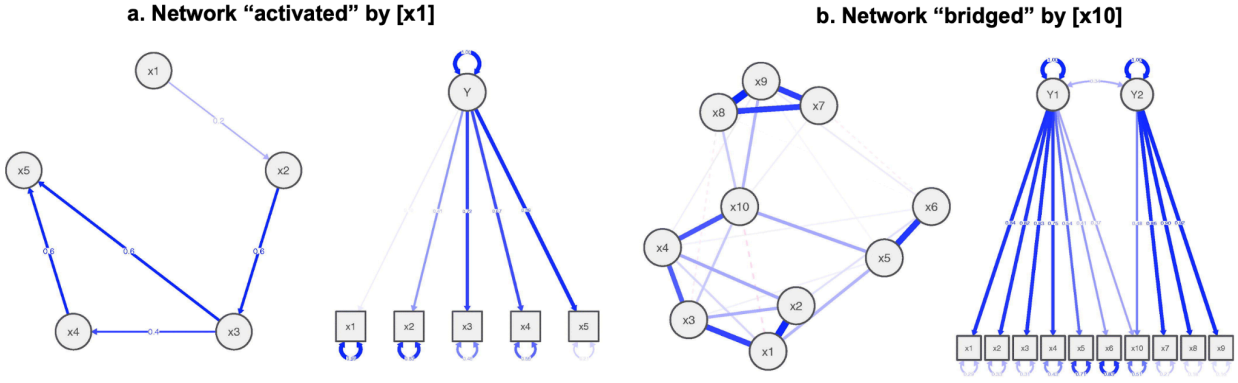
Understanding what is being measured: The above models differ greatly in the way they distinguish between innate abilities and developed skills. The single *g* factor theory leans heavily

on the assumption that a core innate process can individually explain a moderate fraction of performance across all tests; and it is often implied that this factor is largely innate (or at least fixed). Sampling theory instead posits that there can be a very large number of underlying processes, while generally still assuming that these processes are innate. Mutualism (and related models) deviate from this perspective by explicitly allowing external inputs that aid in the development of certain processes, which then propagate through over time. Thus, these models present completely different interpretations of the mind and how it interacts with the exterior world. These issues persist at the more granular subtest level, where subtests with similar loadings can have completely different interpretations under the different models (see above).

Designing tests that measure what we want to measure: Models are needed to decide whether a given item or subtest on the test should be included/excluded to measure the quantity we actually want to measure. Without models, a data-driven approach is typically taken where items are removed if they decrease the reliability of the test or have weak factor loadings. However, (Fried 2020) showed through simple simulations that important test items can fail these criteria when the assumed model doesn't match the true model (see figure below). In the first example, a directed causal network model is weakly "activated" by one subtest/item which then produces a cascade of responses. In a factor model, this item loads poorly on the general factor and dropping it would increase consistency/reliability of the entire test (because scores on the activating item change over time and are thus "unreliable" by definition). **Following the factor/reliability model and dropping this item would thus remove the most important causal component in the system**, which initiates the other responses. In the second example, an undirected network model consists of two clusters that are connected/bridged by a single item. In a two-factor model, this "bridge" item again loads poorly on either factor and would likely have been removed to improve the overall model fit. However, this "bridge" item may be of most interest from a causal/biological perspective as it provides a connection between otherwise disparate concepts and be an important point of intervention.

Factor interpretation of non-factor models can lead to erroneous conclusions

*(**a**) In the true network model (left) [x1] activates a cascade of events measured by [x2-x5]. Dropping [x1] increases reliability of the test and the apparent factor variance, while actually removing the fundamental causal primer. (**b**) In the true network model (left) [x10] is a bridge between two major clusters of items. However, an inferred two-factor model [x10] loads poorly and would likely be removed. Figure from (Fried 2020)*



Identifying and interpreting test bias: The above demonstrations of improper test construction with erroneous models can naturally lead to misinterpretation of test bias. Group-specific bias is a major concern in testing and a big focus in the industry. However, without well established models, approaches to correct for bias may be purely superficial. The typical method for bias identification is called Differential Item Function (DIF) and the basic idea is to identify items on the test which produce different rates of success from different groups after matching on underlying ability. **This creates an obvious chicken-and-egg problem: in order to identify bias in the test, we need to match on underlying ability, and in order to match on underlying ability, we need an unbiased measure of the ability**. Moreover, these methods almost always assume a *single* underlying ability. Without a model of the ability process, this problem can only be resolved superficially. For example, if two groups are showing DIF, it could be that certain questions are biased for individuals matched on a single underlying ability (consistent with *g* theory) or that the two groups have multiple abilities that have developed to different extents (consistent with sampling theory) or the two groups have the same abilities but with different dynamic interactions (consistent with mutualism). Without the right model of latent abilities, truly biased questions may not exhibit DIF and be retained (see (Wicherts and Dolan 2010) for an empirical example), while unbiased questions may exhibit DIF and be dropped. A common backup strategy is to evaluate whether the test is equally predictive of some other outcome across groups, but it is mathematically possible to have unbiased predictive regressions while still measuring the underlying process with bias (see (Millsap 2007) for derivations and more discussion about how predictive invariance has been misused in evaluating test bias).

Developing and evaluating an intervention: A major goal of studying cognitive function is to develop and evaluate interventions on cognitive dysfunction. This requires validity of each of the above points: understanding what is being measured, understanding whether it is being measured accurately, and identifying any group-specific bias. Imagine an educational intervention is being piloted that leads to improved test scores but does not improve the principal factor (that is, does not increase the shared component of the tests). Under causal g theory, this intervention may be considered a failure: individuals have not improved on the “core” causal mechanism. In contrast, under sampling theory this same observation would merely imply that the intervention targeted those processes which are not shared across tests and may have been a success. In a mutualist model, the outcome could be interpreted as an increase in a specific domain which will later translate into dynamic increases in other domains (or block those domains from deteriorating). Similar reasoning applies to the alternative case where an intervention does increase the principal factor: g theory: success! Sampling theory: it depends on the processes as gains in processes with more overlap may be less important/lasting than gains in specific processes. Mutualism: an increase in the relationships across domains (leading to a higher positive manifold) may have no beneficial effect or even long-term negative effects (for example, by driving an individual to “spiral out” when they experience negative inputs). **It is also worth remembering that just because a factor correlates strongly with outcomes does not mean that an intervention on that factor will correlate with improved outcomes**: height may be correlated with basketball aptitude but giving an adult stilts will not make them a better basketball player (and will likely make them worse). Thus, theories are critical to understanding whether a treatment is having the effect we desire it to have.

Thus, *even if* one only cares about IQ as a clinical instrument to identify outliers and one does not believe it represents an underlying construct, models are important to ensure stability, generalizability, and unbiasedness of your instrument.

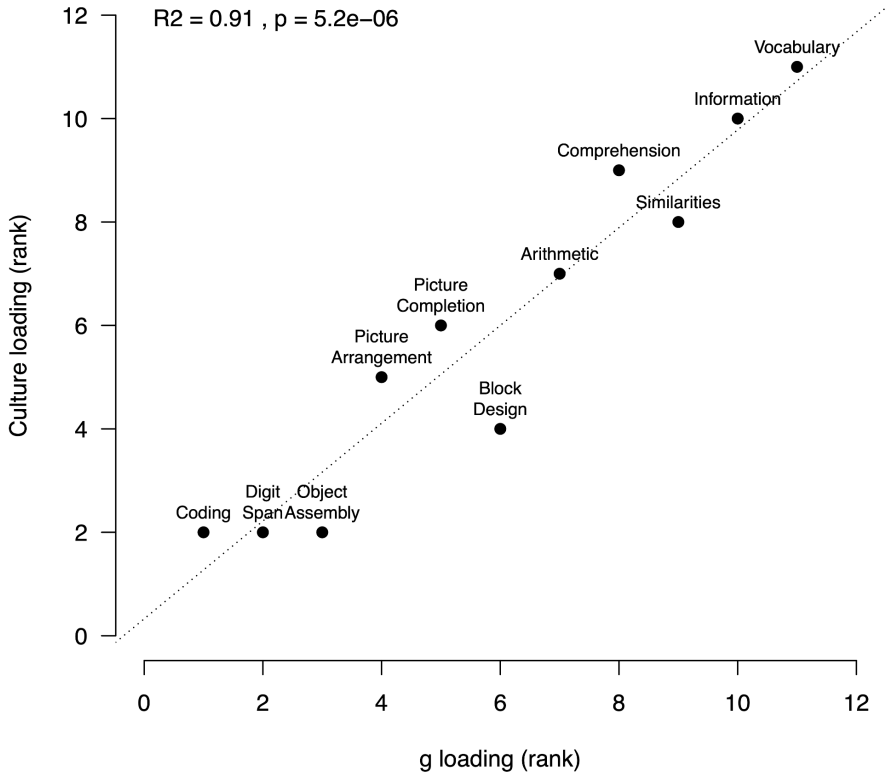
6.4 | The measurement of IQ and five paradoxes

"*g* loading" is cultural loading

Given the uncertain nature of *g* itself, people often look to the "*g* loading" of various subtests to make sense of what g is capturing. These inferences can often get quite circular: since *g* is seen as a measure of intelligence it can be tempting to interpret *g* loaded tests as those that are "better" measures of intelligence. From a statistical perspective, higher *g* loading simply implies that performance on those tests is more correlated with the shared variance across tests; which can be true for tests that are simple or complex (or systematically biased). (Kan et al. 2013) took a creative approach to investigating this question by comparing subtest g loading (using the WAIS/WISC IQ tests) to the corresponding subtest "cultural" load, defined as the number of test questions that had to be altered when the test was adapted for use in other countries. **The *g* loading rank of each subtest correlated nearly perfectly with the corresponding cultural load rank (Spearman correlation > 0.9)**, with comparable correlation observed even for the raw loadings (Pearson correlation > 0.8); both correlations were highly significant. The three most "*g* loaded" subtests were unambiguously culturally specific: Vocabulary, Information (which tests general knowledge, like "what is photosynthesis?"), and Comprehension (which tests situational knowledge like "why store money in a bank?"); and the three least "*g* loaded" subtests tapped processes relating to memory and matching: Coding (matching digits to symbols), Digit span (repeating a series of numbers), and Object Assembly (arranging physical shapes). The tests that contribute more to the leading factor (i.e. share the most variance) are thus also the tests that have the most cultural specificity.

General factor (g) loading is highly correlated with test cultural loading

*(x-axis) rank of g loading: derived from the WAIS/WISC manuals as the loadings on the first principal component and averaged. (y-axis) rank of cultural loading derived from the WAIS/WISC manuals as the number of items that had to be modified when extending the test to other cultural groups. Figure adapted from (Kan et al. 2013) [**code**].*



The second interesting observation from this analysis was that subtest cultural load was also significantly positively correlated with familial "heritability" estimates from twin studies. These estimates, like pedigree "heritability" (see [**2.6**]), reflect a complex mix of genetic influences, gene-environment interactions, and twin-specific environmental differences (see [TBD]). Taken literally, they indicate that monozygotic twins have higher correlations than dizygotic twins on the more culturally loaded subtests (and by extension on the more *g* loaded subtests).

These two findings remain mysterious and there are multiple possible interpretations:

- Under a mutualist model, stimulating/nurturing environments are more likely to provide culturally-relevant development (for example, parents reading to their children) which will propagate across the latent processes and lead to stronger *g*/culture correlation. If genetically similar individuals (e.g. MZ twins) "match" into more similar cultural environments, this will also induce a correlation with twin "heritability". This was the interpretation proposed by (Kan et al. 2013).
- An alternative explanation for the relationship between "heritability" and culture load is an *interaction* between genetics and the shared environment, which will make MZ twins (who share all the interactions) appear more similar than DZ twins (who share half the interactions).
- Finally, a fully environmental explanation is that IQ tests are easier to "game" on the more culturally loaded subtests (e.g. through practice or drills) and such practice will also be more transmitted among closer relatives: for example, MZ twins being more likely to study together than DZ twins (we can think of this as a gene-environment interaction but with no underlying genetic effect).

Regardless of the underlying explanation, it is clear that *g* is driven by cultural knowledge tests, and the corresponding twin correlations are indicative of interactions or correlations with culturally specific environments.

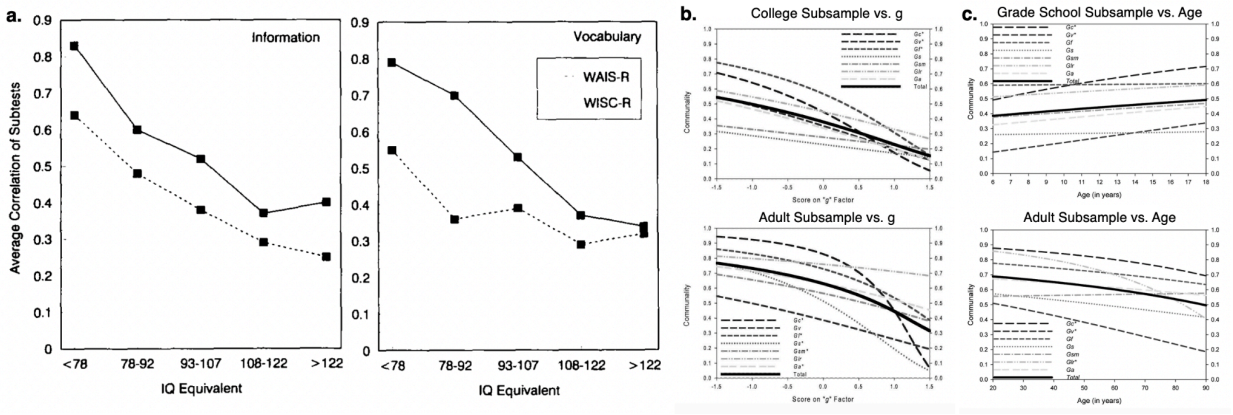
Lower IQ, more g / Ability differentiation

Further interesting patterns emerge when individuals are split into groups by cognitive function: **individuals with lower IQ tend to exhibit a much higher positive manifold and thus, in a sense, more *g*** ("ability differentiation", (Detterman and Daniel 1989)). This pattern is quite striking, with individuals in the lowest IQ group exhibiting >2x more average correlation across scores than individuals in the highest IQ group. Notably, this result was not strongly influenced by differences in test accuracy/reliability in the groups and replicated across multiple large studies and more complex factor models (see figure [b] below) (Tucker-Drob 2009). In a follow-up, Detterman proposed a tongue-in-cheek interpretation in the spirit of *g* theory: "*[Spearman] thought that it was g that produced the correlations among tests, and that people differed in the g they had. Logically, then, groups with the highest correlations among tests should have the largest amount of g. Because, in both data reported by Spearman and in my data, the low-IQ groups had the highest correlations among tests, they also must have the largest amount of g. In other words,* ***g correlates negatively with intelligence, so g must be stupidity***" (Detterman 1991).

A more direct interpretation is simply that individuals with lower IQ tend to do poorly on most tests, whereas individuals with higher IQ tend to do well on some tests much more than others. In the context of the cultural load results above ([**]), this would imply that those who perform poorly on one culturally loaded test are likely to do poorly on all tests, but those who perform well on culturally loaded tests (which contribute the most to IQ scores through their intercorrelation) perform more sporadically on the other tests. **An individual with cognitive disability or a language barrier or test anxiety will struggle with all tasks**, whereas an individual with a strong command of cultural knowledge may still have poor numeric memory or shape rotation. This distinction suggests that IQ scores may be capturing fundamentally different underlying parameters at the low versus high end, in addition to heterogeneity by culture.

The positive manifold increases with lower IQ/g (ability differentiation) and higher age (age differentiation).

*(**a**) Increased correlation of subtests (y-axis) as a function of lower IQ score [Figure from (Detterman and Daniel 1989)]. (**b**) Replication of (a) as a function of g and across different factors [Figures from (Tucker-Drob 2009)]. (**c**) Changes in correlation of subtests (y-axis) as a function of age for grade school (top) and adult (bottom) individuals [Figures from (Tucker-Drob 2009)]. Gc: comprehension knowledge; Gv: visual–spatial thinking; Gf: fluid reasoning; Gs: processing speed; Gsm: short-term memory; Glr: long-term retrieval; Ga: auditory processing.*



Age differentiation

Interestingly, the reverse pattern is observed with respect to age ("age differentiation"): as grade school children get older, the correlation between subtest performance increases slightly and then as individuals enter old age the correlation between subtests decreases (panel [**c**] above and (Tucker-Drob 2009)). In other words, even though low IQ individuals have a higher positive manifold, developing children exhibit an increasing positive manifold and declining adults exhibit a decreasing positive manifold. **Taken together, these three observations are fundamentally incompatible with a singular/fixed model of *g***. For example, under sampling theory one could explain the pattern of ability differentiation by proposing that individuals with cognitive disabilities are sampling from fewer latent processes (thus producing more correlation across tests). However, this would imply that cognitive decline in old age should also lead to fewer available processes and a higher positive manifold – yet the opposite is observed! Under factor theory one could explain the same pattern of ability differentiation by proposing that individuals with more advanced cognitive function operate in settings that develop more specialized skills and thus decrease their positive manifold. However, this would imply that cognitive growth in kids should also lead to a decrease in the positive manifold – yet the opposite is observed!

A dynamic mutualist model can, in principle, unify these three findings: (1) as children develop, their latent processes accumulate interactions leading to an increase in the positive manifold; (2) as the elderly decline, the relationships between their latent processes atrophy leading to a decrease in the positive manifold; (3) individuals with low cognitive function have fewer nodes/latent processes and so reach a higher positive manifold than high function individuals with more processes (and thus more complex and more gradual mutual relationships). This is just one speculative explanation, but it is notable that a dynamical model is easily capable of explaining these otherwise paradoxical observations.

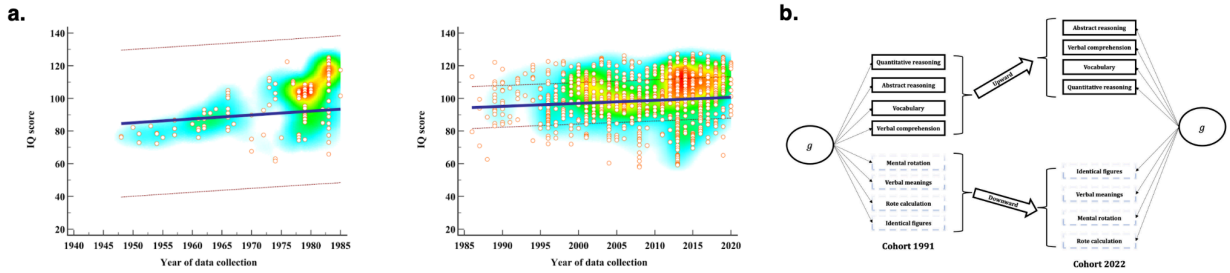
Increasing IQ / The Flynn Effect

In the same way that IQ is not static across age groups, IQ has not been static within societies. Many studies have shown that IQ has steadily risen across the world, a phenomenon known as "The Flynn Effect". **A recent meta-analysis of nearly ~300,000 tests found an average 16 point IQ gain (roughly 1 standard deviation) over the 72 years from 1948-2020** (Wongupparaj et al.

2023)**, or ~2 points per decade**, using the Standard Progressive Matrices test of "fluid" IQ (i.e. mental reasoning and manipulation). These changes were most pronounced for teenagers in the study (2.5 points per decade) and least pronounced for <12 year olds (1.2 points per decade), **implicating cultural shifts more so than improvements in early nutrition or maternal health (though a specific cause remains unknown)**. Even larger gains have been observed on more holistic IQ tests, but it is difficult to rule out test bias or non-invariance (which would violate the assumption that the tests are measuring the same statistical quantity). For example, (Gonthier and Grégoire 2022) showed evidence of temporal Differential Item Functioning (DIF) in the WAIS IQ test, which produced a raw estimate of 1.0 IQ point gain per decade (1989-1999), but a DIF-corrected estimate of 3.9 IQ point gain per decade from the same data.

The Flynn Effect: increasing IQ test scores over time, age, and country

*(**a**) Estimated increase in IQ on Progressive Matrices from 1945-1985 (left) and 1985-2020 (right) in a meta-analysis [Figure from (Wongupparaj et al. 2023)]. (**b**) Estimated increase in IQ on higher "g loaded" subtests and decreases in IQ on lower "g loaded" subtests from 1991 to 2022 [Figure from (Colom et al. 2023)].*



Regardless of the precise estimate, broadly increasing IQ is widely accepted and presents a paradox for the interpretation of IQ. Backcasting the ~2 pts/decade estimate would imply that the average individual in the 19th century had an IQ<70 i.e. mild intellectual disability. This seems highly unlikely given what we know about 19th century society and suggests instead that whatever the IQ test is measuring has changed over time. Indeed, (Colom et al. 2023) showed that while overall IQ scores are increasing, **these gains come from increasing scores on the abstract, verbal, and quantitative subtests (which are the most "g loaded"), whereas scores may actually be decreasing on rote calculation and mental rotation subtests (which are the least "g loaded")**. *Which* people performed better/worse was also not uniform: with gains on abstract subtests primarily coming from the low/middle IQ participants and losses on rote subtests coming from high IQ participants. Thus, this IQ measurement of the current generation is not just higher but fundamentally different from the IQ measurement of prior generations. Finally, single-country studies have shown additional temporal heterogeneity in the Flynn effect: such as a significant increase followed by a significant decrease in a Norwegian cohort (Bratsberg and Rogeberg 2018). Interestingly, these effects were also observed using a within-family analysis, ruling out genetic variation or shared environment as potential causes and further underscoring the likely role of broad environmental changes.

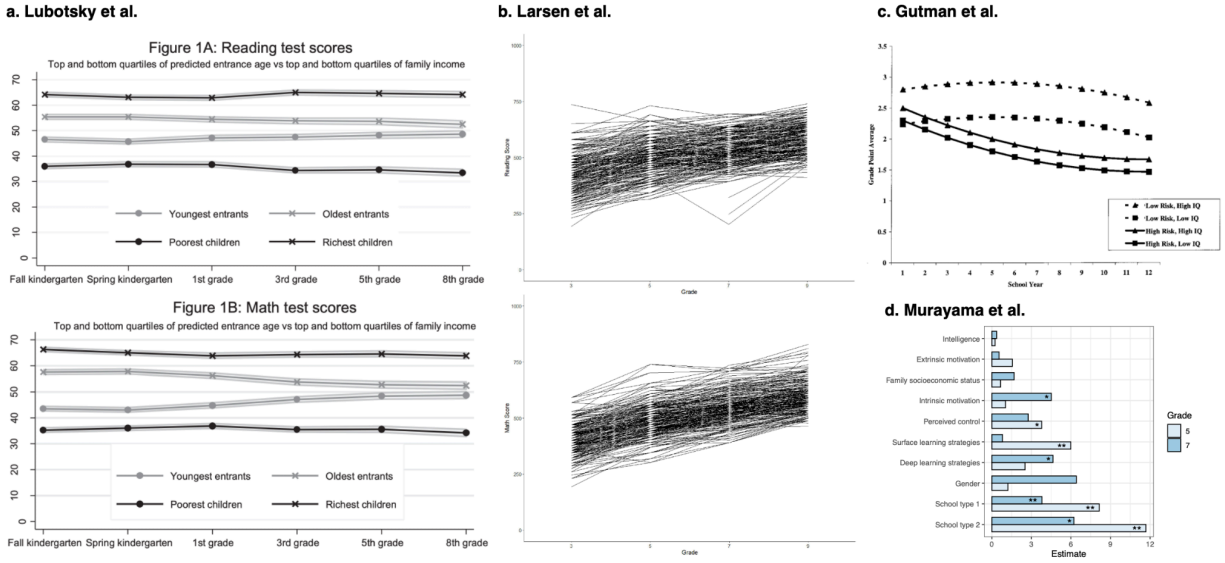
Taken together, these findings suggest a sustained increase in IQ that is consistent with broad cultural shifts acting on different skills in different individuals. As Flynn himself put it: "*society causes the development or atrophy of cognitive skills in terms of its own priorities*".

IQ does not beget more IQ / Matthew Effect

Given the complex patterns of IQ differentiation and longitudinal change, it is worth asking how IQ changes over time *within* an individual. It's commonly assumed that IQ must exhibit a "Matthew effect" where "the smart get smarter" or more precisely, that baseline IQ is also positively associated with increase in IQ per unit of time leading to overall IQ divergence. In fact, **multiple studies have shown the absence of a Matthew effect or even the opposite – a gradual convergence in IQ over the course of learning**. Several are summarized below, focusing on recent studies that used innovative methods or older studies that are highly cited.

IQ/achievement at baseline does not predict growth in achievement

*(**a**) Reading and math test scores converge between kindergarteners who entered young (dot) versus old (x) but do not converge for richer vs poorer children [Figure from (Lubotsky and Kaestner 2016)]. (**b**) Individual growth curves for reading (top) and math (bottom) from 3rd to 9th grade show a negative relationship with starting scores: students with higher scores progressed slower [Figure from (Larsen and Little 2023)]. (**c**) GPA growth curves from 1st to 12th grade stratified on high/low preschool IQ (diamonds vs squares) and high/low environmental risk scores (solid vs dashed) show no longitudinal differences [Figure from (Gutman, Sameroff, and Cole 2003)]. (**d**) Features associated with growth in math achievement from grade 5 or grade 7, IQ assessed at each time point was not significantly associated even though sturdy strategies were significantly associated [Data from (Murayama et al. 2013); **code**].*



A brief summary of these studies:

- (Lubotsky and Kaestner 2016) used age at starting kindergarten as an approximately exogenous cause of variation in initial abilities – with older kindergarteners scoring significantly higher on reading and math tests – and then tracked student performance through 8th grade. Strikingly, while initially the older/higher scoring students improved more rapidly, **after 1st grade the dynamics switched and older/higher scoring students showed consistently slower improvement, such that by 8th grade the two groups were nearly identical in performance on both tests**. No convergence was observed between

richer and poorer students, highlighting the potential confounding effect of family wealth. The use of an exogenous instrument rather than achievement itself also limits potential biases from winner's curse / regression to the mean.

- (Larsen and Little 2023) quantified growth trajectories in two very large Australian datasets of student reading and math scores from 3rd to 9th grade. Again, a convergent negative relationship was observed between the starting score (intercept) and the change in score (slope): **students with higher starting scores were progressing more slowly than their lower scoring peers**. Importantly, the underlying reading/math tests showed high reliability and employed a series of "anchoring" questions to norm the scores across grades and ensure comparability.
- (Murayama et al. 2013) investigated a longitudinal cohort of ~3,500 German students from grades 5th through 10th in their math ability. IQ was assessed (in grade 5 and 7) using a non-verbal reasoning test in addition to a number of school and studying-related factors. Anchoring questions were again used to derive achievement scores that were comparable over time. As expected, IQ (as well as school track) was one of the strongest associations with baseline achievement. However, **IQ had no significant association with growth in achievement**, either at grade 5 or at grade 7. Notably, factors related to learning strategies and motivation were significantly associated with growth in both years, suggesting that the study was statistically powered to identify some associations.
- A highly cited study by (Gutman, Sameroff, and Cole 2003) evaluated verbal IQ and mental health / risk factors in >100 4 year olds and then tracked their academic performance through 12th grade. Notably, children with more risk factors had lower IQ scores, suggesting a significant relationship between these factors even at an early age. While IQ was associated with average GPA, **it was not associated with the change/slope of GPA** (nor with attendance) in a growth model, leading the study to conclude that "*there is no greater acceleration in GPA or number of absences for children with higher intelligence*".

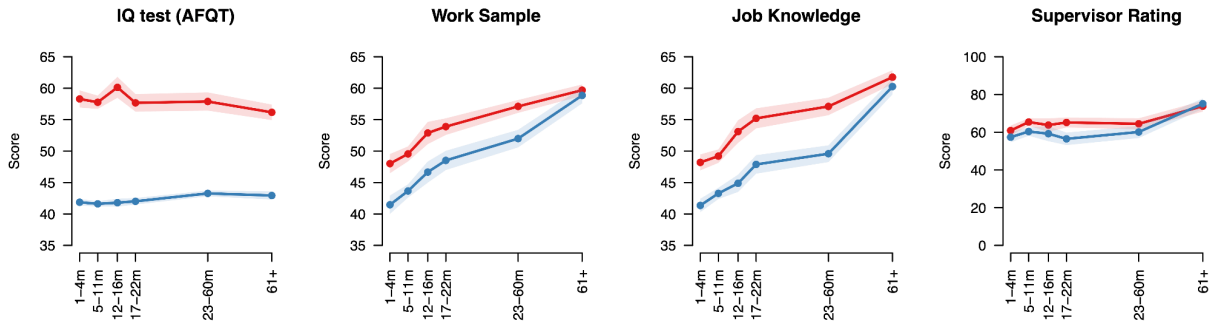
In short, a multitude of different populations, study designs, and statistical models have shown that higher starting IQ/achievement does not lead to an increased growth in cognitive/achievement and may even lead to convergence. Collectively these studies included all ages from kindergarteners through to adolescents and generally employed well established models for comparison of scores over time.

One aspect that all of these studies do share is they are in the academic setting where the school environment may be compensating to limit IQ divergence: for example, if schools systematically invest more resources into helping lower IQ students learn. I'll highlight one more study that investigated the effect of IQ on skill growth in a very different environment. (Schmidt et al. 1988) used data from ~1400 military personnel in four different positions evaluated cross-sectionally over a period of five years. Because this was a military validation study, all participants were systematically tested at entry using the standard Air Force Qualifying Text (AFQT) and evaluated cross-sectionally across multiple different outcomes: work samples simulating specific job tasks and evaluating performance, a formal job knowledge test, and a summarized supervisor rating across 14 dimensions of performance. In this sink-or-swim military environment where individuals are largely developing new abilities, do we see divergence by initial IQ? **Not at all. The study**

found no evidence of divergence on any of the evaluation criteria and, in fact, the participants had nearly converged in their performance after 5 years, even though their IQ test performance was still >1 standard deviation apart (see figure below). Moreover, performance as evaluated by supervisor ratings (arguably the most complete characteristic) was barely different between the high/low IQ groups at the start and actually reversed after five years! Note that this study is quite old and the cross-sectional design may lead to bias towards convergence due to attrition (as the authors discuss). However, recent studies have shown that the relationship between IQ and work performance has, if anything, only gotten weaker (more on this later).

IQ at baseline does not predict divergence in job performance metrics

*IQ test scores for the low/high groups, followed by cross-sectional averages as a function of time on the job. All results plotted as "T-scores" with mean 50 and standard deviation of 10. Data from tables in (Schmidt et al. 1988) was re-analyzed by inverse-variance weighted meta analysis across all job categories [**code**].*



Taken together, these findings raise a paradoxical question: if IQ is not associated with faster development of skills, and developing skills is how one does better academically, why is IQ associated with baseline academic achievement to begin with? Likewise, if IQ is not associated with faster growth in workplace skills, why is it associated with higher baseline workplace skills? One explanation is that IQ reflects very early developmental growth that has effectively plateaued by the time children enter school but continues to act as a fixed offset on academic and workplace achievement. This may be consistent with the finding in (Lubotsky and Kaestner 2016) that high reading/math scoring kindergarteners initially diverged from their classmates but then started converging after 1st grade (see above). **An alternative explanation is that *g* is primarily formed by confounding variables that also influence baseline achievement but not cognitive growth**.

Socioeconomic status does beget more IQ

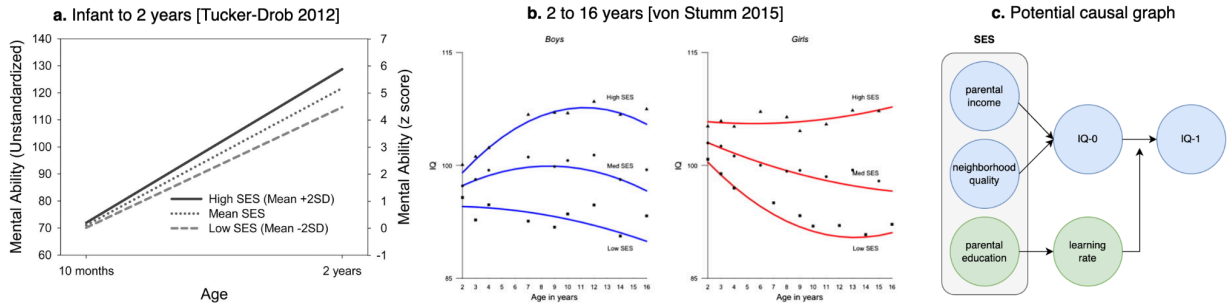
One factor that does appear to be substantially associated with growth in IQ/achievement is, unsurprisingly, socioeconomic status (SES). Using a large cohort of UK twins, (von Stumm and Plomin 2015) investigated the relationship between SES and longitudinal IQ testing. SES was defined crudely, as a simple sum of normalized parental education, occupation, and income; yet this measure was significantly associated with IQ at all ages, with the association increasing over time (from r=0.10 at age 2 to r=0.35 at age 16). In a growth curve model, SES was significantly positively associated with both the intercept and linear slope, **demonstrating that SES can influence the rate at which IQ increases**. On average, children in low SES families started at 6 IQ

points below those from high SES families at age 2 and ended at 15-17 IQ points below by age 16. In a follow up study of the same cohort, a positive relationship between SES and growth in academic achievement was shown even after adjusting for longitudinal IQ itself (which may be reverse causal), (von Stumm 2017) confirming that SES also has meaningful downstream effects on academic growth independent of IQ. Though cognitive ability prior to age 2 is hard to evaluate and even harder to define, (Tucker-Drob et al. 2011) showed that SES is also associated with growth in mental ability from 10 months (where there is no association with SES) to 2 years (where the association with SES is already highly significant). **Taken together, these studies show how SES emerges as a major driver of cognitive growth during the highly sensitive early age period** (see next).

How can we reconcile the fact that SES is associated with both baseline IQ and with IQ/academic growth but baseline IQ itself is not associated with IQ growth? Since SES is a crude composite of multiple factors, one simple explanation is that some components influence baseline IQ only and others influence IQ growth/learning rate, and the effect of the latter on baseline IQ is small (see schematic in [**c**] below). In other words, the focus on cross-sectional IQ measurements may be zeroing on the least important features of cognitive development.

Socioeconomic status predicts IQ growth and divergence across the early life-course

(a) *Significantly faster growth in mental ability from 10 months to 2 years. Figure from (Tucker-Drob et al. 2011).* ***(b)*** *Higher SES is associated with faster growth / slower decline in IQ in both boys (left) and girls (right). Figure from (von Stumm and Plomin 2015).* ***(c)*** *One potential casual graph where SES is a composite of factors that influence baseline IQ (IQ-0) and other factors that influence the learning rate, but IQ-0 does not influence the learning rate.*



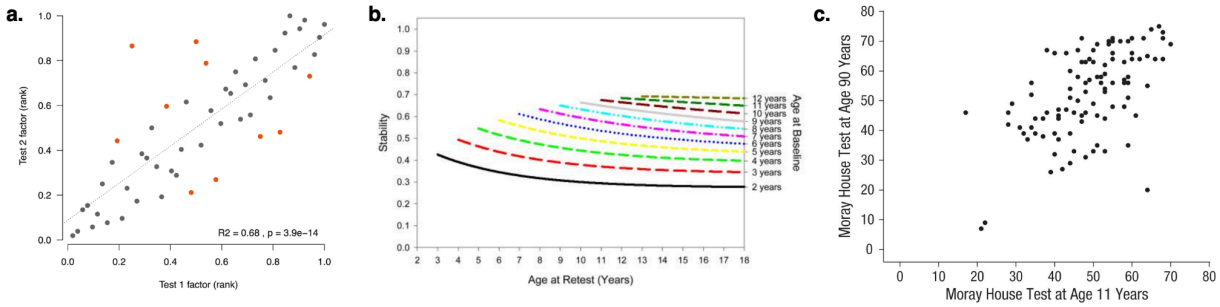
IQ in adulthood is consistent but may be influenced by motivation

Finally, we can ignore the complexity and simply ask how the rank of IQ or general factor scores changes over time, and this rank ordering indeed appears to remain moderately stable. Over the short term, (Fawns-Ritchie and Deary 2020) collected IQ test measurements using the UK Biobank battery on 52 individuals who retook the test ~30 days apart. The overall correlation of the general factor was high (r = 0.82), however some individual level changes were still notable: 20% of individuals changed their rank by at least 10/52, including one individual that went from 13/52 (bottom 25%) to 45/52 (top 15%). Over the longer term, (Tucker-Drob and Briley 2014) fit models to the relationship between age and IQ test stability in a large (N>10,000) meta-analysis of retest data. **Overall phenotypic stability was moderate (r = 0.49) with low levels in infants (r = 0.3) increasing to high levels in adolescents (r > 0.7)**. Finally, these estimates are broadly aligned with a *very* longitudinal study in the Lothian Birth Cohort, which has tracked individual IQ

tests from age 11 through age 90. The correlation from age 11 to age 65-79 was 0.63 using a general factor and 0.67 using the same test (Deary et al. 2012). The correlation from age 11 to age 90 was 0.54, and down to 0.45 after removing outliers (Deary, Pattie, and Starr 2013). Ironically, the lowest scoring individual at age 11 scored roughly in the middle by age 90, an anecdotal example of how substantially IQ can change through the lifecourse. Notably, no association was observed between baseline age 11 IQ and the rate of cognitive decline in a growth model (Gow et al. 2011), **implying that low IQ is not associated with a faster decline in old age, just as high IQ was not associated with faster increase in IQ in adolescence**.

Retest and age stability of IQ and the general factor

*(**a**) Retest correlation of the general factor in the UK Biobank. Data from (Fawns-Ritchie and Deary 2020). (**b**) Stability of the general factor as a function of age (model fit from a growth model). Figure from (Tucker-Drob and Briley 2014). (**c**) Lifelong stability of IQ. Figure from (Deary, Pattie, and Starr 2013).*



Finally, one can ask how the testing environment itself influences test performance. Work in this area has been surprisingly limited. (Duckworth et al. 2011) meta-analyzed several fairly old interventional studies of motivation/incentives on IQ test performance, where individuals were effectively bribed to do better on the test. **A significant relationship between motivation and performance was observed (Hedge's g=0.51) with the effect nearly double in lower IQ groups (Hedge's g=0.94)**; meaning that incentives increased IQ scores by nearly a full (pooled) standard deviation in lower IQ groups. For example, two studies gave participants "tokens" for each correct answer (which could then be exchanged for prizes) and showed mean performance increases of 12 points (Devers, Bradley-Johnson, and Johnson 1994) and 8 points (Blanding et al. 1994) relative to a control group. The effect on performance also exhibited a dose-response relationship with larger incentives leading to larger increases. **However, it's worth noting that this meta-analysis is mostly a provocative curiosity, as the underlying studies were sometimes of low quality**: small, conducted by a limited group of investigators (thus potentially susceptible to shared biases or data issues), and decades old. Given that research-based IQ tests are often administered in a low-motivation setting, the extent to which motivation may be a separate and confounding process remains an important question to disentangle.

6.5 | Empirical evidence for theories of the positive manifold

Which theory best corresponds to the true IQ test process is an ongoing debate. I will not attempt to summarize all of the research in this area but I will highlight a few examples that provide face validity to different theories.

Longitudinal analysis

Since mutualist models make predictions about the longitudinal dynamics of the positive manifold and cognitive function more broadly, the most direct support can come from longitudinal analyses of cognitive test performance. Specifically, gains in one domain would be expected to propagate through to other seemingly unrelated domains; whereas g theory would indicate that only gains on g itself can propagate through to other specific abilities.

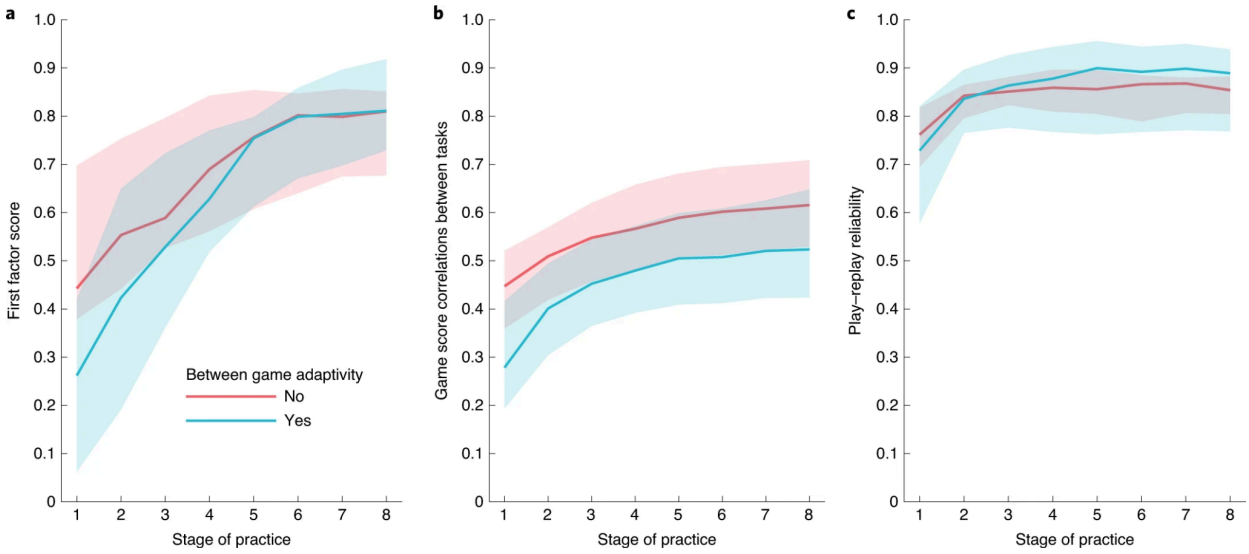
- (S. J. Ritchie, Bates, and Plomin 2015) used a "cross-lagged" twin design where reading and IQ were evaluated repeatedly over ages 7, 9, 12, and 16: reading differences at earlier ages were associated with gains in IQ at later ages. Importantly, in addition to being associated with the general factor, **reading was directly associated with gains in non-verbal IQ subtests** (picture and matrix completion), consistent with gains in one process cascading into broader gains on other processes. The unique identical twin design allowed this study to control for both genetics and shared environment, meaning that the effect of reading was environmental and potentially intervenable.
- (Kievit et al. 2017) investigated three different models using longitudinal data from ~500 participants who evaluated for Matrix Reasoning and Vocabulary over a gap of 1-2.5 years. The two tests were intended to capture fluid (general) and crystalized (knowledge-based) domains. The change in scores in each domain was then modeled as the sum of a "self-feedback" process parameterized by the previous score in the same domain and a "coupling" process parameterized by the previous score in the other domain. This framework was then used to evaluate three models: (1) a single latent factor that influenced both domains and the change in both domains (i.e. a g-like model); (2) a unidirectional "investment" model where fluid (i.e. Matrix) abilities influence the gains in the crystalized (i.e. Vocabulary) domain but not the other way around; (3) a bidirectional/mutualist model where improvement in a given domain depends on prior ability in the same domain and also prior ability in the other domain. **When applied to the data, the mutualism model provided a substantially better fit (RMSEA of ~0) than either the g factor (RMSEA of 0.11) or investment (RMSEA of 0.10) models;** which was also confirmed by an approximate likelihood comparison and a nested model test. Both "coupling" parameters in the mutualism model were positive: with Vocabulary having a moderate association with growth in Matrix Reasoning and Matrix Reasoning having a small/moderate association with Vocabulary. Interestingly, this relationship is the exact opposite predicted by the "investment" model.
- In a follow up study, (Kievit, Hofman, and Nation 2019) applied the same models to new data from three waves of testing across a much younger cohort. **Again the mutualist model provided a better fit to the longitudinal data (RMSEA of 0.03) compared to the g factor (RMSEA of 0.21) or investment (RMSEA of 0.13) models. Moreover, the "coupling" parameter was substantially higher in this younger sample than in the previous analysis of adolescents**, with the cross-domain effect of vocabulary on matrix reasoning again stronger than the effect of matrix reasoning on vocabulary. This increase in coupling in younger individuals had been hypothesized in the prior study. An alternative statistical methodology where the intercepts of one domain influence the slopes of the

other domain (akin to a growth model) also showed significantly better cross-domain than within-domain fit: i.e. mutualism provided a better model than a within-domain "Matthew effect". To evaluate whether the mutualist model was potentially "overparameterized" and could provide a better fit regardless of the generative process, the authors simulated 1,000 studies from a g theory process and showed that the g factor model was, correctly, preferred in 99.9% of them. Thus, the study was sufficiently large to identify a general factor model if it was the underlying cause (at least in simulation).

- The authors propose several of possible interpretations of the coupling effects observed in the data: (i) better vocabulary directly helps in developing the ability to decompose problems, which translates into more efficient Matrix Reasoning; (ii) better vocabulary matches individuals into environments (e.g. advanced classes) where they also end up developing ability in other domains (gene-environment interplay); (iii) or that Matrix Reasoning is itself indexing components of both fluid and crystalized abilities. **Even though the mutualist model was able to explain the longitudinal data significantly better than other models, one should still be cautious about interpreting these relationships causally**. (Sorjonen et al. 2023) recently noted that covariate adjustment and regression to the mean can induce non-causal, statistical associations between domains. The converging evidence in (Kievit, Hofman, and Nation 2019) employing multiple statistical models suggests their findings are robust to covariate adjustment but formal causal analysis is still needed.
- (Steyvers and Schafer 2020) used a unique dataset that highlights how this line of research may move towards more granular longitudinal measurements. Rather than using conventional IQ/achievement tests, they used data from *Lumosity*, a brain games/training website, encompassing ~36k users and ~50M plays. The games broadly mimicked the cognitive domains indexed by IQ tests and, in a factor analysis, exhibited a general factor correlated with doing well on all games (as well as five additional "specific" factors). **Interestingly, the general factor was low for initial players and eventually doubled in magnitude as participants progressed through more games (see figure below)**. This pattern is consistent with mutualism/process overlap theory, where improving in one area leads to improvement in all areas. Importantly, while a progressive increase in the general factor mimics the age dedifferentiation observed in development (see above), here it was observed in the setting of a specific intervention: **demonstrating that environmental inputs can lead to a cascade of cross-task gains and produce an increase in the positive manifold**.
- See (Kievit 2020) for additional examples of coupled/bidirectional relationships observed in prior studies, including those that did not explicitly contrast factor versus mutualist models.

A cognitive intervention leads to an increase in the general factor

(a) The general factor score increases as individuals progress through more stages of practice in brain training games. (b) Same but shown as correlation across different cognitive tasks. (c) Demonstrating that game reliability does not change substantially enough to explain the observations in (a,b). In all instances, games are split into those with "adaptive" (blue) and fixed scoring. Figure from (Steyvers and Schafer 2020).

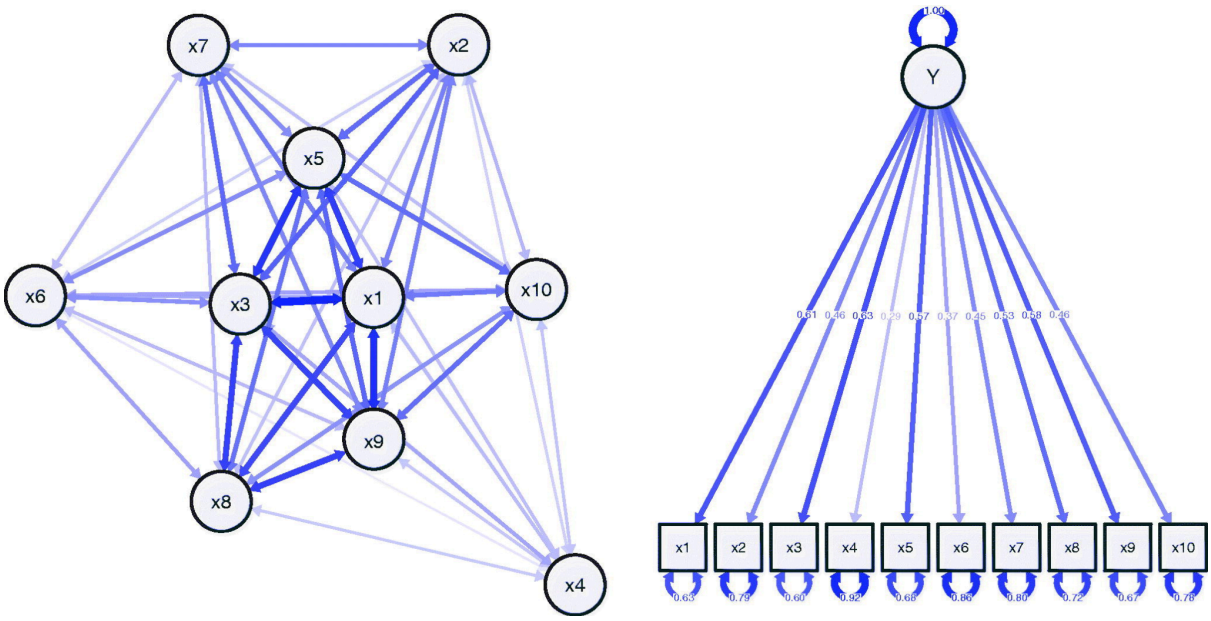


Cross-sectional analysis

Perhaps the most commonly deployed but also the *weakest* approach to evaluating competing theories is quantifying their fit to static or cross-sectional data (i.e. data measured across individuals at a single point in time). This approach is "weak" for several reasons. First, completely different models can often provide equally good fit to the data (see figure below for an example of unidentifiable factor and network models from (Fried 2020)). Second, models must be evaluated (confirmed) in an independent dataset from where they were constructed (explored) and ensuring dataset independence is not trivial if similar biases/artifacts are present in multiple studies. Third, evaluation of model fit requires a predefined model likelihood or loss function which can bake in some of the assumptions the theories are attempting to evaluate (i.e. the error process). Fourth, we can never test all possible models and thus even the best fitting model we've identified may be severely suboptimal relative to some other model we did not explore.

Two completely different causal models with equivalent factor goodness of fit

Ten tests simulated from either a network model (left) or a single factor model (right) that produce statistically indistinguishable goodness of fit. Figure from (Fried 2020)



With all of that said, if a model produces consistently poor fit to the data then some kind of explanation is warranted. So how have the various models of IQ held up? Network/mutualist models have now demonstrated superior fit over factor models in independent data in multiple studies. In some instances, network models also provide meaningfully different interpretations of IQ test data, highlighting how models matter:

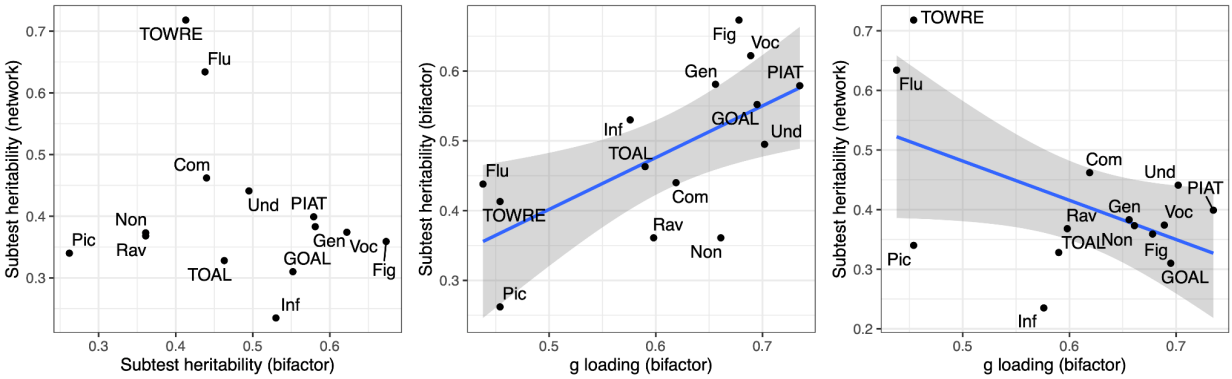
- (Kan, van der Maas, and Levine 2019) compared network models to two factor models, a hierarchical g model and an oblique (no g) model, IQ test data from three different cohorts. **The network model provided a substantially better fit than the factor models to large-scale WAIS IQ data in-sample (RMSEA of 0.02 versus 0.07)**. Simulations were then employed to show that the network model was never preferred if the underlying generative process was one of the factor models, suggesting that improved fit was not simply a consequence of more flexibility in the network model. In a second sample with individual-level data, the network model was fit on one half of the data and confirmed on the other half, again showing superior fit to the factor models (RMSEA of 0.08 vs 0.12) with fewer free parameters. In a third cohort measured over multiple age groups, the factor model did not provide an acceptable fit at all while the network did and demonstrated age-specific differences in network relationships.
- (Kan et al. 2020) compared network and factor models in two WAIS IQ datasets from different countries. Models were fit to data from the US and then confirmed in independent data from Hungary. **Again the network models explained the held-out data better than factor models (RMSEA of 0.037 versus 0.056 for a hierarchical g model)**. Better network model fit in this same data was independently replicated by (Schmank et al. 2019).
- (Knyspel and Plomin 2024) compared network models with factor models in a large sample of twins across a wide range of cognitive tests. A network model provided a substantially better fit to the data (RMSEA of 0.014) than a bifactor model (RMSEA of

0.049) or a single-factor g model (RMSEA of 0.10). Notably, when evaluating genetic correlations through twin comparisons, multiple significant and negative partial correlations were observed: with some pairs of tasks exhibiting opposite genetic effects after conditioning on the rest of the network. **These negative partial correlations imply that the "first order" positive manifold may be burying more complex negative relationships between tasks**. Estimates of twin "heritability" and the relationship to the general factor g loadings were also substantially different between the network-based and factor-based analysis. In fact, general factor g loading correlated most strongly with the *difference* between factor model and network model twin "heritability" factors, indicating that the subtests that share the most variance are also the ones with the greatest disagreement in familial relationships inferred by the two models (see figure below).

- **In short, though goodness of fit is a *weak* test, mutualist models have yielded a better fit to the data in multiple IQ studies, exhibit identifiability in simulations, and provide substantially different interpretations of twin-based estimates.**

Completely different relationships between twin "heritabilities" and loadings estimated from factor and network models

*(**left**) Relationship between bifactor model and network model twin additive genetic variance estimates from twins. (**middle**) Relationship between bifactor model general factor loading (x-axis) and bifactor model additive genetic variance estimates from twins. (**right**) Relationship between bifactor model general factor loading (x-axis) and network model additive genetic variance estimates from twins. Data from (Knyspel and Plomin 2024) [**code**].*



Brain neuroimaging / "neuro-g"

Several studies looked for evidence of g theory in neuroimaging data on structure (matter volume), function (regional activity), or connectivity (regional co-activity). This is, to some extent, a chicken-and-egg problem since neuroimaging suffers from similar issues of construct validity: it is hard to know what different imaging modalities are measuring and most analyses rely on simple correlations (in particular, it is very difficult to know how to model error and uncertainty in the neurological measurements). **The one consistent finding across studies is that nothing like a "neuro g" is observed in the data: structural data does not form a unidimensional latent factor mapping to IQ nor do structural correlations from different test batteries strongly overlap; network models generally fit the relationship between connectivity data and IQ tests best; and studies of focal brain injuries show local rather than general effects**. Disparate secondary

findings can be interpreted as evidence against essentially every major theory, underscoring the chicken-and-egg problem. Some representative studies are summarized below, focusing on their hypotheses.

- **Multiple studies have ruled out a simple structural "neural g" by demonstrating that neuroimaging data does not fit well under a general factor model**. (Kievit et al. 2012) fit various latent variable models directly to structural MRI data and IQ data from 80 participants. They showed that a "biological g" model where a single general factor was causal for both the structural imaging and IQ data did not fit the data at all, concluding that "*for this data set, neurological measurements cannot be considered measurements of g*". Nor did the data fit well under a model with a single separate neurological general factor: "*despite the fact that these measures correlate independently with g, they do not intercorrelate positively*". The best fitting model was one where the latent general factor was an aggregate of multiple structural neuroimaging components (with both positive and negative loadings), which was then measured by the IQ test: "*we can consider neurological measurements to jointly predict a unidimensional g, although they do not themselves form a unidimensional scale*". (Haier et al. 2009) investigated a "neural g" hypothesis by comparing structural MRI and the general factor from 40 and 40 individuals measured with two different IQ tests respectively. If *g* is an index of a general underlying process, then estimates of *g* from different tests should be correlated with structure in the *same* parts of the brain. While general factor values were significantly correlated with various measures of structural gray matter, the authors concluded that the overlap between the two test groups was limited: "*the limited overlap is contrary to the prediction based on the presumed equivalence of g-factors*". This lack of overlap is further complicated by findings that structural (volume) and functional (activity) measurements also do not overlap in their correspondence with intelligence (Basten, Hilger, and Fiebach 2015), indicating heterogeneity even within the neuroimaging modalities.

- Another hypothesis is that regional "connectivity" in the brain (i.e. the correlation of activity between regions) should mirror the correlation structure implied by different IQ test theories. To this end, (Anderson and Barbey 2023) investigated static functional "connectome" data measured at resting-state followed by IQ testing in ~300 participants. They found that global network models of the connectome data were as good or better than local models in predicting the general factor and were more robust/reliable, **suggesting that network interactions between multiple brain regions may better reflect the underlying cognitive processes**. (Soreq et al. 2021) analyzed dynamic fMRI measured during a series of short cognitive tasks from 60 participants, finding that correlated activity in the data was consistent with network/sampling theories: each IQ subtest was correlated with activity in multiple different but overlapping brain regions; pairs of IQ subtests that were correlated also showed correlated patterns of brain activation/connectivity; **network connectivity models provided high task classification accuracy (i.e. which task was being tested); and dynamic network models (additional modeling changes between test/rest periods) were even more accurate**. It's worth reiterating that lack of theory for the fMRI data and the employment of highly complex models makes it difficult to draw clear conclusions from these results, which are

essentially model fitting exercises. Still, they show that both the general factor and individual IQ subtests are correlated with global co-activity throughout the brain and are at least plausibly consistent with network models of intelligence.

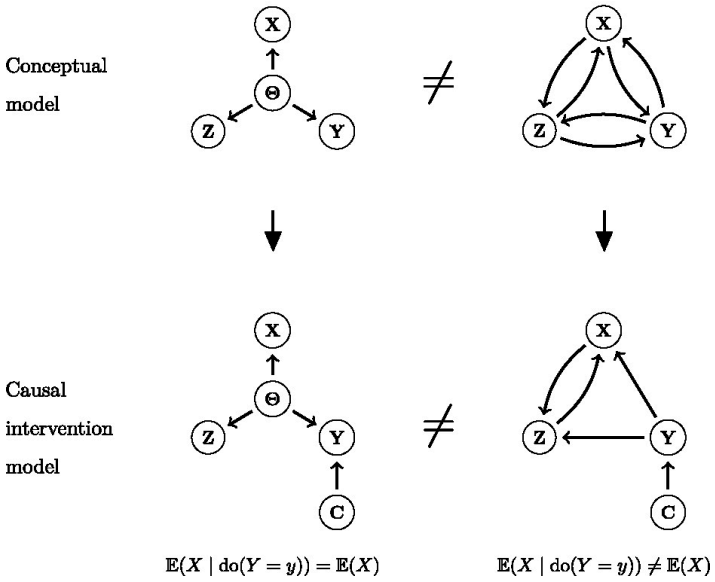
- In contrast to the above correlative studies, (Protzko and Colom 2021) sought to use brain damage as a causal instrument to investigate cognitive theories. Sampling theory may imply that focal brain lesions only influence a small number of tasks (assuming only a small fraction of the underlying "bonds" is impacted); network theory may imply that focal brain lesions should translate to broader cognitive deficits over time (assuming a highly mutualist network node is impacted); g-theory may imply that a focal lesion should either translate into highly specific task deficits or broad cognitive deficits (depending on whether the lesion impacted the neurological cause of a specific or general ability). To some extent, the prediction from each theory rests on a circular assumption about the function of a brain lesion. Nevertheless, Protzko and Colom surveyed the literature and found that **focal brain lesions generally have highly local effects**. For example, damage to the brain that leads to worse impulse control does not tend to translate into lower vocabulary/reading ability. **This lack of propagation contradicts certain mutualist and hierarchical factor theories, which would predict that damage to one ability eventually propagates to others; but could be consistent with sampling theory or g-theory (under the above assumptions)**. They additionally find evidence of "cognitive reserve", where higher IQ individuals are better able to mask the effects of the lesions on specific tasks, which also contradicts certain hierarchical factor theories. The authors note, however, that a key test of dynamic mutualism would include data from affected children followed over a long period of time, but this data was largely unavailable in the literature (in fact, most studies specifically excluded children). Additionally, ability differentiation (i.e. the observation that lower IQ individuals have "more g") suggests that cognitive deficits may function fundamentally differently (and more "g like") than cognitive gains, and it may thus be the case that brain damage is not informative of brain development. In short, while findings from brain lesions provide some evidence against a mutualist model of cognitive decline in adulthood, they rest on a large number of assumptions that remain mostly unexplored.

Interventional analysis

Perhaps the one study design that's even better than longitudinal measurement is longitudinal measurement with a randomized intervention. Intervention presents an opportunity to investigate how IQ tests respond to a specific and unconfounded cause and can distinguish between theories that are otherwise identical in cross-sectional data (see figure below). Interventional studies are, unfortunately, extremely rare or highly task-specific (such that they tell us little about general processes). (Stine-Morrow et al. 2024) recently conducted such a study and summarized the prior state of the field thusly: "*Oddly … intervention studies examining the effects of skill training or the introduction of new everyday activities often rely on pretest-posttest designs without longitudinal follow-up, so that they are not actually designed to detect mutualistic effects. With one-shot measures of performance at posttest, any generalization to a novel task would have to occur on the first exposure to the task.*".

Two different conceptual models that can be resolved through interventional study

(left) A factor based model that predicts an intervention [C] on [Y] will not influence [X]. (right) A network based model that predicts an intervention of [C] on [Y] will first influence [X] and [Z] and then propagate between [X] and [Z]. Figure from [(Marsman et al. 2018)].



To address this gap, **Stein-Morrow et al. designed a clever study to evaluate whether cognitive training regimes corresponding to specific theories resulted in more substantial gains**. The study consisted of a randomized Phase 1 with different training approaches applied for 10 days, followed by a Phase 2 focused on a specific skill (the "target skill", which aimed to develop working memory or the ability to simultaneously process and store information) applied for 10 days, followed by a posttest IQ evaluation 2 weeks later (which included an evaluation of working memory). In Phase 1, participants were randomized into four groups: (1) a "different mixed" group where participants practiced two reading/memory related tasks that were different from the Phase 2 target skill; (2) a "different single" group where participants practiced one reading/memory related task that was different from the target skill; (3) a "same single" group where participants practiced one reading/memory task that was the same as the target skill; (4) and a placebo control group where participants practiced a task that did not involve memory at all. Then they quantified how quickly each group developed the target skill in Phase 2 and working memory in posttesting.

What would different theories predict here? General factor theory (or "direct transfer" in the paper) would predict that training a specific task only produces gains on that task and does not "flow up" to general gains, thus only the "same single" group should exhibit improvements in working memory (i.e. the group that only trains working memory through both Phase 1 and Phase 2). Mutualism theory would predict that training one skill translates into gains on other skills and so the "different mixed" group (which trains multiple different skills) would do as well as the "same single" group (which trains the target skill), and the "different single" group (which trains fewer different skills) would land somewhere in between. Mutualism would additionally predict that the advantages of the different groups would develop over time, as these skills cascaded into other skills. What did the study find? **Surprisingly the only group that had a significant**

increase in the posttest result was the "different mixed" group: individuals who trained two different memory related tasks in Phase 1 which were not the target task! While this result is clearly more consistent with mutualism than with g-theory, it is in some sense a deviation from all theories: different mixed training didn't just match pure target skill training, it exceeded pure target skill training. 10 days of "priming" with diverse skills followed by 10 days of target skill development was thus even more effective than 20 days of target skill development! A secondary finding of the study was that, in Phase 2 (target skill development), the "different mixed" group lagged behind the other groups in the first day but then caught up in the second day. This may also be consistent with a mutualist model where gains on diverse tasks take time to translate into gains on other tasks (though mutualism does not make specific predictions about the timing of such skills transfer). In short, a cognitive training intervention exhibits mutualist patterns where training diverse skills transfers into bigger gains on untrained skills. While this is just one study and needs to be replicated/expanded, it "*challenges the imagination*" as noted by the authors, and is a compelling model for future experimental studies of cognitive theories.

6.6 | Putting it all together

So what does IQ measure? The short answer is that IQ measures your performance on a battery of tests; people who do poorly on one test tend to do poorly on many of them, whereas people who do well on average tend to excel in one or a small number of domains. The g-factor score is simply a re-weighted average of the IQ score where the weights ("*g* loadings") closely correspond to how culturally-specific the test tends to be (higher weight for vocabulary, lower weight for number recall, for example). It should then be no surprise that in societies where culturally-specific knowledge correlates with success, *g* scores will also correlate with success (and all the things success correlates with) since that is exactly what *g* is indexing.

What is the process that causes variation in IQ/g scores? **The one thing that is clear is that IQ/g does not behave at all like a single latent process**. In fact, multiple lines of evidence indicate that IQ/g scores estimate and sum a complex patchwork of disparate processes. First, the neurological basis is highly heterogeneous: IQ correlates with structure and function in many different parts of the brain; measuring IQ/g with different test batteries leads to limited overlap in structure/function; and yet focal brain damage in adults only tends to impact single cognitive domains, indicating some amount of compartmentalization. Unsurprisingly, dynamic network models often provide the most accurate fits/predictions of the relationship between neurological measurements and IQ scores, but this is really just a restatement of the fact that neurological patterns are not explained by simple latent variables. Second, as individuals age the correlation across their scores increases and both longitudinal and (limited) experimental data show that past performance in one domain translates into future performance in another. This is again consistent with complex interactions between domains, where the underlying processes that IQ scores measure are changing dynamically within each individual.

IQ also cannot be intuitively interpreted as "mental energy" akin to an engine, **because baseline IQ is not predictive of either the rate of cognitive growth or the rate of decline in old age**. If two car engines are operating at different speeds then the gap between the cars will grow, but

the IQ gap between two individuals with different IQ scores does not grow. Rather, higher IQ is more like one car getting a head start while otherwise operating at the same capacity. This is also in direct contrast with socioeconomic status (SES), which is both correlated with IQ at baseline and the growth in IQ. This could be explained by having more opportunities to identify and develop specific abilities that one excels in (also explaining ability differentiation), or more opportunities not to let one ability drag the others down (see [**5.7**]). Thus, SES factors (and surely other factors) act as persistent confounders on the IQ measurement by modulating the rate at which individuals learn how to improve their IQ score. Finally, IQ growth is also observed at the societal level, with increasing scores across countries and time-periods, particularly in the young adult period where learning and cultural exposure is most intensive. The patterns of growth are themselves complex, with the latent nature of IQ in a given population also likely changing over time.

Cross-sectional IQ score is thus indexing a bundle of multiple different and confounded processes: population-level heterogeneity via ability differentiation, past individual-level growth via confounding by SES, and societal-level growth coupled with latent change via the Flynn Effect. To return to the car analogy, we are attempting to learn how an engine functions by observing the relative position of cars in a photograph of a race, while uncorrelated and unknown external factors make certain cars go faster than others and the cars farther ahead drive fundamentally differently than the ones behind. **In short, there is no good reason to think that IQ scores are more *causal* or *biological* than any other social achievement index (EA, SES, material deprivation, etc) and are in fact likely to be confounded in ways that are even more complex to disentangle.**

6.7 | Further reading

IQ theories:

- (Bartholomew, Deary, and Lawn 2009) : Sampling theory and connections to the general factor.
- (van der Maas et al. 2006), (Van Der Maas et al. 2017) : Perspectives and reviews of dynamic mutualism and network models.
- (Dickens and Flynn 2001) : Perspective and gene-environment correlation theory of the Flynn Effect
- (Savi et al. 2019) : Review and historical perspective on multiple IQ theories.
- (Kievit 2020) : Review of coupled/mutualistic relationships between IQ subtests.
- (Protzko and Colom 2021) : High-level overview of multiple competing IQ theories in the context of brain lesion studies.

Methods:

- (Borsboom et al. 2021) : Primer on methods for network psychometrics.
- (Knyspel and Plomin 2024) : Example of network psychometrics applied to twin data.

Commentary:

- (Fried 2020) : Perspective on the need for strong theories
- (Conway et al. 2020) : Commentary and response to Fried 2020
- (Deary and Sternberg 2021) : Discussion between Ian Deary and Robert Sternberg about the history of IQ research, the relevance of theories, and how IQ relates to intelligence.

Genetic variation within and between groups

Concepts: Drift and Selection

8.0 | Read these books instead!

The goal of this section is to provide a crash course of population genetics concepts needed to read and understand studies of groups and group differences. The focus will therefore be on the most relevant processes: weak additive and polygenic selection in human-sized populations over the relatively recent period in human history (<100,000 years). But population genetics is a very rich field with a number of thrilling historical developments and colorful personalities and to understand the field one really needs to study it comprehensively and from foundations. It also bears mentioning that (spoiler alert) not much interesting evolutionary development has happened in recent human history, and thus some of the most fascinating aspects of evolutionary biology – which occur over much longer time scales and often between species – will not be covered here. To that end, I recommend a number of excellent *foundational* resources (many of them free):

- **Coop – Population and Quantitative Genetics** [free]: Thoroughly covers the fundamentals of genetic variation, the coalescent, mutation, and selection with many inter-species examples.
- **Pritchard – An Owner's Guide to the Human Genome** [free, in progress]: More brief but more human-focused treatment of genetic variation and selection, going all the way through to human disease and GWAS.
- **Hartl & Clark – Principles of Population Genetics** [not free, ebook]: A classic pop gen textbook that covers the principles of genetic variation as far as modern genomic studies but stops before the GWAS era.
- **Walsh & Lynch – Evolution and Selection of Quantitative Traits** [not free, available in print or pdf]: A remarkably comprehensive, almost encyclopedic, overview of evolutionary genetics with detailed derivations and examples for nearly all commonly used models.
- **Holsinger – Population Genetics Interactive Apps** [free]: A number of interactive R-Shiny apps for visualizing various processes in population genetics.

Lastly, code for generating all of the original figures in this section is available in an **open source repository** and are also linked in each figure legend.

8.1 | Summary

- **Common variants are very old**. The average neutral polymorphism is estimated to be ~13,000 generations old (~390,000 years) and variants with >1% minor allele frequency are expected to be older, in most cases *much* older, than the migration out of Africa (Rasmussen et al. 2014).
- **Variance due to neutral population differentiation (i.e. genetic drift) is very limited since migration out of Africa**. A 5% allele will have accumulated approximately 1% drift variance, a 50% allele approximately 5% of drift variance (Waples 1989).
- **A fundamental measure of genetic drift is F_{ST}**, which is informally defined as the correlation of random alleles within a subpopulation relative to the correlation of random alleles in the "total" population at a single site (Wright 1951). F_{ST} has a relationship to population size, divergence, and migration under very strict demographic assumptions but **an infinite number of demographies can produce the same F_{ST}**.
- Formally, F_{ST} has been derived in two ways – Nei's F_{ST} and Hudson's F_{ST} – which can differ substantially in real data (Bhatia et al. 2013). F_{ST} also depends strongly on the variants used to estimate it, their frequencies in the contemporary and ancestral populations, and the number of populations being analyzed (Alcala and Rosenberg 2022). **Thus F_{ST} is a fundamentally sample-specific parameter.**
- Under neutrality, **the group difference in a polygenic trait is bounded by the product of (Hudson's) F_{ST} and the trait heritability** (Edge and Rosenberg 2015b). For divergent continental populations (e.g. African/European) this is expected to be <1.5% of trait variance for a typical trait with 10% h2g.
- **Realistic weak directional (i.e. positive/negative) selection is not sufficient to substantially alter allele frequencies between populations.** Under estimates of a

selection coefficient of $s=10^{-4}$ observed from disease GWAS, all common variants are expected to remain common after only ~2,200 generations (65,000 years).

- For stronger selective coefficients ($s>10^{-4}$) sample sizes of ~100's **are well powered to identify differential selection between populations** (Waples 1989). In contrast, very weak selection is "effectively neutral" and cannot be distinguished from random drift.
- Expected frequency changes since the African migration are **even slower under stabilizing selection** (selection for a specific fitness optimum) than under directional selection, which is a likely form of selection on common complex traits. Paradoxically, **stabilizing selection increases the apparent differentiation at fitness-influencing variants** even if the trait optimum is identical between the populations (Yair and Coop 2022).
- Stabilizing selection under shifts in the fitness optimum behaves in phases: a rapid phase of directional selection, and then a gradual phase of drift and the purging of genetic variation. **Variants that fix after the new fitness optimum are largely arbitrary** (Hayward and Sella 2022)**.**
- Under stabilizing selection, **genetic differences between groups can either be a reflection of a difference in fitness optimum or a difference in the environment under the same fitness optimum** (Harpak and Przeworski 2021). Group differences must therefore be interpreted in their environmental context.
- We can alternatively think of heritability as a parameter that defines the phenotypic response to selection in a controlled breeding experiment (i.e. The Breeder's Equation), and **controlled selection experiments have produced highly stable and predictable responses**.
- In contrast, **there are many examples of selection on natural animal populations which elicited no response or even a negative response** (Pujol et al. 2018). Quantitative modeling of these populations has identified potential causes such as bias in the heritability estimates, environmental confounding of the fitness trait (i.e. the wrong trait is being selected on), and complex shifts in the environment. **The apparent stasis in response to selection in animals underscores the challenges of quantifying evolutionary parameters related to heritability and selection**.

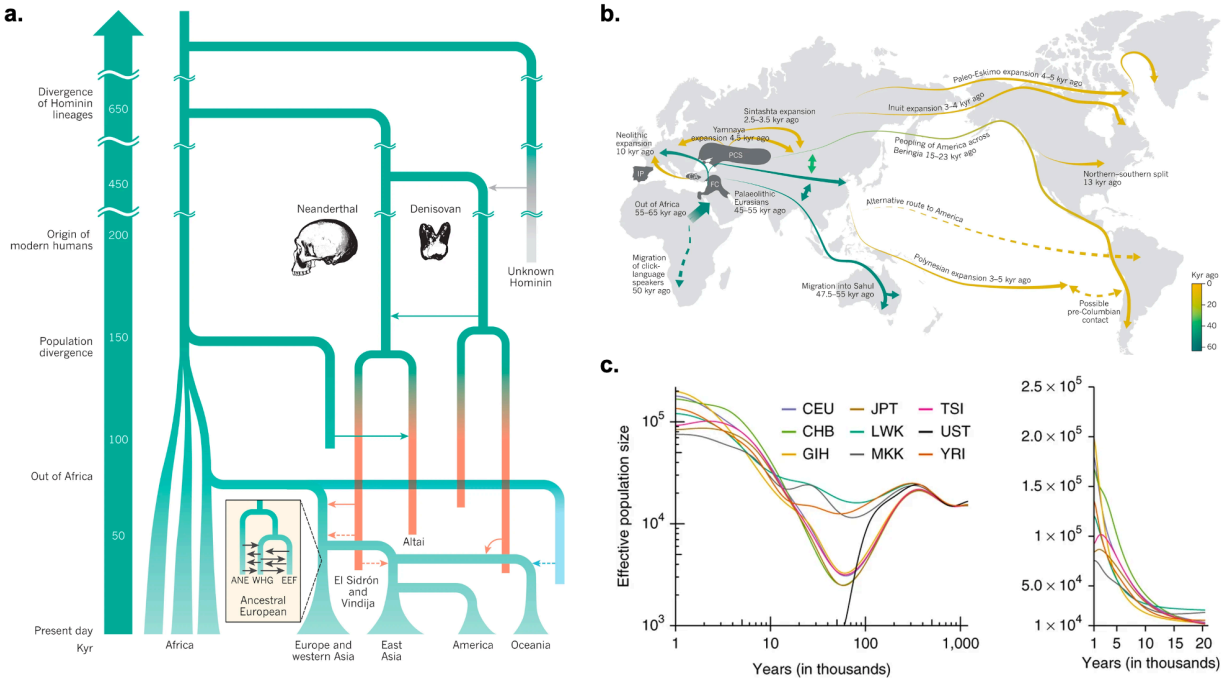
8.2 | Populations in time

Most population genetics models are derived in terms of free parameters, which makes them highly flexible and generalizable but also somewhat abstract relative to real world phenomena. To make these models more concrete we will fix three specific parameters to their approximate real world values: generation **time**, population **size**, and the **selection** coefficient. All of the relevant notation and parameters used in this section are provided below, and we will then derive and justify each one:

t	Time (in generations)	2,100
N_e	Effective population size	10,000
s	Selection coefficient	0.0007
p	Minor allele frequency	
q	Alternate allele frequency	
m	Migration	

The first key parameter is **time**. The figure below (panel **a**) provides an overview of modern human lineages, including extinct lineages from which only ancient DNA is available. The time we will primarily focus on is the period after the African migration approximately 65,000 years or **~2,100 generations** ago (assuming an average generation time of 30 years). Generations are the fundamental unit of genetic transmission in the models of population genetics, though of course large human populations are continuously reproducing.

Population history, migration, and inferred effective population sizes.
*(**a**) Rough illustration of population history from present day (bottom) to hominin divergence (top). (**b**) A geographic representation of population migrations. [Figures from (Nielsen et al. 2017)] (**c**) Inferred effective population sizes from molecular data [Figure from (Terhorst, Kamm, and Song 2017)].*



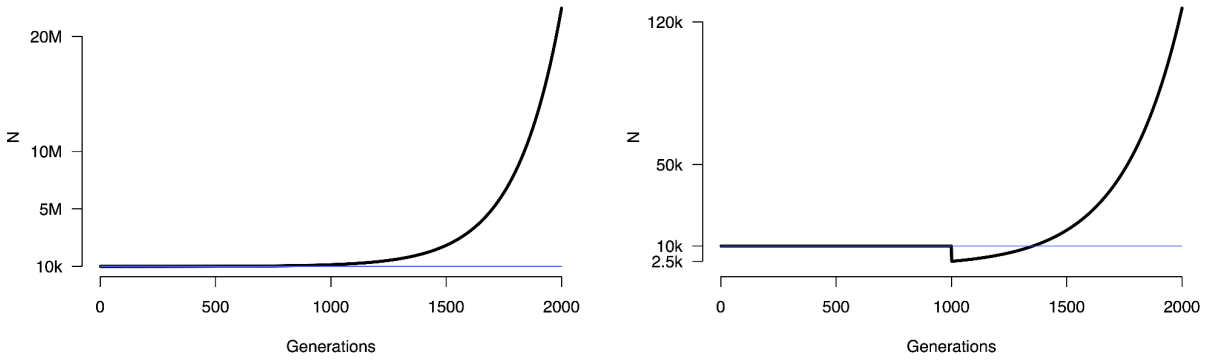
The second key parameter is population **size**. In truth, human populations are and have been continuously expanding (or shrinking), migrating, and intermixing. But in many cases it's much easier to model a *hypothetical* constant size, randomly mating population. To relate these models to real data, we define a term called the ***effective* population size** (**Ne**) which is the size of the hypothetical population that would produce the same level of genetic diversity (or genetic *drift*, see next section). Ne is thus a mathematical abstraction that makes for easier inference by turning the messy real world into the clean statistical model (see also: (Waples 2022) for a

different derivation of Ne in terms of the mean and variance in offspring). Moreover, in the case that Ne varies over time, a corresponding constant size Ne can be derived as the **harmonic mean** across generations (this will be justified later). The harmonic mean is heavily weighted towards lower population sizes (e.g. the harmonic mean of 100 and 1,000 is 181; the harmonic mean of 100 and 10,000 is 198) and is thus dominated by any bottleneck events (see figure below). As a consequence, Nes will generally be low and similar in populations that experienced bottlenecks.

Many methods exist to estimate Ne from genetic data, including over time, as shown in (panel **c**) in the figure above taken from (Terhorst, Kamm, and Song 2017). The major shifts here are: (1) non-African populations (CEU, CHB, GIH, JPT, TSI) experiencing a major population bottleneck ~50k years ago; (2) African populations (LWK, MKK, YRI) experiencing a mild bottleneck 10k-100k years ago; (3) all populations experiencing recent exponential growth. For European populations prior to the very recent growth the constant **Ne** is generally taken to be at least **10,000** and we will use this as the representative parameter for models in this section. The figure below provides some examples of populations with exponential growth and/or bottlenecks that still produce an Ne = 10,000 in the past 2,000 generations.

Two populations with Ne=10,000

*(**left**) exponential growth from 1,000 to N=~22M; (**right**) bottleneck to 25% followed by exponential growth to N=~120k. [**code**]*



8.3 | Allelic drift and age

With **time** and population **size**, we can start to reason about changes in the frequencies of genetic variation within a single neutral population, known as genetic **drift**. Variants under neutral drift stay at the same frequency in expectation (because no directional force is acting on them) but fluctuate due to the randomness of generational transmission. A polymorphism starting at frequency **p** (and alternative allele with frequency **q** = 1 - **p**), drifting for **t** generations through an **Ne**-sized population will have drift variance approximately equal to:

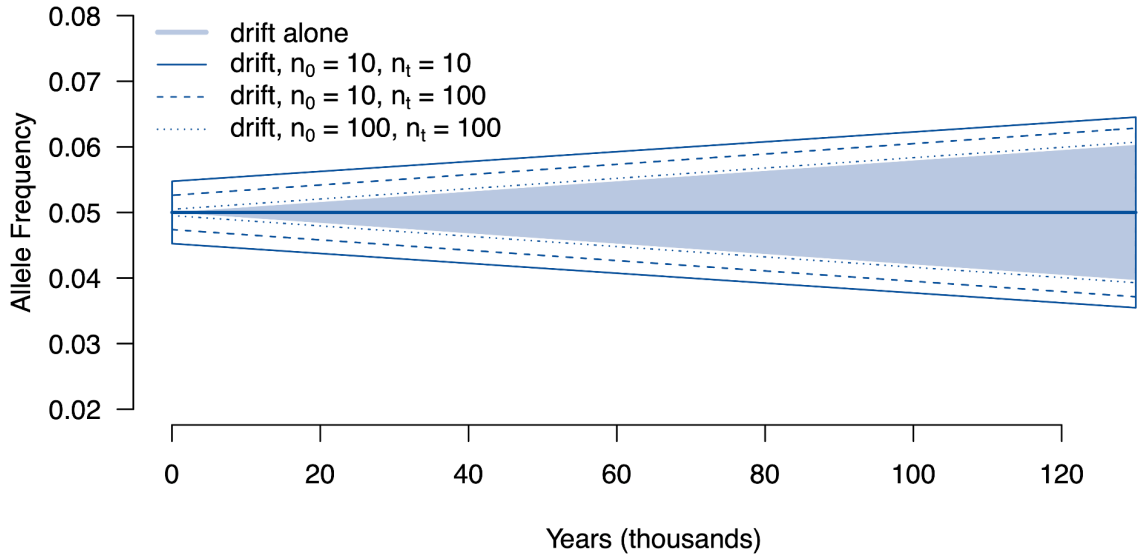
$$Var(p_t) \approx \frac{pqt}{2N_e}$$

See (Waples 1989) for a complete and exact derivation.

A useful distributional parameter to keep in mind is that if alleles are drawn from an n=2 Binomial distribution with mean **p**, then the variance across draws is [2**p**(1-**p**) = 2**pq**], and we will see some flavor of this variance term reappear in many of the subsequent derivations. In this equation we can see that drift variance increases in proportion to the starting variance of the polymorphism itself, the length of the drift process in generations, and inverse of the Ne (meaning larger populations have "slower" drift or less drift variance). In practice, this is a bounded process and when the polymorphism drifts past the boundary (0 or 1) it is **fixed** and no longer polymorphic in that population. **For moderately sized populations like humans after the out of Africa migration, drift is quite *slow***. For example, a 5% allele drifting for 2,100 generations in a population with Ne=10k will have drift variance of 0.05*0.95*2,100/20,000 = 0.5%, or an approximate 95% confidence interval ranging from 0-19%. In real data, population allele frequencies also need to be estimated and this adds an additional bit of sampling variance, shown in the figure below (in modern datasets with thousands of individuals this variance is negligible).

Variance due to drift and sampling.

*The expected variance in allele age for a 5% allele: shaded region shows the variance of the population frequency over time, lines show the additional variance due to sampling under different ancient (n_0) and modern (n_t) sample sizes. [**code**]*



We can also think about drift in the opposite direction: for an allele of a given frequency **p**, how long did it take to drift there (i.e. the expected allele age) or, for a brand new allele in the population, how long would it take to drift to frequency **p**. The expected allele age in generations is:

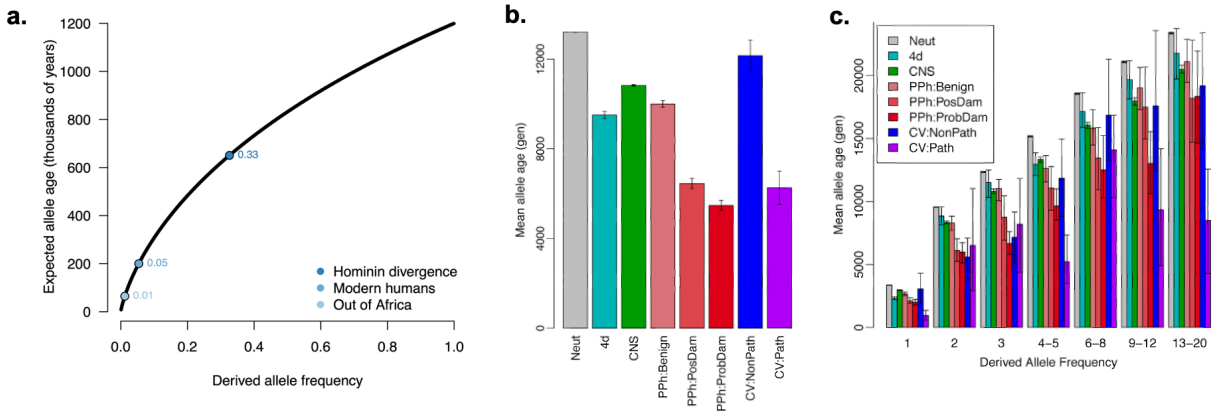
$$\text{age}(p) = -4N_e \frac{p \ln(p)}{q}$$

See (Kimura and Ohta 1973) for initial derivation and (Slatkin and Rannala 2000) for review, including derivation of confidence intervals and alternative estimators.

Intuitively, allele age increases with frequency/variance (it takes longer to get to a higher frequency) and with Ne (drift is "slower" in larger populations). Taking our 5% allele from above, it's expected age is -4*10,000*ln(0.05)*0.05/(1-0.05) = 6,306 generations (or ~190k years, approximately the origin of modern humans). In other words, **just as drift is slow, common variants are *old***. As shown in (panel **b**) in the figure below, 1% alleles are approximately as old as the out of Africa migration, 5% alleles are approximately as old as modern humans, and 30% alleles are approximately as old as the divergence of hominin lineages.

Allele age in theory and real data.

*(**a**) The expected allele age as a function of derived allele frequency. (**b**) Estimated average allele ages from real data by functional annotation. (**c**) Estimated allele age from real data by derived allele count (out of 108 genomes), (**c** and **d**) Figure from (Rasmussen et al. 2014). [**code**]*



While the above derivation relies on a simplistic population model, more recent methods can estimate allelic age while using information across multiple polymorphisms. One such method – ARG Weaver (Rasmussen et al. 2014) – relies on inferred "recombination graphs" and was applied to large scale whole-genome sequencing data to estimate allele ages in different functional regions. As shown in (panel **c**) of the above figure, the average estimated age of a neutral allele was ~13,000 generations (390k years: between the divergence of hominid lineages and the origin of modern humans). The "youngest" allele category were likely damaging coding variants, with an average allele age of ~5,000 generations (150k years: between the origin of modern humans and the start of the migration out of Africa). In (panel **d**) of the above figure, the alleles are further broken down by derived count, where we again see that neutral low frequency alleles (1 out of 108 or ~1%) are on average 4,000 generations old (~80k years ago) while more common alleles (4-5 out of 108 or ~5%) are on average ~15,000 generations old (~450k years ago). Again, the more functionally important / damaging alleles are consistently "younger", likely due to the action of negative selection which we will discuss next.

8.4 | Alleles under selection

The third key parameter is the **selection** coefficient, which relates genetic variation to fitness and deviations from neutrality. We can think of **fitness** in two ways: as a measure of *fertility*, the expected number of offspring per individual; or of *viability*, the probability of surviving from birth until reproduction. Because we are often modeling relative dynamics, fitness is further normalized to some mean/baseline to define ***relative fitness (w)***. Finally, the *additive* **selection coefficient (s)** defines the *change* in relative fitness for each allele of a polymorphism: [$w_{aa} = 1$, $w_{aA} = 1 + \mathbf{s}$, $w_{AA} = 1 + 2\mathbf{s}$]. Thus, s = -1 means the A allele leads to complete infertility, s = 0 means there is no change in fitness and no selection, and s = 1 means the A allele heterozygotes and homozygotes have 2x or 3x the relative fitness. Selection coefficients can also be defined more generally to model non-additive fitness but we will stick to additive effects here. As we saw in [**4.1** and **4.4**], common traits are generally driven by tens of thousands of common variants each of which has a weak effect on the trait and is under weak or neutral selection. As a representative selection coefficient, we will use **s = -0.0007**, the average estimated in a study of 28 common traits (Zeng et al. 2018) and broadly consistent with other recent estimates of **s** in the range of 10^{-4} to 10^{-5} (Simons et al. 2022).

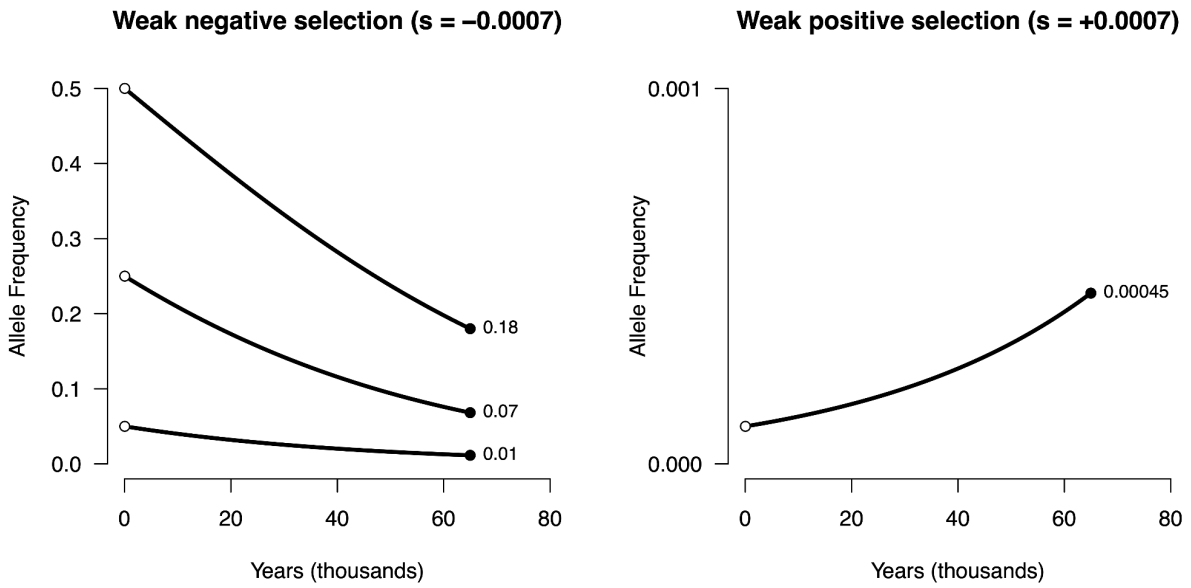
Given an allele of frequency **p** and an additive selection coefficient **s**, we can then compute the expected number of carriers of each allele in the next generation and renormalize to get the expected frequency change. Specifically, the per-generation change in frequency is:

$$\Delta p = \frac{spq}{1 + 2sp} \approx spq$$

See the work of JS Haldane (Haldane 1933) for derivations.

As this is a per-generational change that depends on the prior allele frequency it can be hard to visualize the long-term trajectories, so let's run the iterative process for ~2,100 generations with an s of -0.0007 starting at different initial frequencies:

Sample allele frequency trajectories under directional selection.
*(**left**) Weak negative selection for variants starting with frequency 0.5, 0.25, and 0.05. (**right**) Weak positive selection for a new variant starting at 1/N. Note these are "exact" estimates of expected frequency and do not account for drift, which will add variance (see above). [**code**]*



A few things to notice in the figure above regarding the 65kya time-frame. First, common variants will generally still be common because the speed of selection depends on the starting frequency. For example, a 5% allele is only expected to drop to a ~1% frequency (or, alternatively, a modern day 1% allele is not expected to have been more common than 5% in the ancestral population). Second, larger frequency shifts happen for more common variants (while still generally remaining common): for example, a 50% allele is expected to drop to an 18% frequency. For such common alleles it is likely that the selective effect must have changed, since a common variant is either neutral variant drifting for a long time or previously under positive selection. Third, new mutations under weak positive selection do not have time to increase to appreciable frequency: an allele that starts at 1/10,000 is expected to increase to just 2/10,000 in 65k years. For this reason, we will generally ignore mutation rate and the contribution of novel variants in recent time (but see [later] on mutational load).

An alternative way to think about these trajectories is in terms of the *expected* time it would take for an allele to move from one frequency to another:

$$t(p_0, p_t) \approx \frac{1}{s} \ln\left(\frac{p_t q_0}{p_0 q_t}\right)$$

See (Crow and Kimura 1972) for derivation.

Thus, with **s** = **-0.0007**, for an allele to move from 95% to 1% (i.e. nearly fixed to low-frequency) is expected to take ~11,000 generations (or ~323,000 years). For an allele to move from 10% to 1% is expected to take ~3,400 generations (or ~100,000 years). **Again we see that shifts from common to rare frequency are very unlikely to occur in the recent ~2,100 generation span**.

Stabilizing selection

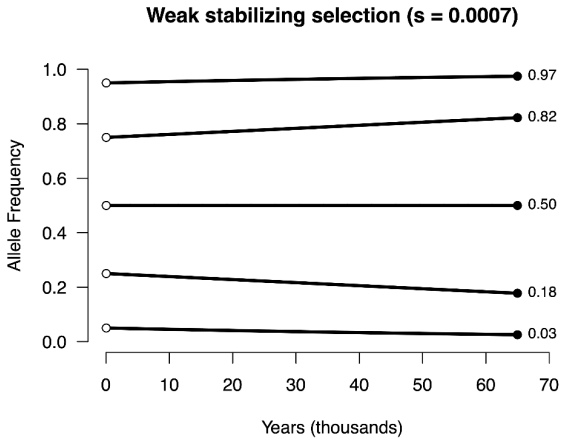
While the above models of simplistic directional selection provide clear intuition, it is more likely that human populations are evolving under *stabilizing* selection. Under stabilizing selection, fitness is maximized when the mean phenotype is at the optimum, with lower fitness below or above the optimum. As an example we can think of weight, where either being extremely overweight or extremely underweight leads to poor health and lower fitness (and this is likely true of many traits). For each allele, this results in competition between the directional effect the allele has on the fitness phenotype (selection wants to maintain alleles that move the phenotype towards the optimum) and the excess variance generated by the allele (selection wants to keep variance low by eliminating heterozygotes). When the trait is at its optimum and the variant has a small effect on the trait (and thus on fitness), the fitness advantage of reducing variance/heterozygosity wins out (also known as underdominance) and alleles are driven to fixation in both directions. Thus, and somewhat paradoxically, stabilizing selection will continue to purge an allele out of the population by moving a more frequent variant to complete fixation and a less frequent variant to complete elimination. For weak, additive stabilizing selection at a fitness optimum, this can be modeled as follows, where the parameters are as above and [β] is the effect of the variant on the fitness trait:

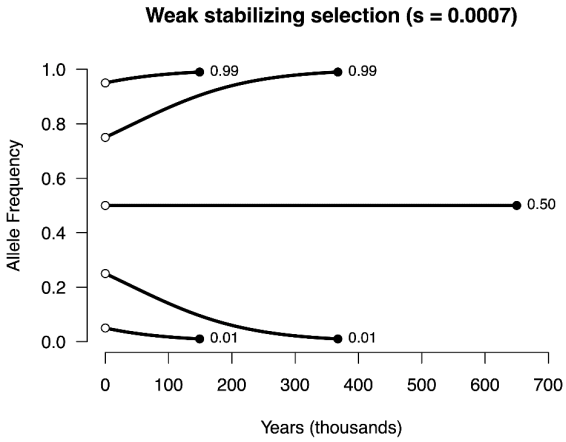
$$\Delta p \approx \beta^2 spq\left(p - \frac{1}{2}\right)$$

See (Koch and Sunyaev 2021) for concise overview and (Walsh and Lynch 2018) for more detailed derivation and historical references.

What does this look like over the recent (65k years) time-scale? Very little. We can see in the equation that alleles are selected against in proportion to their deviation from 50% (with alleles residing perfectly at 50% not experiencing selection at all). So a 25% allele will be pushed down to 18% (compared to 7% under pure negative selection), whereas a 10% allele will be pushed down to 3% (compared to 1% under pure negative selection). We can zoom out to 650k years and start to see more substantial changes: a 10% allele will become rare after ~150k years; a 25% allele will become rare after ~375k years. In other words, stabilizing selection penalizes heterozygosity and moves alleles away from being common (in both directions) at a rate that is even slower than pure directional selection.

Sample allele frequency trajectories under stabilizing selection.
*(**left**) Expected allele frequency after thousands of years (x-axis) of stabilizing selection at s=0.0007 and with β (the effect on the fitness trait) set to 1.0. (**right**) Same as left but over a longer time period. For each mutation, plotting is stopped when the minor allele frequency drops below 1% (i.e. no longer common). [**code**]*





8.5 | Selection with drift and "effective neutrality"

The above derivations of selection trajectories are "exact" and do not include variance due to drift (which is why they do not rely on **Ne**). One way to incorporate drift into our modeling is to compare the probability of fixation (going from being in one individual to present in all individuals) for an allele under selection to the probability of fixation for an allele under neutral drift. For alleles under strong selection, fixation should be impossible, but a question we may be interested in is whether certain selection/drift dynamics are sufficient to keep or slow deleterious mutations from fixing. This *scaled* **fixation probability** is derived as:

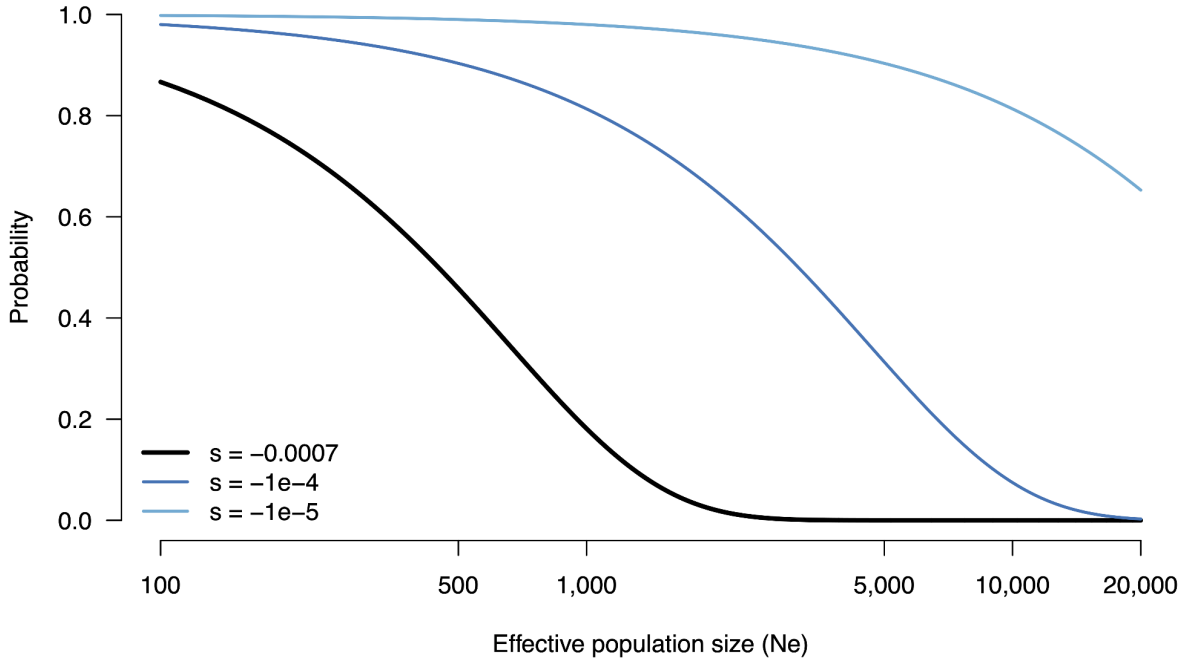
$$P(\text{fixation}) = \frac{4N_e\ s}{1 - e^{-4N_e\ s}}$$

See (Kimura 1957) for initial, and quite complex, derivation and (Cash 1977) for a simpler one.

Notably, the relationship is only dependent on [**4*Ne*s**], a key population genetics parameter. When [**4*Ne*s**] is much less than 1, alleles are **effectively neutral**, meaning their probability of fixation (and general movement through the population) is similar to that of a neutrally drifting allele (for **Ne** of 10,000 this corresponds to an **s**<2.5×10^{-5}). Now let's look at this relationship as a function of Ne for a few different weak selection parameters:

Probability of fixation relative to neutral drift.

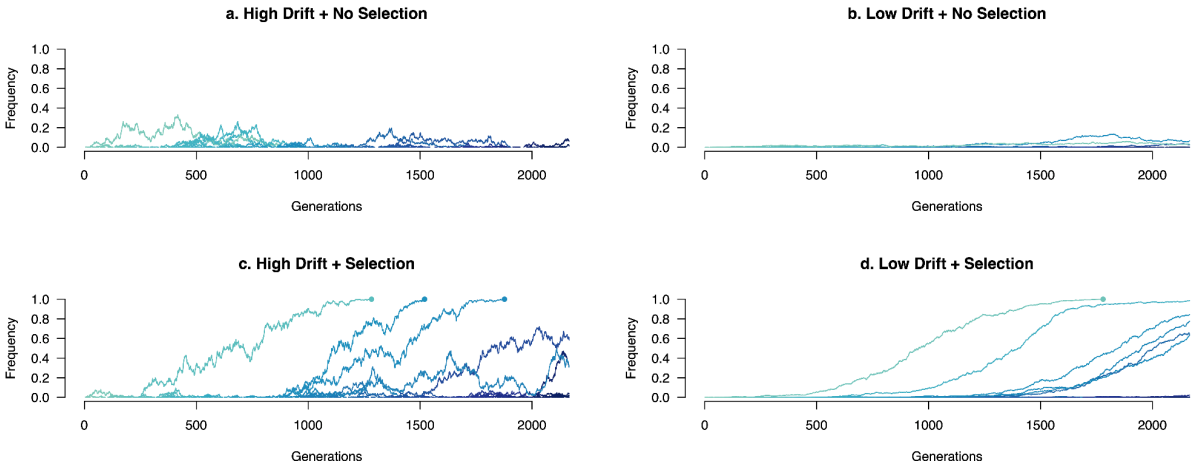
*The relationship between Ne (x-axis) and the scaled probability of fixation (y-axis) for three different values of [s]. [**code**]*



What we see is that **for human sized populations (Ne>10,000) selection is able to keep new deleterious variants from fixing for weak s of at least -0.0007, similar to what is seen for a typical GWAS variant**. It is only for very weak **s** of -10^{-4} or -10^{-5} that variants start to behave like neutral alleles drifting through the population, and can reach high frequencies. We can put these concepts together and look at what happens to novel alleles under different drift and strong *positive* selection parameters. As expected, drift increases the variability in allele frequencies over time, and positive selection moves alleles closer to fixation. However, for GWAS-level selection we appear to be primarily in the (panel **b**) regime of low drift and nearly neutral selection.

Allele frequency trajectories under drift and selection.

*(**a**) High drift (Ne=500) with no selection; (**b**) Low drift (Ne=10,000) with no selection; (**c**) High drift (Ne=500) with moderate selection (s=0.005); (**d**) Low drift (Ne=10,000) with moderate selection (s=0.005). Figure adapted from (Desbiez-Piat et al. 2021). [**code**]*

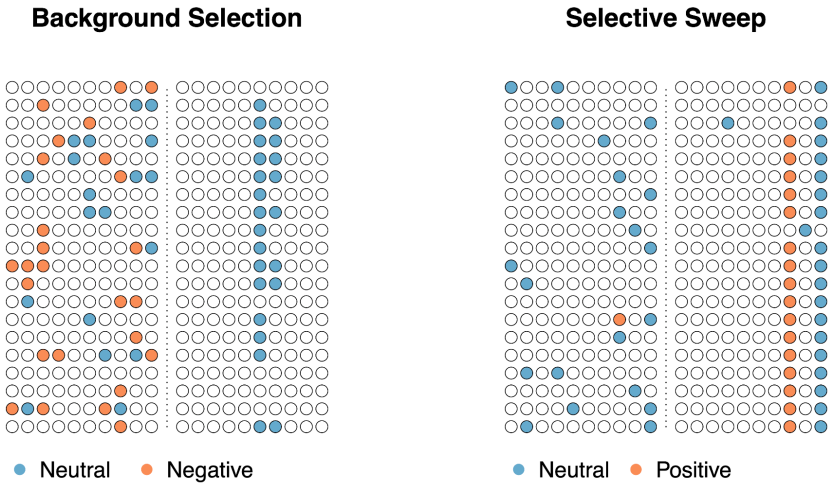


8.6 | Linked and background selection (BGS)

So far we have only considered individual alleles under selection, but selection can additionally exert an influence on nearby variants in linkage disequilibrium (LD) with the selected allele (i.e. "linked" variants). Due to the relatively slow process of recombination, negative/positive selection will pull down/up any other neutral alleles near the selected variant. Linked selection is typically further subdivided into "background" selection (BGS), which removes negative fitness haplotypes; and "selective sweeps" which drive positive fitness haplotypes to fixation. **This process results in the reduction of local neutral genetic variation and is expected to be stronger in regions of low recombination rate**. We can think of linked selection as akin to a local reduction in **Ne** (due to the reduction in the number of individuals/haplotypes from which offspring are sampled) and an acceleration of "local drift".

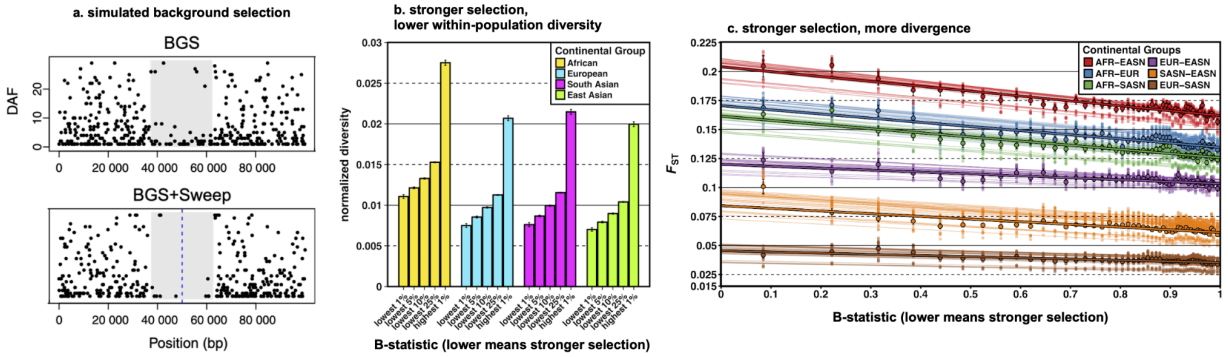
Toy schematic of background selection and selective sweeps

(left) Low fitness functional variants (red) are purified out of the population together with any linked neutral alleles (blue), reducing the overall genetic diversity. (right) A high fitness functional variant (red) is "swept" up to higher frequency along with any linked neutral alleles (blue).



While BGS is a very slow process outside the range of recent population divergence, its influence on neutral variation can be amplified by recent demographic events. In the figure below, (Torres, Szpiech, and Hernandez 2018) show that European populations have experienced a more substantial reduction in neutral variation in regions that are under stronger background selection (quantified by the "B statistic", for which low values indicate stronger selection) likely due to serial population bottlenecks after the African migration. This reduction in within-population diversity also translates into an increase in cross-population divergence, i.e. more "local drift" between populations (see next section for derivation of the relevant F_{ST} statistic). Migration between populations will act as a partially opposing force: decreasing within-population diversity in those populations that did not experience bottlenecks while also decreasing cross-population divergence. **The complicated relationship between BGS, recombination, diversity, and divergence can be a particularly challenging confound for inference of genome-wide selection parameters and population size (see [8.10]).**

Background selection in simulated and real data reduces diversity and increases divergence
*(**a**) Background selection (BGS) in simulated data with a locally lower recombination rate (gray region) further decreases diversity. Bottom panel shows how BGS can mimic/mask the effect of a selective sweep. [Figure from (Huber et al. 2016)]. (**b**) Regions with stronger background selection (lower B-statistic) exhibit lower within-population diversity of neutral variation. (**c**) Regions with stronger selection exhibit higher between-population F_{ST}. [Figures from (Torres, Szpiech, and Hernandez 2018)].*



8.7 | Differentiation within/between populations / F_{ST}

Definition

Having established the dynamics of drift at a single time in one population, we may also be interested in quantifying genetic drift/differentiation between populations. This concept is parameterized by the "Fixation index" or **F_{ST}** (where "S" stands for subpopulation and "T" stands for total population). F_{ST} is a fundamental population parameter and its definition, interpretation, and estimation has been approached from many different perspectives. The classic definition of F_{ST} for a single site is "*the correlation between gametes chosen randomly from within the same subpopulation relative to the [total] population*" (Wright 1951; Holsinger and Weir 2009). In its simplest form, F_{ST} is then defined as:

$$F_{ST} = 1 - \frac{H_S}{H_T}$$

where $[H_S]$ is the *heterozygosity* (i.e. $[2^*\mathbf{p_S}^*\mathbf{q_S}]$) in the sub-population (or averaged across sub-populations) and $[H_T]$ is the heterozygosity in the "total" population ($2^*\mathbf{p_T}^*\mathbf{q_T}$). F_{ST} will be high if individuals in a subpopulation are much more likely to share an allele (i.e. be correlated) than individuals in the total population (i.e. heterozygosity in the subpopulation is low); F_{ST} will be zero if $[H_S = H_T]$ and individuals in the subpopulation are no more similar/correlated than in the total population (aka panmixia).

This definition seems simple enough, but what precisely "total population" means has been a source of some dispute. The total population is sometimes treated as an ancestral/base population (Cockerham 1969), "replicates" of the current population (Weir and Hill 2002), or the combined sample (Nei 1973, 1986). See (Bhatia et al. 2013) for a detailed discussion of

interpretation in their historical context, which we'll rely on for most of the following overview. As a consequence, **there are two primary F_{ST} parameters** – a parameter related to in-sample variance and a parameter related to population drift. We will define these in turn.

Nei's (1973) F_{ST}

The classic parameter of (Wright 1951; Nei 1973) is defined in terms of variance/correlation in the sampled data. We note the year (1973) to distinguish this parameter from a redefined F_{ST} in (Nei 1986) which differs by a factor of two. If we define total-population frequencies $\{\mathbf{p_T},\mathbf{q_T}\}$ as the average of the within-population frequencies, then F_{ST} is derived in terms of the ratios of the average within-population heterozygosity and the total-population heterozygosity. For two populations {1,2}, this is:

$$p_T q_T = \left(\frac{1}{2}\right)(p_1 + p_2)\left(\frac{1}{2}\right)(q_1 + q_2)$$
$$= \left(\frac{1}{4}\right)(p_1 q_2 + p_2 q_1 + p_1 q_1 + p_2 q_2)$$

$$F_{ST}^{\text{Nei73}} = 1 - \frac{\left(\frac{1}{2}\right)(p_1 q_1 + p_2 q_2)}{p_T q_T}$$
$$= \frac{(p_1 - p_2)^2}{4 p_T q_T}$$

See (Coop 2022) for a succinct derivation and connection to Wright's F-statistics.

We see our old friend [2**pq**], the variance of a single site, and Nei's F_{ST} is thus often interpreted to estimate the total genetic variance attributable to "between population" variance, or one minus the variance attributable to average "within population" variance. A second form is also shown, to connect this parameter to the squared difference between the alleles [$(\mathbf{p}_1 - \mathbf{p}_2)^2$] normalized by twice the total-population variance ([$2^*2\mathbf{p_T q_T}$]).

Hudson's F_{ST}

The more recent parameter of (Hudson, Slatkin, and Maddison 1992; Reich et al. 2009; Bhatia et al. 2013) instead defines the "total population" as a hypothetical ancestral/founder population. This provides additional useful interpretation for F_{ST} *between* modern-day groups that are derived from the ancestral population (with strict assumptions of random mating and no migration). Specifically, F^i_{ST} for population [i] can be defined as "*the correlation between randomly drawn alleles from a single population relative to the most recent common ancestral population*" (Weir and Hill 2002; Bhatia et al. 2013). For a biallelic polymorphism with current and ancestral population allele frequencies $\{p_i,p_{anc}\}$ respectively, the population-specific F^i_{ST} is the total drift variance since the ancestral population:

$$E[p_i \mid p_{anc}] = p_{anc}$$
$$Var[p_i \mid p_{anc}] = F^i_{ST} p_{anc} q_{anc}$$

$$F_{ST} = \frac{F^1_{ST} + F^2_{ST}}{2}$$

Generative model from (Bhatia et al. 2013) for population-specific F^i_{ST} and cross-population F_{ST} in terms of variance on the derived alleles from an ancestral population. [p_i] are frequencies in population [i] and [p_{anc}] are frequencies in an ancestral population.

The F_{ST} *between* two contemporary populations is then just the average of their F^{i}_{ST} to the ancestor (shown on the right). Importantly, F_{ST} is now defined in terms of hypothetical populations rather than the samples in the data. Of course, it is rare to have genetic data on the ancestral population and know [p_{anc}], but these relationships provide intuition for the generative process and how to think about F_{ST} between contemporary groups. Finally for an allele {$\mathbf{p_1}$,$\mathbf{p_2}$} in two contemporary populations respectively, F_{ST} is derived as:

$$F_{ST}^{\text{Hudson}} = 1 - \frac{p_1q_1 + p_2q_2}{p_1q_2 + p_2q_1}$$

$$= \frac{(p_1 - p_2)^2}{p_1q_2 + p_2q_1}$$

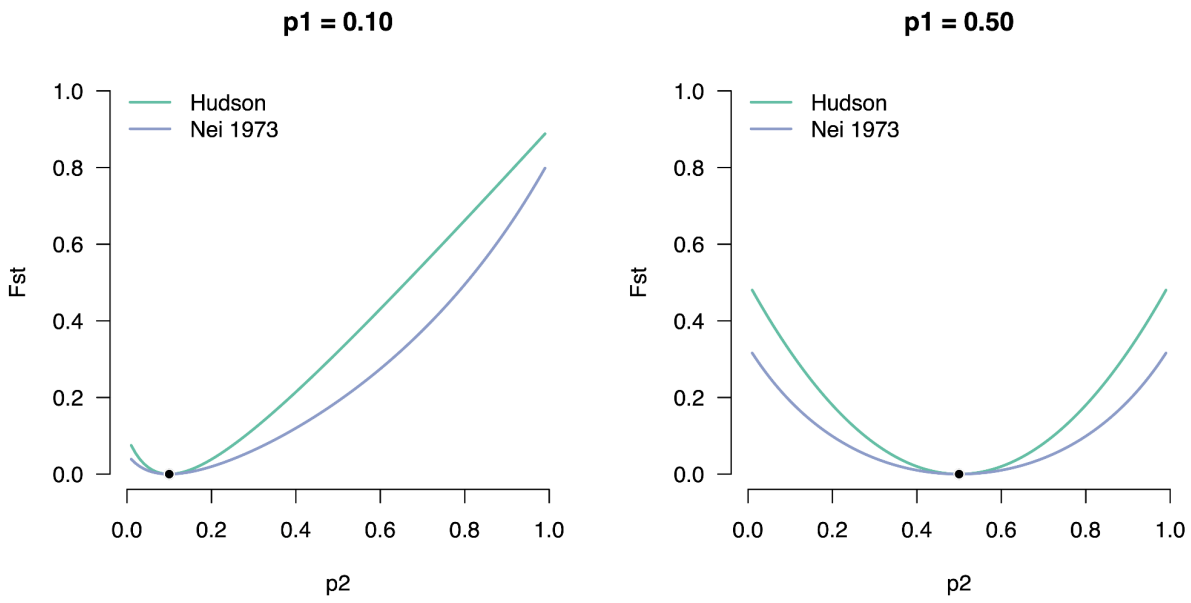
See (Hudson, Slatkin, and Maddison 1992; Reich et al. 2009; Bhatia et al. 2013) for derivation and relation to population drift.

Practical differences

These two formulations have created some confusion when different studies used different parameters (in addition to estimating them in different ways). Nei's F_{ST} is perhaps the most widely referenced (it is currently the Wikipedia **definition** in an alternative form). Whereas, Hudson's F_{ST} is more commonly applied to population genetics analyses due to its implementation in software such as EIGENSOFT (which, ironically, was used to generate the **figure** for the Wikipedia definition). By comparing the above derivations, we can see that Hudson's F_{ST} differs from Nei's F_{ST} only in the way it defines the denominator i.e. the total/between-group heterozygosity (specifically, Hudson's F_{ST} denominator omits an [$\mathbf{p_1q_1}$+$\mathbf{p_2q_2}$] term). This translates into nonlinear differences between the two parameters as a function of allele frequency (see figure below). **In short, the choice of $\mathbf{F_{ST}}$ parameter can have a substantial impact on the results**.

Behavior of F_{ST} parameters as a function of frequency.

*Estimated F_{ST} for a single site as a function of the allele frequency in one population (p1) and range of frequencies in the other (p2). [**code**]*



Relationship to other population parameters

When defined as above in terms of average drift from an ancestral population, Hudson's F_{ST} relates directly to the corresponding **Ne** over time:

$$F_{ST}^{i} = 1 - \prod_{t=1}^{g}\left(1 - \frac{1}{2N_{e,t}^{i}}\right)$$

See (Bhatia et al. 2013) for derivation. [i] is the sub-population, [g] is the number of generations to the ancestral population, and [$N_{i,t}$] is the population-specific effective population size in each generation.

Here we can see components of the Waples drift variance equation from earlier but without consideration of allele frequency (because F_{ST} is a population-level estimate of drift). In principle, if either the divergence time in generations (**g**) or the effective population size history ($\mathbf{N_{e,t}}$) is known, then F_{ST} computed from data can be used to estimate one parameter from the other.

Alternatively, under a simple island model where multiple populations have diverged to fixed Ne's but continue to mix with a migration rate of [**m**], Nei's F_{ST} can also be related to these population/migration parameters as:

$$F_{ST} = \frac{1}{4N_e m + 1}$$

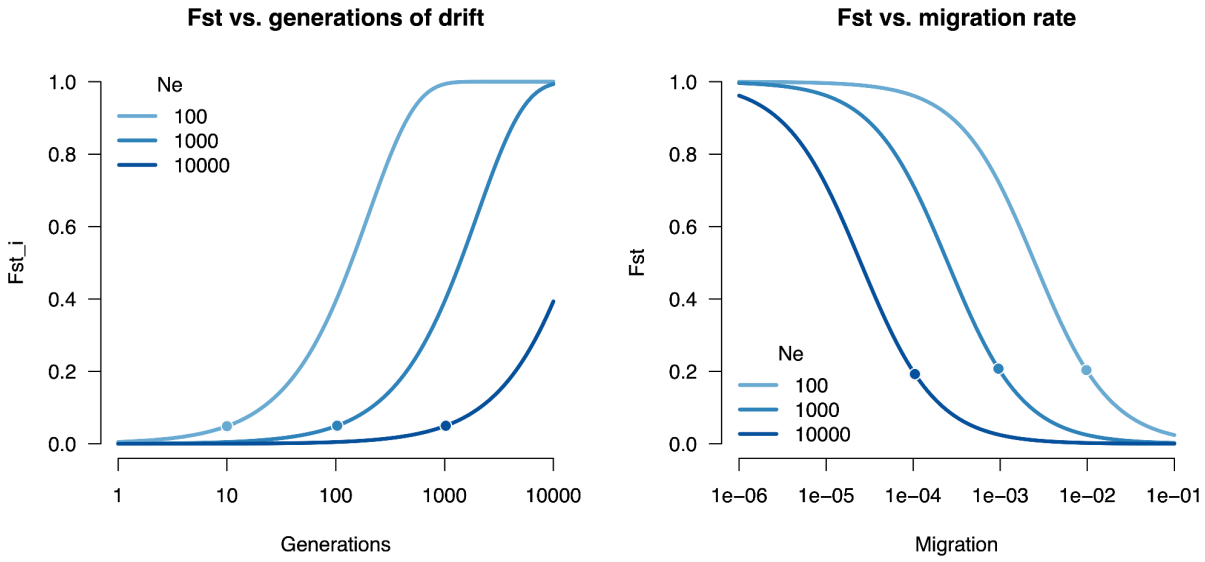
See (M. C. Whitlock and McCauley 1999) for derivation and caveats. Where [m] is the migration rate in an island model.

A direct consequence of these relationships is that **the same F_{ST} value is compatible with many different population demographics**. See (Myers, Fefferman, and Patterson 2008) and (Bhaskar and Song 2014) for more discussion of this "identifiability" issue and its applicability to inference

from the broader site frequency spectrum. For example, in the above population divergence model, F_{ST} will be the same for any fixed [**Ne*g**], meaning that small populations that diverged recently will have the same F_{ST} as large populations that diverged long ago (because drift is slower in large populations). And in the above island/migration model F_{ST} will be the same for any fixed [Ne*m], meaning that small populations with large migration rates will have the same F_{ST} as large populations with small migration rates (again, drift is slower in large populations so the migration rate needs to be smaller to keep divergence high). We can see these equivalences for different parameter settings in the figure below.

F_{ST} as a function of divergent drift or island migration.

*(**left**) Within population F_{ST} as a function of generations of divergence (x-axis) under a fixed Ne. (**right**) F_{ST} as a function of migration rate (x-axis) in an island model under a fixed Ne. In both figures results are shown for Ne of 100, 1000, and 10,000 and points are indicated for a single representative case where multiple parameters produce the same (Hudson) F_{ST} values. [**code**]*



Keep in mind that these are just illustrative examples, as population sizes are never constant, and F_{ST} does not account for the influence of new mutations or selection. More advanced methods have been developed that use other F-statistics within and across populations for more complex demographic inference (Peter 2016), but the challenge of identifiability remains.

Estimation

In the above derivations, F_{ST} is defined at a single hypothetical site and without consideration for sampling. In practice, F_{ST} needs to be estimated from sampled data and also, typically, aggregated across sites to get a population-level average. These steps introduce a surprising amount of complexity. Just as there are multiple definitions of F_{ST}, there are multiple estimators and ways to average them. **When sample sizes are small or differ greatly between populations, these estimation choices have led to substantial differences in interpretation of population history**. (Bhatia et al. 2013) is again highly recommended for a detailed discussion of these challenges and applications to real data. Here, we will briefly reiterate their recommendations.

First, they derive a Hudson F_{ST} *estimator* that is not heavily biased by different sample sizes in the two sub-populations. Specifically, given samples from two populations with estimated allele frequencies [p~] (with the ~ used to indicate a sample average), and sample sizes [n], the Hudson F_{ST} estimator (Hudson, Slatkin, and Maddison 1992) is derived as:

$$\hat{F}_{ST}^{Hudson} = \frac{(\tilde{p}_1 - \tilde{p}_2)^2 - \frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1 - 1} - \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2 - 1}}{\tilde{p}_1(1-\tilde{p}_2) + \tilde{p}_2(1-\tilde{p}_1)}$$

Hudson FST between two populations from (Bhatia et al. 2013). [~p1] and [~p2] are the estimated frequencies in the two populations; [n1] and [n2] are the sample sizes.

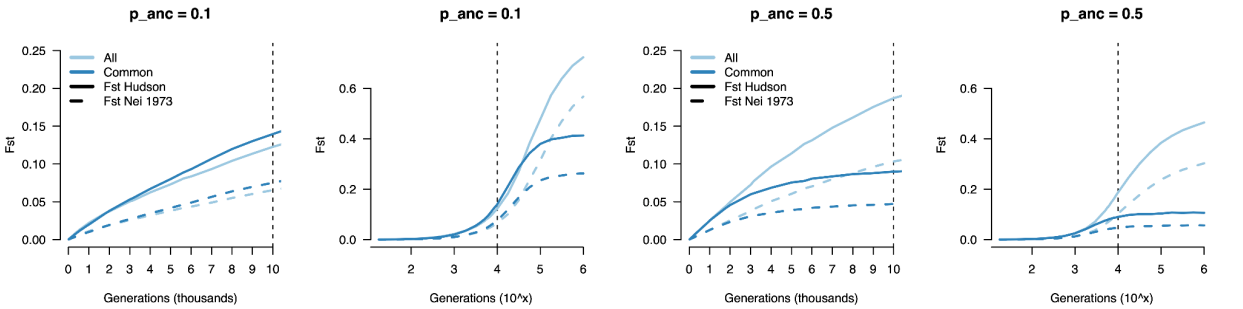
Second, they propose a "ratio of averages" for aggregating estimates across multiple markers. Computing the average numerator and denominator separately and then taking the ratio substantially reduces the variance of the estimate and potential bias from rare variants with highly uncertain estimates. This choice can have meaningful effects, with F_{ST} estimates sometimes dropping in half when using an average of ratios in real sequencing data with rare variants. Third, being clear on how the SNPs used to compute F_{ST} were selected because F_{ST} is highly specific to a given set of variants. More on that in the next section.

Ascertainment biases and theoretical bounds

F_{ST} estimates can be heavily influenced by the variants they are being estimated from (i.e. the variant *ascertainment*). As every variant needs to be polymorphic in at least one of the sub-populations being tested in order for heterozygosity to be defined, a choice needs to be made for which polymorphisms to include. Additionally, analyses restricting to common variation (as is typically collected from SNP arrays) may produce different estimates from those using all variation. The impact of frequency-based ascertainment on the estimated F_{ST} will have a complex relationship to the underlying demographic history (Bhatia et al. 2013). Restricting to common genetic variation will focus the estimates on older alleles (see [**8.3**]) and the drift from that time range. At the same time, excluding alleles that have fixed in the population, which are some of the oldest drifting variants, will reduce the apparent drift populations and place a bound on the estimated differentiation. We can see this phenomenon in the simulation results below for drift in a population with constant Ne:

F_{ST} estimated in simulated drifted populations with SNP ascertainment.

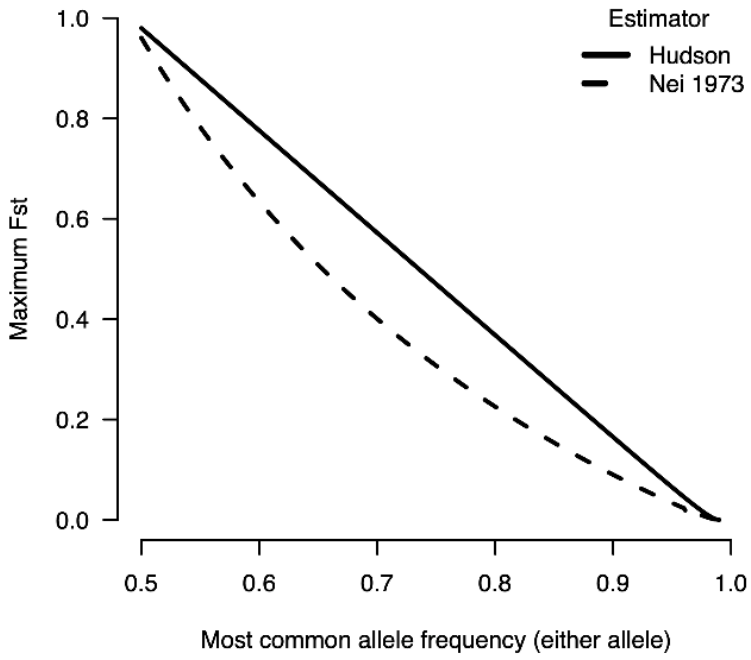
*Each panel shows F_{ST} estimates (y-axis) in a simulated population with Ne=10,000 and generations of drift (x-axis). The light blue lines show the estimates from all variants and the dark blue lines show the estimates restricting to common SNPs in the contemporary population. [**code**]*



In both simulations thresholding on common variants eventually induces an upper bound on the F_{ST} estimate. The magnitude of the bound was also dependent on the frequency distribution in the *ancestral* population at that time: if variants in the ancestral population are common, they will drift to fixation faster and the bias induced by common variant ascertainment will be more substantial (right two panels versus left two panels). In particular, comparing common variants across highly differentiated populations can produce very misleading results. For example, in the simulations starting from common ancestral alleles (right panels) F_{ST} hits an asymptote at ~10,000 generations and does not increase substantially even after 100,000 or 1M generations. **In other words, the F_{ST} estimate is specific to the variants it is being estimated from.** While an out-group population can sometimes be used to select the SNPs to mitigate some of this effect (Bhatia et al. 2013), out-groups without historic admixture or migration are rarely available.

A second, more underappreciated, aspect of F_{ST} is that **it is bounded by the frequency of the most common allele** in the total population. See (Jakobsson, Edge, and Rosenberg 2013) for general derivation, (Edge and Rosenberg 2014) for tighter bounds when the number of alleles is known, and (Alcala and Rosenberg 2022) for derivation in multiple populations. Moreover, the bound decreases (i.e. becomes more constrained) as the most common allele becomes more common. F_{ST} estimates from common variants (for which the most common allele is of moderate frequency) will thus have a higher bound than F_{ST} estimates from rare variants (where the most common allele can be of very high frequency). In the figure below, the bound is shown for Hudson and Nei F_{ST} (the latter derived in the work cited above), both of which decrease with the highest allele frequency. This can lead to confusing interpretations when comparing FST values estimated from classes of variants with different bounds.

Bounds and behavior of F_{ST} estimators for two populations as a function of allele frequency.
*Upper F_{ST} bound as a function of the most common allele frequency for a biallelic polymorphism for the Hudson (solid) and Nei (dashed) estimators. The bound was estimated by sampling and smoothing, see analytical derivation in (Jakobsson, Edge, and Rosenberg 2013). [**code**]*



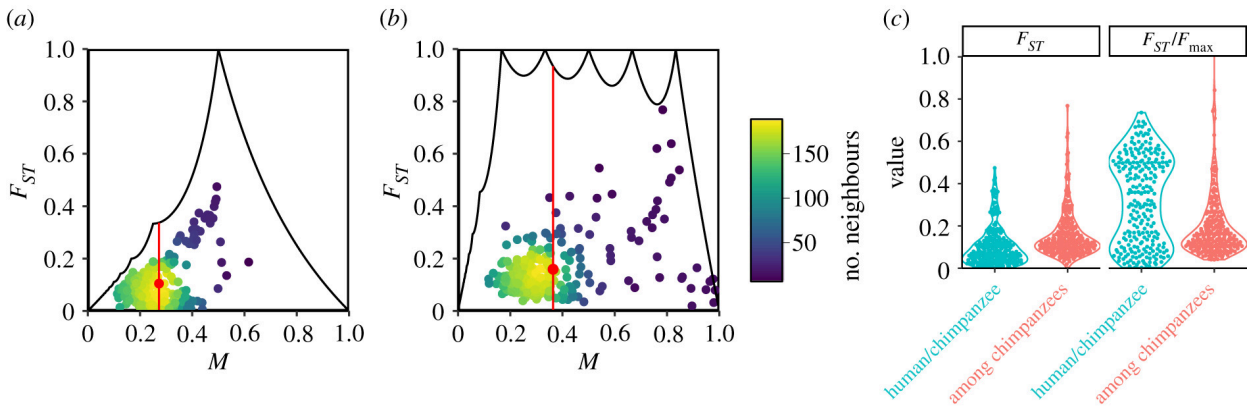
More than two populations

The relationship between frequency and F_{ST} bound is more complicated for multiple populations, such as when comparisons are made across multiple species groups. Specifically, (Alcala and Rosenberg 2022) showed that when multiple subpopulations are considered, the upper bound on F_{ST} can be much higher than for two populations, and exhibits a non-linear relationship with the frequency of the most common allele (see figure below). These substantial differences in F_{ST} bounds can produce paradoxical results, such as higher values within six chimpanzee subpopulations (F_{ST}=0.16) than between humans and chimpanzees (F_{ST}=0.10). (Alcala and Rosenberg 2022) demonstrated in real data that this difference was largely eliminated when normalizing by the expected maximum F_{ST} in each comparison, which produced higher values of differentiation between humans and chimpanzees – consistent with intuition. **Thus, F_{ST} is also specific to the populations, number of populations, and number of alleles it is computed in.**

Theoretical and empirical F_{ST} bounds are much higher within chimpanzees than between chimpanzee/human analyses.

*(**a**) For two populations, the theoretical FST bound as a function of the most common allele (M) is shown with black line and the empirical FST estimates for humans versus chimpanzees is shown in the heatmap, with the mean shown in red. (**b**) Same as (**a**) but for six chimpanzee subpopulations. (**c**) Raw and normalized estimates show normalization substantially increases the F_{ST}/F_{max} in the human/chimpanzee comparison.*

Figure from (Alcala and Rosenberg 2022).



8.8 | Complex trait differentiation / Q_{st}

Most common traits are highly polygenic (see [**4.1**]), and so it is of interest to understand how much the genetic component of a polygenic trait can differ between populations or groups simply through the process of neutral drift. This question was investigated in (Edge and Rosenberg 2015a) under a restricted haploid model and then in (Edge and Rosenberg 2015b) for arbitrary ploidy and allele frequencies. Population differentiation for a quantitative trait has previously been proposed under an analog of F_{ST} called Q_{ST} (see (Michael C. Whitlock 2008) for review). Surprisingly, Edge and Rosenberg find that, with respect to group means, **a polygenic quantitative trait behaves just like a single drifting polymorphism!** Using derivations based on a neutral model in a homogenous environment they prove that:

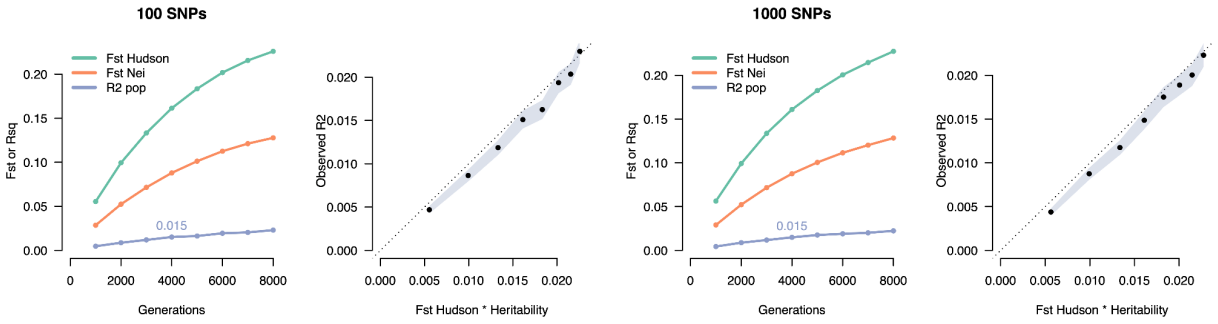
1. The difference in the trait mean across groups is centered at zero and symmetric (as expected from neutral drift).
2. The variability in the group mean difference does not depend on the number of variants contributing to the trait (i.e. polygenicity).
3. As a consequence, "*the proportion of heritable variance in the trait attributable to genetic differences between the populations*" (Q_{ST}) is approximately equal to the cross-population (Hudson) F_{ST} (which (Edge and Rosenberg 2015b) rederive as $F_{ST,I}$). This quantity also does not depend on polygenicity.

Putting this together, for a neutral trait under homogeneous environments, the variance in *total* phenotype that can be explained by genetic differences across populations is **the product of the average Hudson F_{ST} (i.e. the genetic variance due to "between population" differences) and the trait heritability (i.e. the trait variance explained by genetic variance).** And this relationship will hold regardless of the level of polygenicity in the trait! *Note*: the relationship is sometimes reported as $2*F_{ST}*h2$, but this is only an approximation for Nei's F_{ST}: Nei's F_{ST} is approximately equal to half of Hudson's F_{ST} when the former is close to 0 or 1 (see [**8.6**]). In real data, Hudson's F_{ST} is often empirically *lower* than Nei's F_{ST} (see [TBD]) due to the complexities of real population dynamics, and so this approximation can be a substantial overestimate.

We can confirm the relationship between F_{ST} and population-explained trait variance in simulations (see figure below). Specifically, we simulate two drifted populations (Ne = 10,000) with polygenic heritable phenotypes (h2 = 10%) under a common environment. Then we compute the squared correlation between the phenotype and the population label (i.e. the variance explained). As expected, the variance in trait that can be explained by population differences is bounded by the product of h2 and Hudson's F_{ST}, and does not depend on polygenicity (tested using 100 and 1000 causal variants). Note this relationship continues to hold for substantially differentiated populations even as alleles drift to fixation.

Proportion of trait variance explained by population differences in simulations.

*(**a**) For two drifted populations, the cross-population F_{ST} (green/orange) and the variance in the trait explained by the population label (blue) as a function of number of generations from the common ancestor population; (**b**) the expected (x-axis) and observed (y-axis) variance in trait explained by population differences (95% confidence interval shown with shading). (**c,d**) repeat the previous panels but for a simulation with 1,000 causal variants. All simulations are for Ne=10,000; h2=0.10; n=500 in each of two populations; averaged over 1,000 runs. Note the relationship between F_{ST} and generations of drift is approximate and will depend on the ancestral allele frequencies. Variance explained for F_{ST} of ~0.15 is labeled (comparable to estimates between individuals with European and African ancestry). Nei's F_{ST} is included for comparison. [**code**]*



Since pairs of modern human populations generally have F_{ST} values <20% (meaning <20% of the total variation at a typical SNP is due to between-population differences), we should generally expect the amount of genetic variation attributable to population labels to be very small. For the typical common trait with h2g=0.10 (see [**4.1**]) and continental F_{ST}=0.15 (as estimated in populations with primarily European/African ancestry, for example) **we would thus expect <1.5% of the total trait variance to be explained by continental genetic differences** (confirmed in simulations above); whereas for a trait like Educational Attainment, with common direct h2g=0.04 (see [**5.3**]), we would expect <0.6% explained by continental genetic differences.

Finally, it is worth recalling that under neutrality (1) the mean difference is expected to go in either direction and (2) differences in genetic values alone are not sufficient to characterize overall phenotypic differences. Any trait-influencing environment (and any gene-environment interaction) likely differs across groups and can thus exacerbate or eliminate whatever differences in genetic means exist (see [**1.1**] for illustrative examples).

8.9 | Polygenic selection

While most of the above derivations were concerned with either locus-specific selection or neutral drift, a more plausible mechanism for selection on complex traits is *polygenic* selection: wherein selection acts on a polygenic trait as a whole, which percolates into weak selection on individual genetic variants in proportion to their effect on the trait. Since most common traits are driven by tens or hundreds of thousands of variants (see [**4.1**]), polygenic selection could explain how humans have adapted to changing environments while exhibiting weak or nearly neutral locus-specific selection effects. This is sometimes also conceptualized as redundancy: very many variants can influence the trait optimum through parallel channels and so no one variant is under strong selection (see (Barghi, Hermisson, and Schlötterer 2020) for a review/perspective of polygenic adaptation and redundancy).

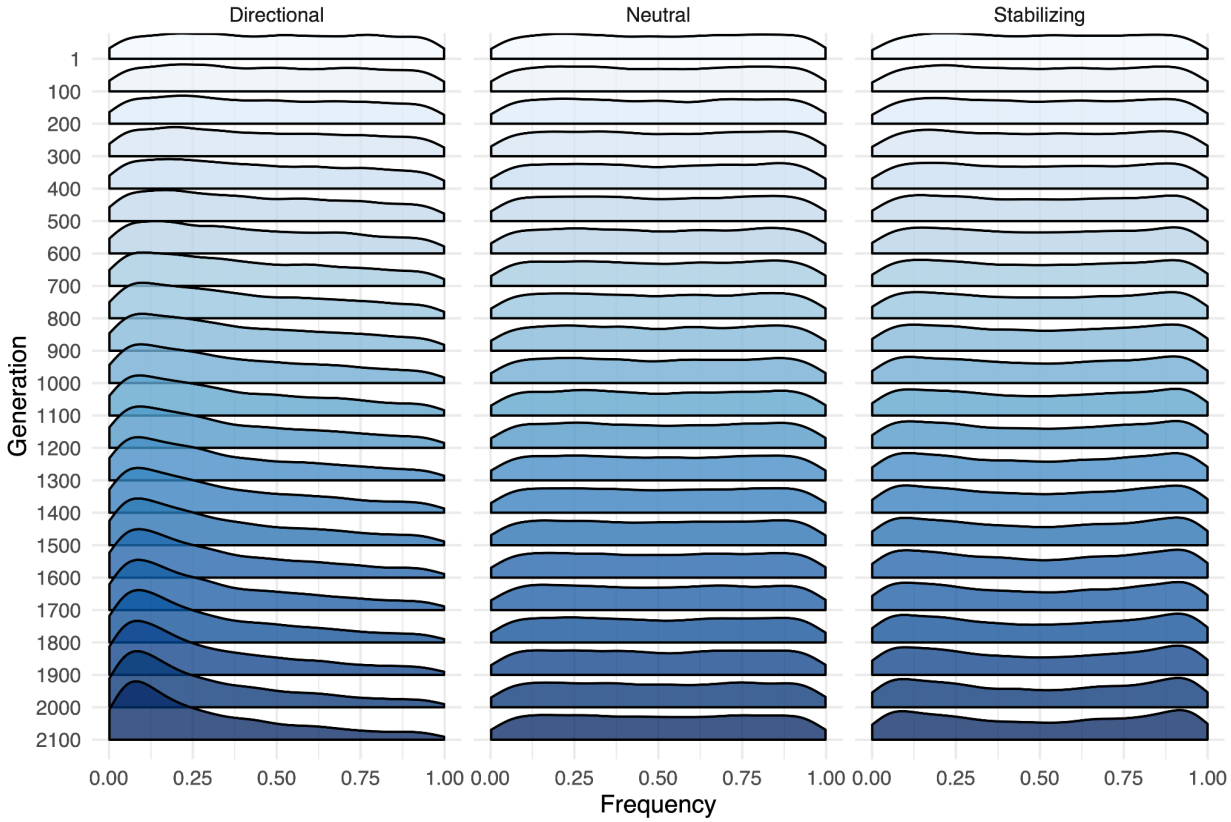
Impact on frequency

Polygenic selection shapes the overall relationship between causal variants and their allele frequency (and, as a consequence, their contribution to heritability). By simply applying the above recursive drift/selection models to multiple variants we can see how the allele frequency spectrum changes over the course of multiple generations:

Common causal variant frequency shifts under different models of selection.

Simulations with 5,000 causal variants, Ne=10,000, s=0.0007, and only common variants (MAF>1%) are

*shown. [**code**]*



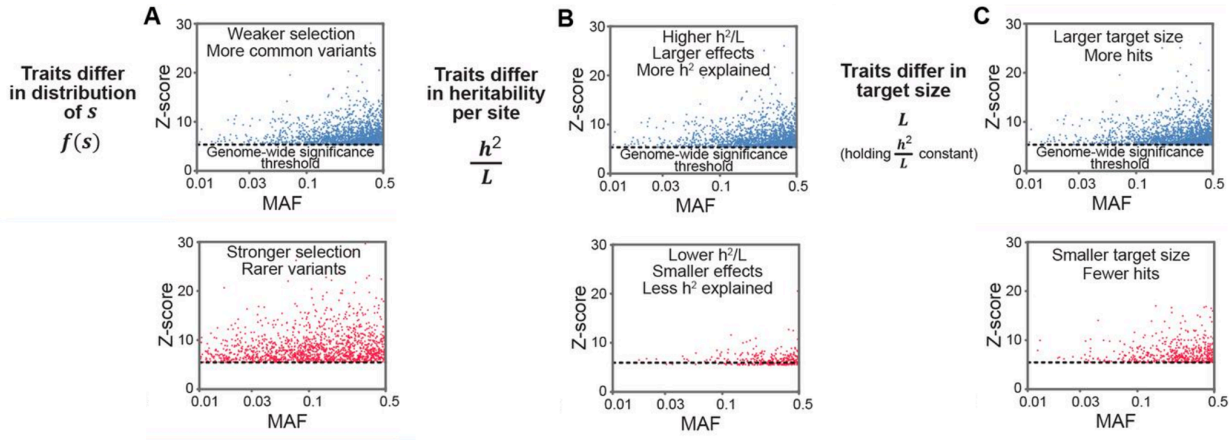
- Under **neutrality**, causal variants are distributed through the entire frequency spectrum and there is no relationship between allelic effect size and frequency. *Note*: even though the allelic effect is unrelated to frequency, rarer genetic variants have less genetic *variance* and will thus still contribute less to the total heritability of the trait.
- Under **directional selection**, alleles with fitness decreasing effects are driven to lower frequency and eventually out of the population.
- Under **stabilizing selection**, heterozygosity is selected against, driving variants to frequency extremes (purging of fixing) similar to directional selection (see [**8.4**]). Over time, only weak/null effect alleles will remain at medium frequencies and thus common variants will explain little of the trait variance. *Note*: these are dynamics at the fitness optimum, see below for shifts in the optimum.

Mutational target size

While the process of selection is generally expected to eliminate genetic variation (except for disruptive selection) it is countered by the introduction of new genetic variation through mutations leading to ***turnover*** in the genetic variants that contribute to traits and fitness. This turnover is the reason we continue to see any genetic variation in the population at all, and many theories have been derived as to potential balance in mutation, selection, and drift in maintaining genetic variation over extended periods of time (which we mostly ignore here as our focus is on relatively short time-scales). Modeling how this process may shape polygenic selection itself requires an additional parameter known as the mutational target size (**L**): the fraction of the

genome that, if altered, would influence the trait under selection (or, alternatively, the probability that a new mutation will influence the trait). This is a particularly difficult parameter to quantify and validate, with a ballpark estimate of 0.15–1.5 Mb (see (Sella and Barton 2019) for a comprehensive review). The relationship between selection coefficients (**s**), heritability (**h2**), and mutational target size (**L**) is concisely summarized in the figure below from (Simons et al. 2022) in the context of variants identified in a Genome-Wide Association Study (i.e. variants that have detectable effects on a trait and reach statistical significance): Higher **s** drives causal variants to have lower frequency; higher **h2/L** drives variants to have larger effects (and be more detectable at a fixed sample size); higher **L** (at a fixed **h2**/**L**) increases the overall **h2** and the total number of variants identified.

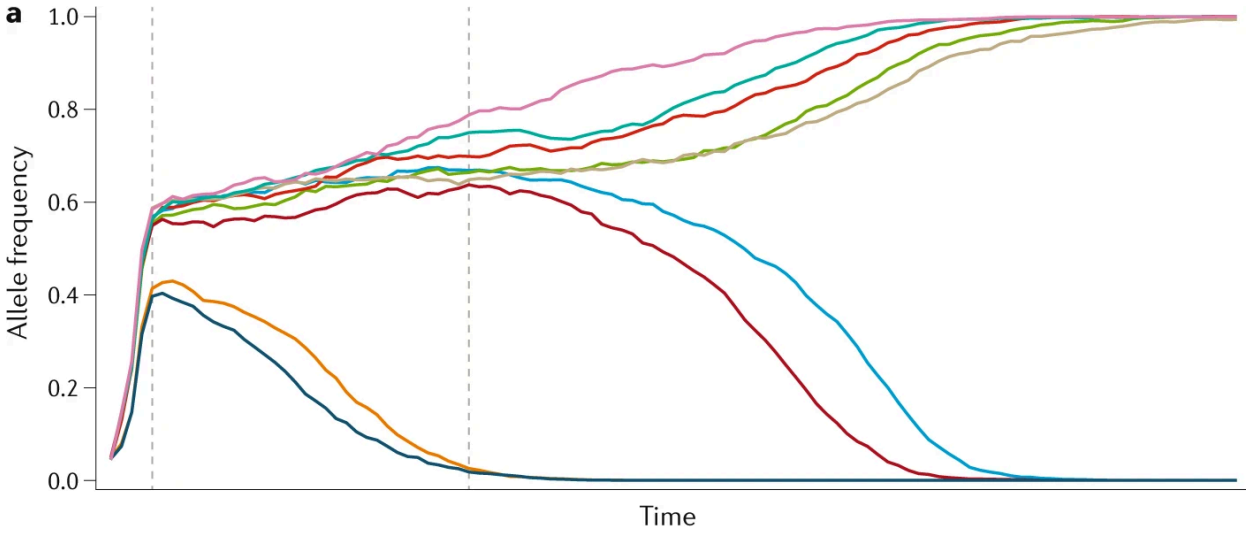
Expected impact of key parameters on the distribution of significant GWAS effects.
*Association statistics (Z-scores) as a function minor allele frequency (MAF) are shown for: (**A**) different selection parameters; (**B**) different heritability-per-site parameters; (**C**) different mutational target sizes. Figure modified from (Simons et al. 2022).*



Response to shifts in the optimum / polygenic adaptation

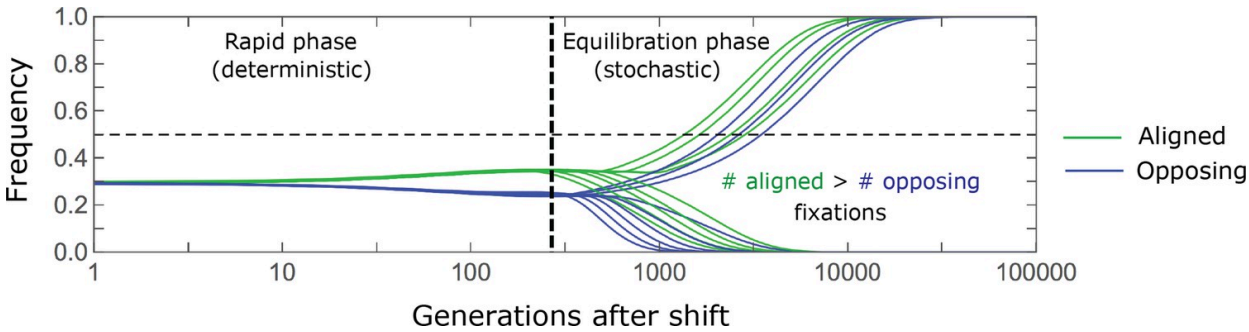
When a polygenic fitness optimum shifts (such in response to an environmental change), selection leads to changes in the trajectories of genetic variation, known as **polygenic adaptation**. Under stabilizing selection, this adaptive process is particularly complex and operates in two phases. In the first phase, genetic variation that moves the trait towards the optimum is strongly selected for and increases in frequency akin to directional selection. In the second phase, once the fitness optimum is reached, moderate frequency genetic variation drifts while high-frequency alleles are fixed in the population and low-frequency alleles are purged. In very large populations, the period of drift may last longer and be treated as second intermediate phase, as shown in the illustration below from (Barghi, Hermisson, and Schlötterer 2020):

Three phase model of stabilizing selection under polygenic adaptation.
*First, directional selection to move to the fitness optimum. Second, drift (depending on the population **Ne**) randomly distributes the alleles. Third, a gradual process where alleles of sufficiently high/low frequency move to fixation or elimination. Figure from (Barghi, Hermisson, and Schlötterer 2020).*



The specific allelic trajectories under stabilizing selection were modeled in (Hayward and Sella 2022). They further observe that the first, directional-like phase is rapid and *deterministic*: alleles that are aligned with the optimum will slightly increase in frequency and alleles that oppose the optimum will slightly decrease in frequency in proportion to their effect on the fitness trait. Whereas the second, equilibrium phase is long and *stochastic*: which specific alleles are fixed or disappear is a process driven by their (mostly arbitrary) starting frequency and the randomness of drift. Even large-effect, fitness-aligned alleles that were unlucky not to have reached moderate frequency by the end of the rapid phase are then expected to be eliminated by stabilizing selection in the equilibrium phase (Sella and Barton 2019; Hayward and Sella 2022). (Hayward and Sella 2022) summarize the consequences as follows: "*the alleles that fix are a largely random draw from the vastly greater number of alleles that affect the trait, both in the sense of being those that happened to segregate at high MAFs at the onset of selection and because of the stochasticity of fixation. Thus, in this plausible scenario, it becomes meaningless to say that any given fixation was adaptive, and arguably uninteresting to focus on the particular subset of alleles that happened to reach fixation*". In other words, **while stabilizing selection in response to a fitness shift can substantially change the allelic distribution, it does so over a very long period of time and in arbitrary ways with respect to the biological function of the alleles**.

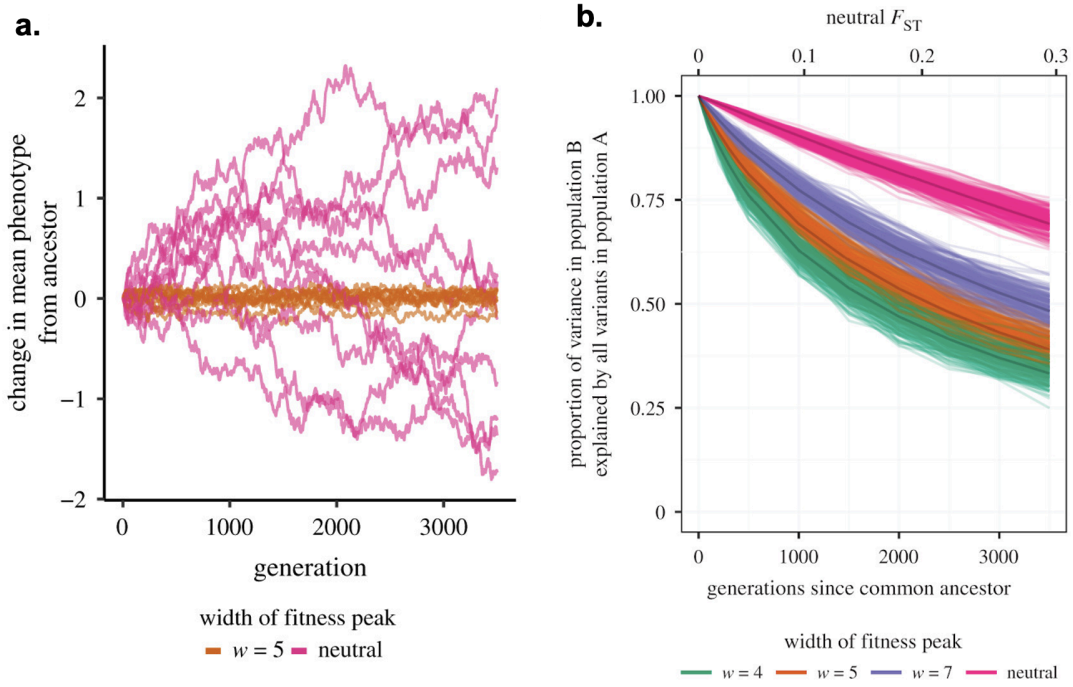
Model-based expectations for the deterministic and stochastic phases in response to a fitness shift.
The trajectory of fitness-aligned (green) and -opposing (blue) alleles is shown over time (x-axis, log scale). Vertical line shows the point at which the trait mean has reached the fitness optimum in the population. Figure from (Hayward and Sella 2022)



Stabilizing selection across groups

The ***stochastic "turnover"*** of mutations under stabilizing selection has important and unexpected implications for comparisons of genetic components across groups, as investigated in (Yair and Coop 2022). For a polygenic trait under stabilizing selection with the same fitness optimum in both groups: (1) the genetic value of the trait will vary less relative to a trait under neutral drift (i.e. selection "stabilizes" the genetic mean and $Q_{ST} < F_{ST}$; see panel [a] in the figure below); (2) genetic variation from an ancestral population (or from the comparison group) will explain less variance in the trait than expected under neutral drift, as it is selected out and replaced by new variation (see panel [b] in the figure below). These two forces lead to seemingly paradoxical scenarios where the difference in mean genetic value between populations is more *similar* than expected from F_{ST} and neutral drift (see [**8.7**]) but many individual trait-influencing polymorphisms are more *different* than expected between the populations (and, as a consequence, as are polygenic scores). **Notably, tests for excess F_{ST} (or similar measures of genetic differentiation) at trait-causing loci may thus appear to be significant even when the fitness optimum and genetic mean does not differ between populations**.

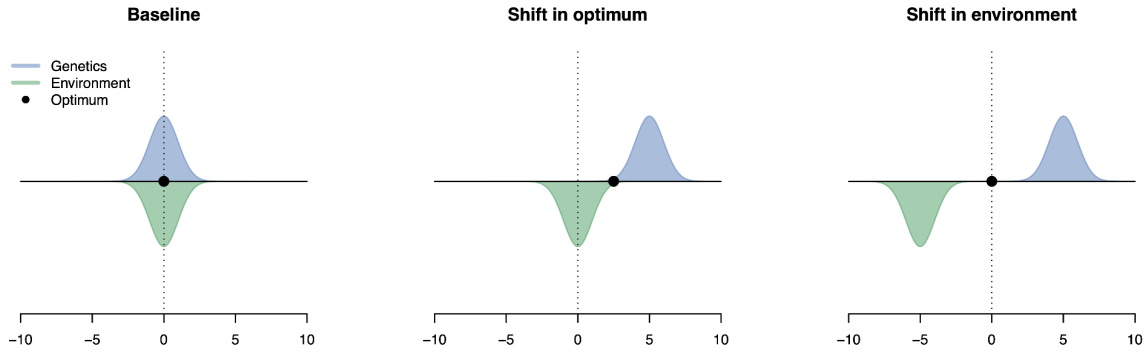
Group differences due to stabilizing selection on a shared fitness optimum.
(a) Stabilizing selection reduces the variance in the mean phenotype with respect to the ancestral population, relative to neutral drift. (b) At the same time, stabilizing selection increases the genetic differences across populations (proportion of variance in one population not explained by variants in the other). Figures from (Yair and Coop 2022).



Same adaptive evolution, different optimum

It is useful to keep in mind that polygenic stabilizing selection acts to keep the *entire* trait at the fitness optimum. Since the trait consists of both a genetic and environmental component (as well as interactions between the two), this implies that the same apparent genetic adaptation can be the consequence of either a fitness shift or an environmental shift (see (Harpak and Przeworski 2021) for a detailed presentation of this phenomenon). As illustrated in the figure below, an identical genetic response to selection can occur whether the fitness optimum changes and the environment stays the same, or the environment changes and the fitness optimum stays the same.

Toy examples of identical genetic adaptation for different environmental contexts. *For a simulated trait that is 50% heritable, the genetic component is shown in the positive range and the environmental component is shown in the negative range. (**left**) A population at baseline where the fitness optimum (dot) is at zero and both the genetic component and the environmental component are centered at the optimum. (**middle**) A shift in the fitness optimum but not the environment leads the genetic component to adapt to a higher optimum value. (**right**) A shift in the environmental component but not the fitness optimum leads the genetic component to adapt to the same higher optimum value. The first and third populations have the same fitness optimum but different genetic values. The second and third populations have the same genetic value but different fitness optimum. Figure modeled after (Harpak and Przeworski 2021). [**code**]*



For example, a population with a nutrient rich environment could adapt to a different mean genetic value for body weight than a population with fewer nutrients even though the fitness optimum and mean body weight remain exactly the same. Likewise, a population where the fitness optimum shifted up so that higher weight lead to more births (for, say, cultural reasons) would exhibit the same adaptation as a population where the environment shifted down to reduce body weight (e.g. lower nutrition) and the fitness optimum stayed the same, with genetics then compensating for the environmental shift. **As argued in** (Harpak and Przeworski 2021)**, this lack of identifiability highlights a broader challenge in defining genetic, environmental, and fitness components in isolation**. Such definitions are further complicated by the fact that selection likely acts pleiotropically on a latent fitness phenotype that is unobserved and genetically correlated to many observed phenotypes, which then interact with the environment (Barghi, Hermisson, and Schlötterer 2020; Simons et al. 2022).

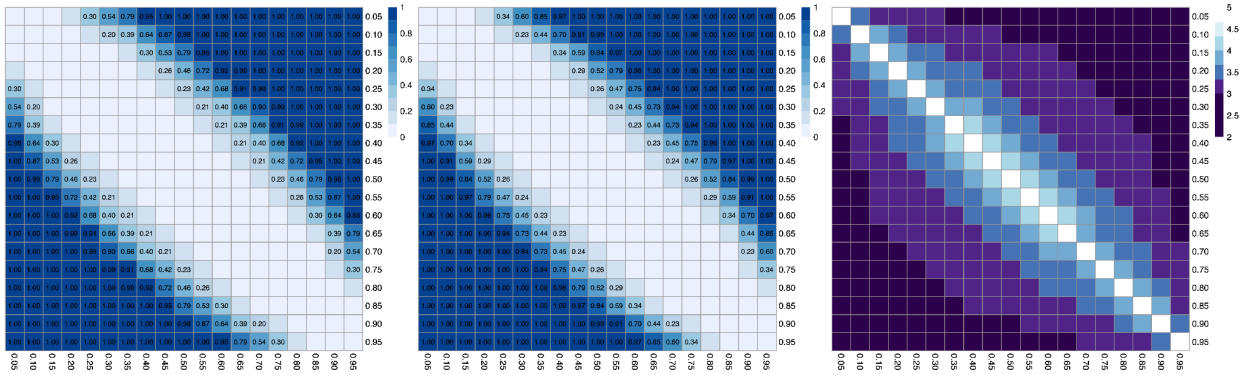
8.10 | Testing for locus-specific selection

Divergent selection between populations

For two populations (or two temporal measurements) the most basic test for selection is to evaluate whether a variant has changed frequency more than would be expected from drift alone. **In other words, rather than testing for specific forms of selection, we test for deviation from neutral drift**. Given the frequencies of the allele in two populations and the population **Ne**'s and divergence, we can derive a test statistic for whether the difference deviates from zero by applying the Waples drift variance equations derived in [**8.3**] to *both* allele frequencies observed (as well as accounting for sampling to estimate the frequencies). While **Ne** is often not known, it can be derived from the data using putatively neutral sites or other approximations. Importantly, if selection is not divergent (i.e. alleles are under the same selection coefficient in both populations) then their frequency difference will not be significant. We can run some simulations and evaluate the statistical power to detect varying levels of selection in this way, using hypothetical data from two modern-day populations with Ne=10,000 and a complete divergence ~2,100 generations ago (e.g. the out of Africa migration):

Power to distinguish selection from drift.

*(**left**) Statistical power to detect selection from drift for pairs of allele frequencies in two populations (at p<0.05) with n=100 samples in each. (**middle**) same as left but with n=1,000 each. Entries with >20% power are labeled. (**right**) The selection coefficient corresponding to each allele frequency shift is shown in -log10; strong selection shown in dark purple (**s**>0.001), weak selection in purple (**s** between 0.001 and 0.0005); nearly neutral selection in shades of blue (**s**<5x10^{-4}). [**code**]*



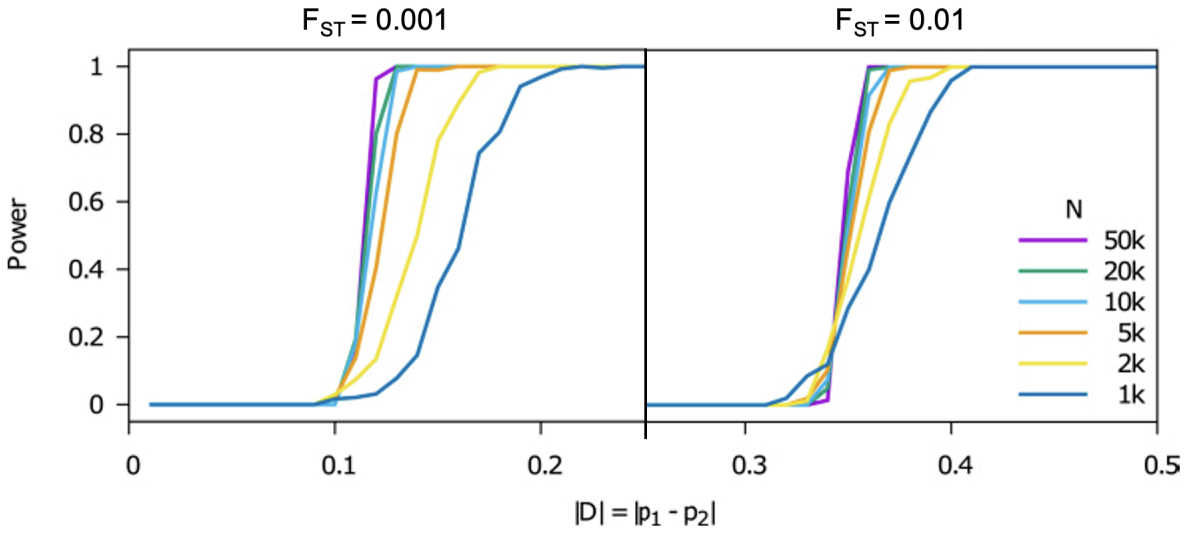
The overall takeaway is consistent with our estimates of the scaled fixation probability: **for alleles under strong selection there is *ample* power to detect them; there is *some* power to detect moderate/weak selection, which just covers the estimated mean for complex traits; but there is no power to detect very weak selection in the nearly neutral range, as expected**. The other observation is that the sample size difference between n=100 and n=1000 (left and middle panels) is mostly negligible, this is because the inability to detect nearly neutral selection is not due to insufficient measurements/observations, but due to hitting a parameter barrier imposed by neutral drift variance.

Continuous population divides

The two population approach has been extended to continuous population divergence (migration or expansion, for example). Rather than testing for a non-null difference in frequencies between the populations, the test is for a non-null *association* between frequency and continuous ancestry: specifically whether the frequency relationship is stronger than would be expected solely from drift along the cline (Galinsky et al. 2016). For a given global ancestry estimate (see [**9.3**] for estimating continuous ancestry from data), every variant can then be tested for excess association akin to a GWAS where ancestry is the phenotype. (Galinsky et al. 2016) evaluated the power of this approach as a function of frequency differences for populations with varying levels of F_{ST}. Sensitivity to detect an association exhibited a phase shift where allelic differences were either impossible to detect, once sufficiently diverged (beyond what is expected from drift) easily detectable from sample sizes of just a few thousand. Drift rather than sample size continues to be the primary statistical barrier for detecting weak selection on individual sites.

Statistical power to detect divergent selection on a population continuum.

Statistical power at $p<8.3x10^{-7}$ for two simulated populations separated by varying F_{ST} (0.001 and 0.01) as a function of frequency difference (x-axis). Results from varying total sample size shown with colored series. Figure adapted from (Galinsky et al. 2016).



Multiple populations

The simple two-population approach has also been extended to multiple populations by modeling expected frequency deviations between pairs of populations as drawn from a **multivariate normal** distribution. The covariance matrix in the multivariate normal reflects neutral population drift between pairs of populations and is typically estimated from putatively neutral alleles in the data (Coop et al. 2010). In testing for selection, this null model is essentially *factored out* of the observed frequencies and the remainder is tested for a significant non-zero difference. This flexible model has subsequently been applied to a variety of population inference tasks including tree-like relationships, migrations, and admixture (Pickrell and Pritchard 2012). The

model will also form the basis for a widely used test for polygenic selection, described in more detail below.

8.11 | The Breeder's Equation and heritability (revisited)

To close this section, we'll link these new concepts around selection to the concepts around heritability that were discussed previously through the lens of a traditional definition of heritability from studies of agricultural and animal breeding.

Theory

A widely used parameterization of heritability is the Breeder's Equation, which relates (narrow sense) heritability to the expected change in phenotype after selective breeding in a controlled environment. Specifically, given a population with a normally distributed phenotype, if one selects a subpopulation with a mean phenotypic difference S (the *selection differential*, formally defined as the mean phenotype in the selected population minus the mean phenotype in a hypothetical unselected population), then the expected phenotypic change (or *response*) R in the next generation in a controlled environment can be modeled as:

$$R = h^2 S$$

For example, if we select individuals with a trait mean of 8 from a population with a mean of 5 and h2 = 0.5, then S = 8 - 5 = 3, R = 0.5 * 3 = 1.5, and the expected phenotype in the offspring after selection is 5 + 1.5 = 6.5. Whereas if h2 = 0, then the same selection will result in a response of zero (i.e. no change in trait mean). We can see how this definition of [h2] differs substantially from earlier definitions of [h2g] (see [**1.1**]): h2 is defined in terms of a causal action (breeding) on a *prospective* phenotype in a controlled environment and is agnostic to the genetic mechanisms; h2g is defined in terms of *correlation* of specific genetic *particles* with a *retrospective* phenotype in its retrospective environment. Notably, indirect effects (see [**3.0**]) do not contribute to the selective response and, since the environment is assumed to be fixed, and therefore should not contribute to h2 defined this way.

While the Breeder's equation accurately predicts the response to a single generation of selection, the dynamics get more complicated when predicting the *long term* response to selection. Selection on a heritable trait restricts the additive genetic variation acting on that trait by (**a**) moving alleles to fixation (as we saw above) and (**b**) drawing previously unlinked variants into negative disequilibrium – a collider bias-like phenomenon known as the **Bulmer effect** (Bulmer 1971). At the same time, competition of causal effects across linked variants can reduce the impact of selection, known as **Hill-Robertson interference** (Felsenstein 1974). In the absence of new genetic variation the overall reduction in genetic variance leads to a decrease in h2 and, as a consequence, a weaker response to selection (still accurately predicted by the Breeder's equation given the new h2 in each generation). Thus, even under controlled breeding with fixed environments, knowing h2 alone is not sufficient to model longer term trends in the phenotype.

The long-term response to selection also depends on the *population and trait architecture* including:

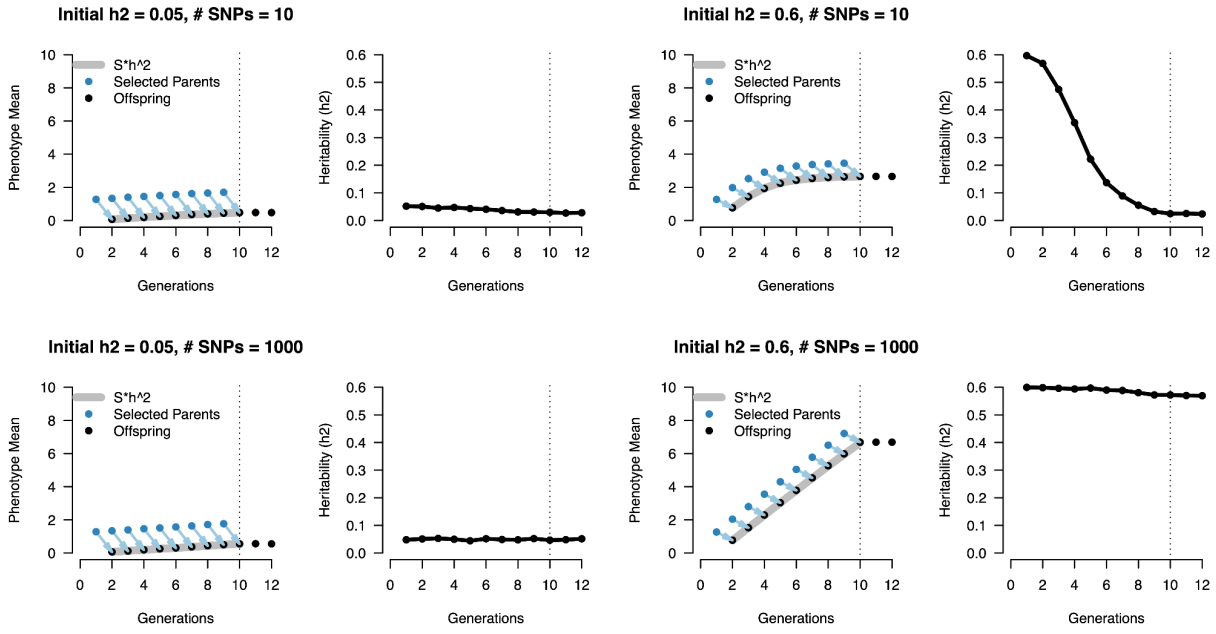
- effective population size, which defines the strength of drift
- frequency, correlation/LD, and effect distribution of causal variants in the starting generation
- recombination rate, which degrades Hill-Robertson interference and the Bulmer effect
- mutation rate, which introduces new genetic variation
- mutational target size, which defines how new mutations influence the trait

Quantifications of the expected cumulative response to selection have been developed under the infinitesimal model (without frequency changes) (Bulmer 1974), under a drift model (without linkage; the Robertson model) (Robertson 1960) and under both (Hill and Robertson 1966).

A simple simulation illustrating these concepts is shown in the figure below. We can see the phenotypic response to long term selection over 10 generations for traits with different h2 and number of causal variants. In each generation, individuals in the top 25% of trait values were selected (blue dots) and then randomly mated to generate the next generation (light blue arrow, with h2 determining how similar the offspring phenotype is to the selected parents). The expectation from the Breeder's Equation is shown in gray and matches the observed phenotypic mean after selection. The true h2 (used in the Breeder's Equation) is shown to the right of each panel and in all instances it decreases over time. We can see that for a trait with 10 causal variants the h2 drops precipitously and the response to selection plateaus, whereas for a trait with 1000 causal variants the h2 drops very slowly and the response is *nearly* constant in each generation (because it takes longer for this many variants to reach fixation). After selection is stopped in the 10th generation, the phenotype and heritability remains relatively constant. This is a simplified simulation with an effectively infinite recombination rate and so these numbers are only illustrative, but the general expectation is that higher polygenicity leads to a more sustained selection response.

The long-term response to selection for simulations of four disease architectures.

*Each panel shows the phenotype mean (y-axis) versus generations of selective breeding (x-axis) with the selected individuals in blue and the subsequent generation of offspring in black (connected with a light blue arrow). The gray line shows the expectation from the Breeder's Equation in each generation. [**code**]*

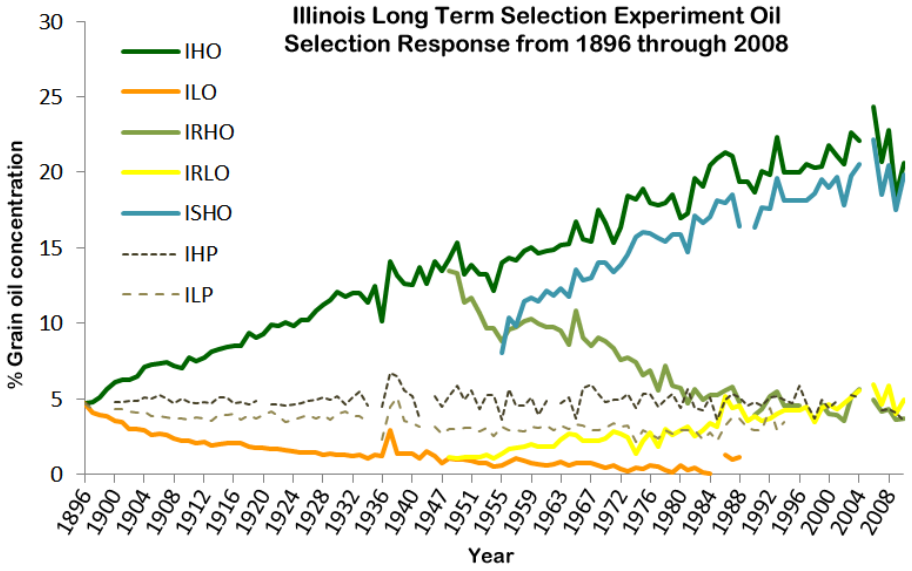


Consistent response to controlled selection

In controlled settings, the response to selection can be strikingly reliable for many generations. A canonical example is the Illinois long term selection experiment, where maize kernels were selected for oil concentration, which has been running for over 100 generations (Laurie et al. 2004). In each generation, truncating selection was imposed to select the top or bottom 20% ears of corn based on oil (and separately protein) concentration. Through many generations of selection, the oil concentration was increased from 5% to >20% for the high-oil (IHO) and to <1% for the low-oil (ILO) strains, with only the ILO hitting the limits of selection and discontinued in the 89th generation. The sustained response is remarkable, and consistent with a highly polygenic architecture. Given the low effective population size (estimated Ne of just 10), quantitative analyses further suggest a substantial contribution to fitness from new genetic variation through mutations (Walsh 2010).

Grain oil concentration in response to selection in maize.

IHO/ILO are two strains that have been selected for high oil concentration whereas IHP/ILP were drawn from the same source population but are not selected and only experience random drift. Other colors represent strains where selection was reversed. Figure from [Moose Lab].



Inconsistent response to natural selection

[🔥I am a human geneticist and this is only a cursory survey of findings from animal genetics]

In contrast to the highly consistent response to controlled selection, natural selection often produces negligible or even opposite results, sometimes referred to as a "stasis paradox" (Bonnet et al. 2017). (Walsh and Lynch 2018) highlight a number of instances in natural animal populations where sustained selection on a heritable trait exhibited a paradoxical response, which are transcribed below.

Examples of natural populations failing to respond to selection.

The organism, heritability (h2), selection intensity (i: the selection differential S scaled by the phenotypic variance), duration, and response are listed.

Transcribed with minor corrections from Table 20.3 of (Walsh and Lynch 2018)

Reference	Species	Species / Trait	h2	Intensity (i)	Duration (years)	Response
Kruuk et al. (2000, 2002)	Red Deer	Antler mass	0.33	0.44	29	Opposite
Kruuk et al. (2000, 2002)	Red Deer	Birth Mass (male)	0.11	0.40	29	None
Kruuk et al. (2000, 2002)	Red Deer	Birth Mass (female)	0.25	0.22	29	None
Milner et al. (1999, 2000)	Soay Sheep	Body mass (Male)	0.12	0.11	12	None
Milner et al. (1999, 2000)	Soay Sheep	Body mass (Female)	0.24	0.07	12	None
Bonnet et al. (2017)	Snow Vole	Body Mass	0.17	0.21	10	Opposite
Larsson et al. (1998)	Barnacle Goose	Tarsus length (male)	0.53	0.03	13	Opposite
Larsson et al. (1998)	Barnacle Goose	Tarsus length (female)	0.53	0.09	13	Opposite

Reference	Species	Species / Trait	h2	Intensity (i)	Duration (years)	Response
Cooke et al. (1990)	Snow Goose	Clutch size	0.20	0.30	20	Opposite
Merilä ̈et al. (2001a, 2001b)	Collared flycatcher	Relative mass	0.30	0.23	17	Opposite
Alatalo et al. (1990)	Collared flycatcher	Tarsus length	0.52	0.12	4	None
Kruuk et al. (2001)	Collared flycatcher	Tarsus length	0.35	0.18	17	None
Sheldon et al. (2003)	Collared flycatcher	Breeding time	0.19	0.22	19	None
Charmantier et al. (2004)	Blue tit	Body mass	0.27	0.31	14	None
Charmantier et al. (2004)	Blue tit	Body mass	0.35	0.42	12	None
Charmantier et al. (2004)	Blue tit	Tarsus length	0.47	0.27	13	None
Charmantier et al. (2004)	Blue tit	Tarsus length	0.48	0.21	12	None
Gienapp et al. (2006)	Great tit	Breeding time	0.17	0.21	30	None
Horak et al. (1997)	Great tit	Egg size	0.80	0.38	7	None
Garant et al. (2004)	Great tit	Fledging mass	0.24	0.21	36	Opposite
Garant et al. (2005)	Great tit	Fledging mass	0.20	0.14	36	Opposite
Garant et al. (2005)	Great tit	Fledging mass	0.29	0.18	36	None

A brief review of these studies highlights many possible explanations for the failure of the selection response, often echoing many of the caveats discussed in this section on selection and prior sections on heritability. While the instances of no selective response may be indicative of widespread stabilizing selection (though it has been difficult to quantify empirically), the negative response is likely an indication of more complex, environmentally driven confounding. **These studies thus provide tangible and compelling examples of the difficulty in accurately estimating and understanding the mechanisms of heritability and selection**, even in seemingly simple populations of mammals and birds. As the specific cases are often interesting in their own right, I have quoted some representative examples:

Bias in heritability estimates and indirect genetic effects.

- (Charmantier et al. 2004): "*Our analyses show large common environment effects, which may be due in part to maternal effects. These maternal effects may in part be due to the mother's genotype, i.e. indirect genetic effects. Such effects can alter the response to selection, and may constrain or even reverse an evolutionary response, depending on the sign of the covariance between the direct and the indirect genetic effects and the respective selection pressures*"

Confounding from selection on an unmeasured trait and/or environmental correlations.

- (E. B. Kruuk et al. 2002): "*The results were however in agreement with all the predictions from the environmental covariance explanation for a lack of response to selection. Under this scenario, breeding success would have been determined by an unmeasured trait*

such as body condition or nutritional state, which was phenotypically correlated with antler mass but for which there was no genetic correlation with antler growth. Increased breeding success would then be associated with increased antler mass, but only because of the environmental covariance between fitness and the trait, generating misleading expectations of evolution in antler size because the true target of selection has not been correctly identified"

Changes in the environment masking or confounding the action of selection.

- (Bonnet et al. 2017): "*Inferred birth dates revealed that snow fallen during the preceding winter is a major ecological factor constraining the onset of reproduction in the spring … This suggests that the shortening of the snow-free season, and thereby selection for lower predicted adult mass, is a novel phenomenon that the population is currently in the process of adapting to.*"

- (Merilä, Kruuk, and Sheldon 2001): "*The estimated microevolutionary change has presumably been concealed by an increasingly negative influence of environmental conditions on the condition index … A plausible agent explaining this deterioration is the large-scale climatic trend that has reduced the caterpillar food supply—the main food of growing nestlings—over the last few decades.*"

- (Garant et al. 2004): "*By combining information about changes in both population breeding density and the early spring temperature over time, we were able to show that the combined action of these two processes can explain a large proportion of the difference between the phenotypic and genotypic responses in this population*."

- (Larsson et al. 1998): "*We conclude that the most likely ultimate explanation for the body-size decline in the main study colony is that a density-dependent process, which mainly was in effect during the very early phase of colony growth, negatively affected juvenile growth and final size. The decline in body size of breeding birds observed in the main colony during our study period was most likely a lagged response to this density-dependent process, that is, smaller locally born birds recruited successively to the breeding population when two to four years old. As a possible density-dependent mechanism we propose that brood-rearing families in very young and small colonies may have access to some highly nutritious but relatively rare food plants, which, when colony size increase only will constitute a minor proportion of the diet of growing individuals*"

Notably, a recent large-scale meta analysis quantified a substantial additive genetic variance on fitness *itself* ($V_A(w) = 0.19$), which contrasted with a much lower heritability of fitness ($h2(w) = 0.03$), suggesting that a large absolute capacity to respond to selection is systematically compensated for by large-scale environmental variability (Bonnet et al. 2022). (Walsh and Lynch 2018) further summarize these and other potential explanations for stasis in the selection response, transcribed in the table below (and see similar discussion in (Hansen, Pélabon, and Houle 2011; Pujol et al. 2018)).

Potential reasons for failure to observe a response to selection
Transcribed from Table 20.4 of (Walsh and Lynch 2018)

Genetic response has occurred, but was not detected.

- Low power to detect a genetic trend.
- Genetic gain countered by environmental deterioration.

The focal trait is not the target of selection.

- Trait and fitness are correlated through an environmental variable.
- Selection on a phenotypically, but not genetically, correlated trait.

Consequence of open population structure.

- Immigration from populations outside of the study area.

Consequence of fluctuating environmental conditions.

- Fluctuating selection differential, with little net selection.
- Fluctuating h2, with smallest h2 when selection is strongest.

Constraints and tradeoffs.

- Direct response on a trait countered by correlated responses from other traits.
- Measured fitness component is an incomplete measure of total fitness.

The debate over the "missing response" (Pujol et al. 2018) in studies of animal evolution has some parallels to the debate over "missing heritability" (Manolio et al. 2009) in human genetics. If we shuffle the terms around and redefine [h2 = R/S], then the table above with [R] exhibiting zero or negative values can be interpreted as a kind of "missing" heritability: pedigree/model-based estimates of heritability being substantially inflated relative to causal observations in the full population. In both cases, population genetics methods with strong assumptions on environmental partitioning were applied to dynamic populations and produced paradoxical results. In some cases, careful molecular and environmental modeling enabled the identification of environmental confounders or interactions that had not been considered. **In thinking about the heritability of human traits, it is worth considering whether we expect humans to function more like maize/cattle in a controlled breeding experiment or like natural animal populations in the wild.**

8.12 | Further reading

Basic parameters:

- (Waples 2022): Review of effective population size (Ne)
- (Slatkin and Rannala 2000): Review of allele age
- (Bhatia et al. 2013): Review of F_{ST} and recommendations for estimating it.

- (Edge and Rosenberg 2015b): Derives the relationship between F_{ST} and trait differences for polygenic traits (Q_{ST}).

Selection:

- (Sella and Barton 2019): Comprehensive review of stabilizing selection and implications for human genetics.
- (Koch and Sunyaev 2021): Concise review of stabilizing selection primarily focusing on polygenic traits.
- (Berg et al. 2019): Theory and analysis for the impact of stratification and background selection on polygenic selection tests.

Heritability/selection in non-human animals:

- (Hansen, Pélabon, and Houle 2011): Perspective on the relationship between heritability and *evolvability* of traits.
- (Pujol et al. 2018): Perspective on the (lack of) relationship between heritability and response to selection in animal populations.
- (Bonnet et al. 2022): Large-scale meta-analysis of the genetic variance and heritability of fitness in animals.

Concepts: race and genetic ancestry

9.0 | Summary

- **Race and genetic ancestry are distinct concepts with distinct causes and consequences.** Race is defined within a social context. Genetic ancestry is defined within the context of reference populations.
- Race, either a historical “essentialist” views or a more contemporary “population” views, provides a poor model of true genetic variation. Genetic variation follows a “nested subset” model where the most variation is observed in Africa and subsets of that variation

are observed in Europe, Asia, and the Americas. **Model fitting of race to genetic data provides a much worse fit than a nested subset model that is incompatible with race** (Long, Li, and Healy 2009)**.**

- Comparing pairs of sequenced individuals, **the largest number of differing sites were within Africa (consistent with a nested evolutionary model)**: a pair of Yoruba/Yoruba individuals have more differences than a pair of Yoruba/French individuals (Biddanda, Rice, and Novembre 2020). Most of the differences between pairs of individuals were because one individual carried a globally common allele and the other did not.
- Estimates of F_{ST} between divergent geographic populations range between 0.11 and 0.15 (Bhatia et al. 2013), in other words, **if we take the individual-level genetic variation at a typical polymorphism and *condition out* population labels, we will still be left with 85% of the original variance**. This is in stark contrast to historic racial models that assumed racial groups were largely homozygous within populations and highly divergent between (i.e. F_{ST} close to 1.0).

- A brief tour of methods for analyzing population structure in genetic data:
    a. Principal Components Analysis (PCA), an eigendecomposition of the sample relatedness matrix, can identify individuals drawn from populations with differing allele frequencies. **Theory indicates that PCA is extremely sensitive and is expected to identify structure in most large datasets** (Patterson, Price, and Reich 2006). While PCA has useful genealogical properties, it is easily distorted by the sampling of individuals (McVean 2009) and can also produce arbitrary non-linearities in the presence of spatially local structure (Novembre and Stephens 2008).
    b. Model-based clustering (STRUCTURE) attempts to identify individuals as mixtures of alleles from a fixed set of populations (Pritchard, Stephens, and Donnelly 2000). **STRUCTURE is similarly distorted by the sampling of individuals, as well as the number of defined populations**, including identifying admixtures that do not exist in truth or missing admixtures that do exist (Lawson, van Dorp, and Falush 2018).
    c. Parametric models (Admixture Graphs) attempt to fit populations to trees or graphs based on tests of cross-population allele sharing. **Admixture graphs can often identify incorrect graphs that provide a better fit to the data than the true graph, or many equally likely graphs**. Reanalysis of published admixture graph studies demonstrated several instances where historical conclusions were drawn from data that was compatible with many different graphs (Maier et al. 2023).
    d. **All ancestry inference methods are biased by the sampling process and/or model parameters, and no method can identify "true" ancestry because the true sampling process is unknown**.

- A brief tour of genetic ancestry in large-scale datasets:
    a. **All large biobanks exhibit continuous population structure that is poorly explained by conventional racial groups** (Wojcik et al. 2019).
    b. When restricting to "homogenous" ancestry populations enriched for European origin, continuous PCs are observed that reflect ancestry from reference populations *within* Europe (Galinsky et al. 2016). When restricting to homogenous

white individuals in a single European country (the UK), county level PCs are observed (Agrawal et al. 2020).

c. The same patterns arise in other countries: A large Chinese biobank identified PCs that correlated with within-city neighborhoods (Walters et al. 2023); a large Japanese biobank identified PCs that correlated with dozens of local regions (Sakaue et al. 2020).

- A brief tour of human history from population genetics:
    a. Diverse studies of modern and ancient DNA have demonstrated that historic admixtures and migrations were ubiquitous and highly dynamic. **Genetic ancestry rarely reflects current geographic patterns and disputes simple models of isolated human development** (Pickrell and Reich 2014)**.**
    b. Modern individuals from the Americas are generally more similar in their ancestry to European than to Native American reference individuals (Moreno-Estrada et al. 2013; Gravel et al. 2013). Native American reference individuals exhibit complex relationships to ancient Siberian genomes as well as modern Polynesian populations (Ioannidis et al. 2020), where the latter appear to have been settled directly by East Asian groups (Skoglund et al. 2016).
    c. European individuals derive ancestry from historic populations that often no longer exist in un-admixed form (Lazaridis et al. 2014; Sikora et al. 2019) or were rapidly displaced (Olalde et al. 2018). In more recent history (the Bronze Age) both extensive migration and population structure have been observed across Europe (Antonio et al. 2024).
    d. Admixture and migration is extensive in Africa in both modern (Fan et al. 2023) and ancient data (Skoglund et al. 2017; Lipson et al. 2020). Yet there are massive gaps in our understanding of African population history including competing theories of continuously mixing pan-African "metapopulations" (Scerri, Chikhi, and Thomas 2019; Ragsdale et al. 2023) versus recent "back to Africa" migrations (Cole et al. 2020).

- In short, human history has been highly dynamic, with extensive admixture, instances of rapid migration, geographic shifts, ancient introgression events, historic populations that no longer exist in unadmixed forms. **Conventional models of race are irrelevant to the study of genetic variation, and even models of simple population relationships are proving to be fundamentally wrong**.

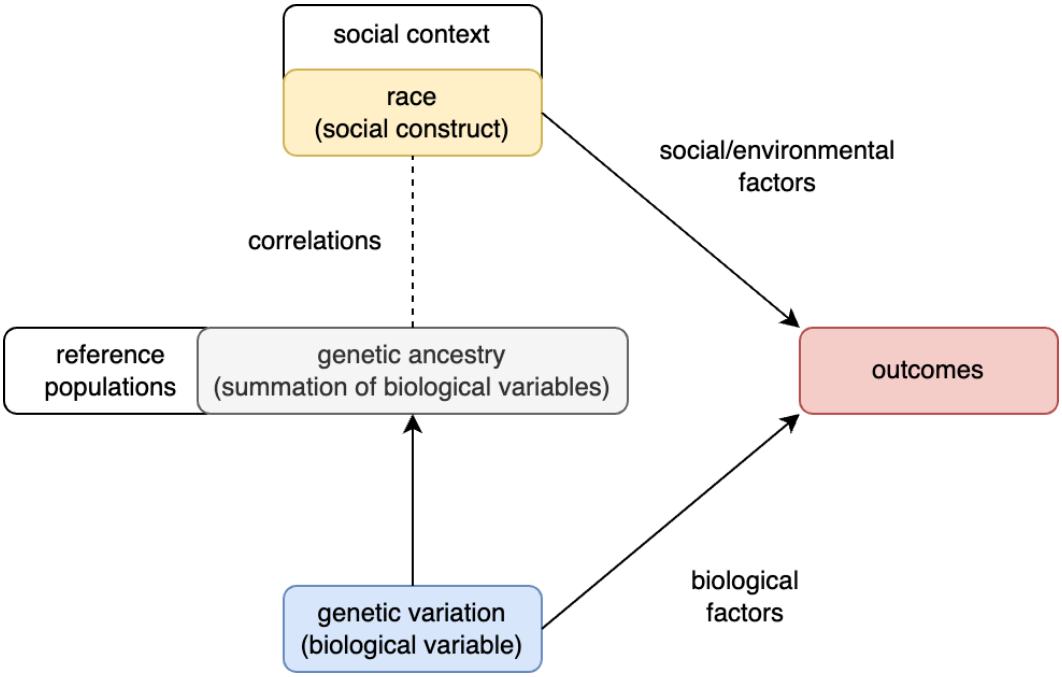
9.1 | Definitions and conceptual models of race

Race is the social categorization of individuals into groups based on perceived (typically physical) traits. It can be further subdivided into (a) self-identified race and (b) race as perceived by others (naturally these two concepts also interact: people who are told they are a given race will start to perceive themselves as that race). As it is a social construct, race is estimated through self-reporting; there are no "biomarkers" or "diagnostics" for race. Race is often *correlated* with physical features (e.g. pigment) and, by proxy, with their genetic underpinnings (e.g. pigmentation

genes). **A common rhetorical trick is to conflate *correlation* with race as *biological causation***: certain race constructs are correlated with darker/lighter skin, but neither self-identifying as a different race nor being perceived as a different race *causally* changes one's skin color or other biology. At the same time, as with any social construct, race can be causal for social/cultural outcomes: race perceived by others can be causal for discrimination, self-identified race can be causal for certain cultural preferences, etc. **There is no contradiction between race being causal for social outcomes but not causal for biology, since society and biology are distinct**.

Genetic ancestry is a quantification of genetic material inherited most recently from a given reference population (typically using contemporary populations as a proxy). Genetic ancestry is thus a relative quantity, as all individuals eventually derive ancestry from the same ancestral populations. Genetic ancestry can be *causal* for certain traits: for example when certain populations carry pigment alleles at higher frequencies, genetic ancestry – the transmission of those alleles – will have a causal effect on their skin color. Genetic ancestry can thus be *correlated* with race through its causal effect on observable traits.

Schematic of the relationships between race, genetic ancestry, and outcomes

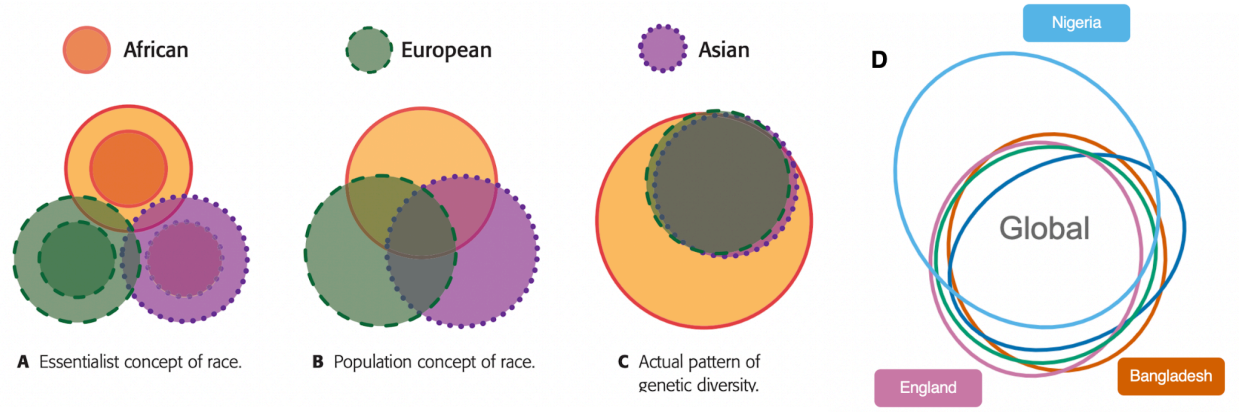


A testament to the broad acceptance of race as a social construct that is distinct from ancestry is that even fringe racists have started conflating race and ancestry: proposing concepts such as "genetic race" or referring to individuals as "genetically black/white". **Since we are interested in distinguishing causes from correlations, we should reject this obfuscation and use clear language**. Moreover, race and ancestry are distinct not only in the way they are *constructed* but also in the way they *model* the world:

Different conceptual models of race fail to reflect genetic diversity.

*(**A**) The "essentialist" concept of race where humans are partitioned into distinct groups based on physical appearance; (**B**) the "population" concept of race where humans are partitioned into semi-distinct clusters of genetic ancestry; (**C**) the "nested subsets" model of genetic diversity; (**D**) "Euler diagram" of the overlap*

*between common variation in real genetic data from populations selected to be racially diverse, three of which are labeled. Figures (**A,B,C**) from [Playing the Gene Card] and (**D**) from [Visualizing Human Genetic Diversity].*



The early "essentialist" models of race advocated for the partitioning of humans into fundamentally distinct groups based on appearance, with some overlap at the margins to acknowledge "mixed-race" individuals. These models operated under the assumption that human races had undergone substantial divergent evolution and that most genetic variation had fixed to different values between racial groups, leading to observable differences in skin and hair. More contemporary population/ancestry based models of race continue to advocate for partitions between "populations" of individuals but rather than base these partitions on hard physical characteristics, they are based on softer genetic ancestry "clusters". **In truth humans spent most of their evolutionary time in Africa, which included the accumulation of the vast majority of common variation (see [8.3]), followed by multiple gradual and complex dispersals and mixtures into other parts of the world**. These dispersals involved population "bottlenecks" that increased drift and thereby reduced the genetic variation in the subpopulations, yielding a **"nested subset"** of populations where most genetic variation present outside of Africa is also present inside of Africa (with non-African populations experiencing a small amount of additional novel variation through admixture with archaic humans). Indeed, using real genetic data from populations selected to be as geographically and racially diverse as possible we see that the observed patterns of genetic variation closely match this nested subset model and have no correspondence to either the essentialist or population-based concept of race (panel **D** above). **Even as an abstraction, race-based models do more to mislead than inform our understanding of contemporary genetic diversity**. A model of race that would even remotely correspond to biological genetic diversity would need to be defined by nested subsets, serial bottlenecks, and extensive recent admixture – in other words, it would be *nothing* like the conventional use of race both historically and today.

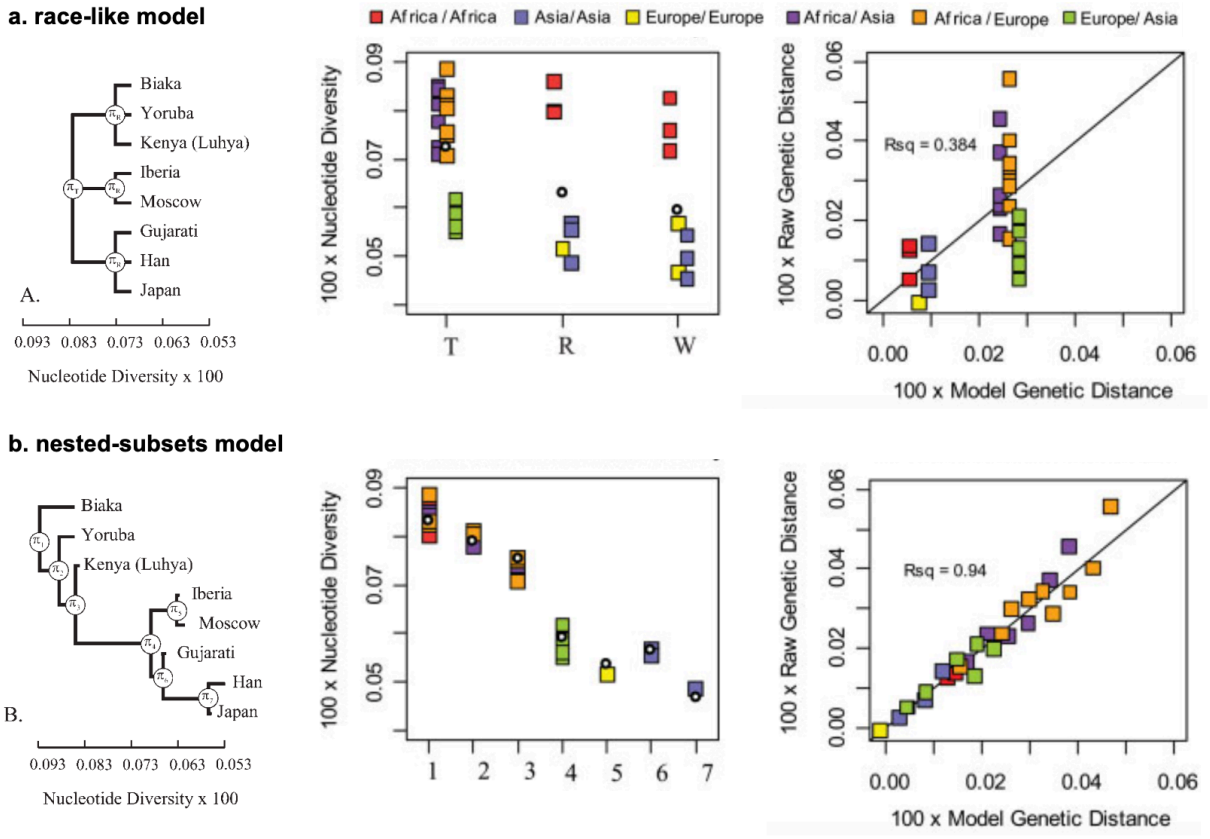
9.2 | Race provides a poor fit to genetic variation

The biological validity of a conventional racial model was formally evaluated in (Long, Li, and Healy 2009), using early targeted sequencing and structural variant data from global populations (the title, "Human DNA Sequences: More Variation and Less Race" should give you a preview of

their conclusions). The authors propose two models: (1) a race-like model where African/Asian/European populations diverged from a common ancestor and evolved independently and (2) a nested-subsets model where populations diverged via a phylogeny (*Note*: these models are called "two-level island" and "expanded hierarchical" in the paper but we'll stick with the simpler prior terminology). The two models are visualized in phylogenies below:

Genetic diversity does not fit a classical racial population model.

*(**a**) A "race-like" model of populations with a total population (T), regional populations (R), and within population (W) groups. Middle and right panels show the model fit to genetic data in terms of genetic diversity (F_{ST}) and genetic distance (normalized F_{ST}). (**b**) Same but for a nested-subsets model with a seven population phylogeny shown. Dots represent the expected values from each model. Figures recompiled from (Long, Li, and Healy 2009).*



These two models were evaluated for how well they fit the genetic distances found in real biological sequencing data using F_{ST}-style statistics (with different normalizations). The race-like model expects the greatest diversity between the higher-level "races" and then decreasing diversity within the "races". **The race-like model fit the data very poorly**: it overestimated the amount of diversity between European and Asian populations and within the European/Asian populations and subpopulations, and it underestimated the amount of diversity within the African populations and subpopulations as well as between some African subpopulations and European/Asian populations. In contrast, the nested subsets model accurately fit the high genetic diversity in Africa and the decrease in genetic diversity as populations become more geographically distant from Africa due to migrations and serial bottlenecks. The same patterns

were observed when using a normalized "genetic distance" metric, which again fit poorly in the race-like model (R2 = 0.38) while exhibiting a precise and linear relationship in the nested subsets model (R2 = 0.94). The nested subsets model was not a perfect fit likely because it did not additionally model admixture and more complex migration. As we will see, broader sampling in general populations identifies a substantial amount of admixture and would thus fail the race-like model even more severely.

Based on these tests, it is clear that a race-like model does not provide a meaningful representation of the biological reality. (Long, Li, and Healy 2009) conclude that attempting to fit a race-like model to evolutionary data can only lead to paradoxical conclusions:

"

The pattern of DNA sequence diversity also creates some unsettling problems for applying to humans the definition of races as groups of populations within which the individuals are more related to each other than they are to members of other such groups ... A classification that takes into account evolutionary relationships and the nested pattern of diversity ***would require that Sub-Saharan Africans are not a race*** *because the most exclusive group that includes all Sub-Saharan African populations also includes every non-Sub-Saharan African population. Moreover, the Out-of-Africa branch would place all Eurasians in the same race, but this would necessitate placing Europeans and Asians in sub-races ...* ***We see no need for such a classification in light of the fact that our evolutionary history gives good guidance for understanding the structure of human diversity***"

9.3 | Genetic ancestry

Having established that race is not useful as a measure of genetic diversity, what then do we see with ancestry-based approaches? Much of the early population genetics analyses involved the human "Haplotype Map" or HapMap project, a kind of global survey of genetic variation (which eventually evolved into the 1000 Genomes Project with the advent of whole-genome sequencing). The primary HapMap samples were: (1) White people from Utah (CEU); (2) Yoruba people from Ibadan, Nigeria (YRI); Japanese people from Tokyo, Japan (JPT); and Han Chinese people from Beijing, China (CHB). These core sites were selected to maximize racial and geographic differences in an attempt to efficiently capture global variation: "*we decided to include several populations from different ancestral geographic locations to ensure that the HapMap would include most of the common variation and some of the less common variation in different populations*." (International HapMap Consortium 2003). **As a consequence, analyses of these data (which are very common and form the basis of fundamental reference panels) will exaggerate the amount of global differentiation relative to representative sampling.**

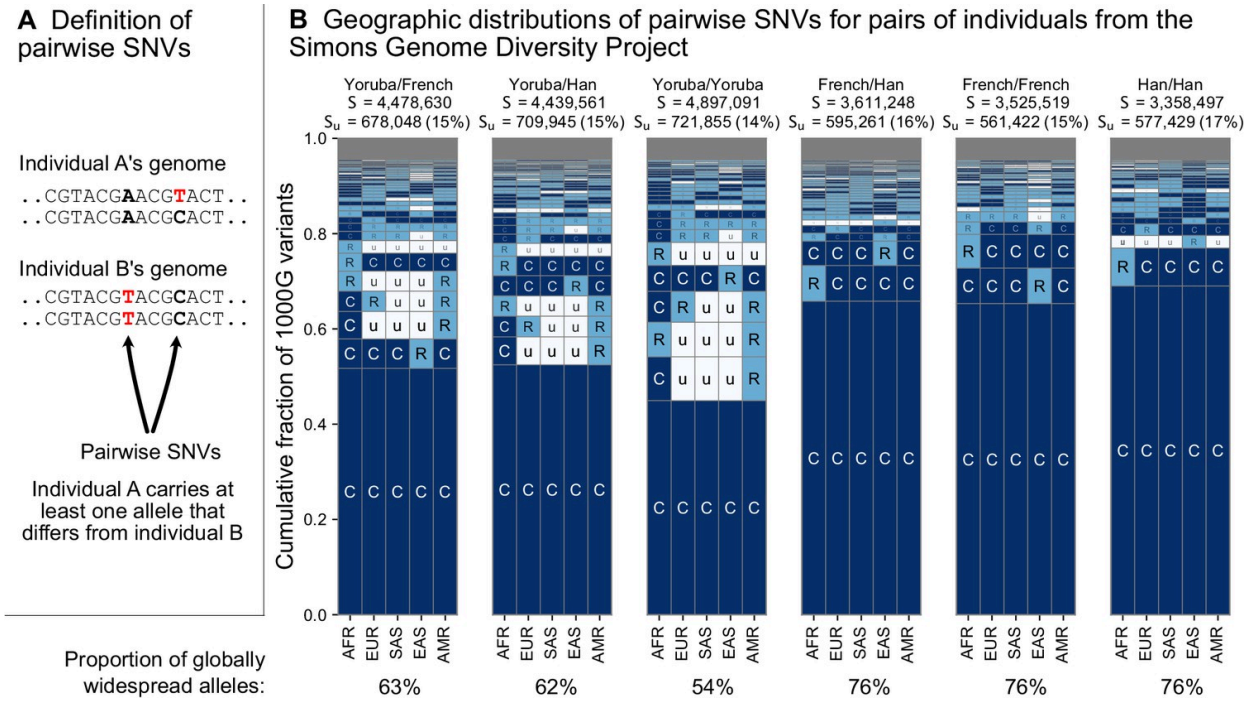
Variant-level differences

Perhaps the simplest quantification of population differences is to take two individuals and ask how many positions of their genome are different. (Biddanda, Rice, and Novembre 2020) carried

out such an analysis across core/continental populations along with a novel way of visualizing the pairwise genetic diversity. Pairs of individuals differed in 3.3M - 4.9M positions across six representative pairs, of which 17-20% were private to one of those two individuals likely implicating variants that were too rare to be seen in the rest of the sampled population. Notably, the largest number of differing sites were **within** Africa: a pair of Yoruba/Yoruba individuals with 4.9M differences. In contrast, a Yoruba/French pair had 4.5M differences and a Yoruba/Han pair had 4.4M differences. This is again consistent with the nested subsets model and the increased genetic diversity in Africa compared to other populations. For the positions that differed between individuals and were observed in reference populations, the majority (54%-76%) were common in all four continental populations. In other words, **most of the differences between pairs of individuals were because one individual carried a globally common allele and the other did not**. As (Biddanda, Rice, and Novembre 2020) conclude: "*The results show how the human population has an abundance of localized rare variants and broadly shared common variants, with a paucity of private, locally common variants*". The nested subset model continues to explain genetic variation better than a race-like model in pairwise comparisons.

Visualization of the frequency of variants that differ in a pair of individuals.

(A) How pairwise differences are defined. (B) Visualization of the frequency of the pairwise differences in each continental population (x-axis: AFR/African, EUR/European, SAS/South Asian, EAS/East Asian, AMR/Indigenous Americans) where colored blocks indicate whether the allele is [C] Common, [R] Rare, or [u] unobserved and are scaled to match the fraction of pairwise differences. S: number of pairwise differences; Su: number of pairwise differences that are not observed in another population; percentage across the bottom: fraction of pairwise differences that are globally common (not [u] in any population). Figure from (Biddanda, Rice, and Novembre 2020).



Genetic drift between geographically diverse populations

We can summarize the overall "genetic distance" between populations using the metric of F_{ST}, which can correspond to a variety of drift and migration parameters in idealized populations (see [**8.6**]). (Bhatia et al. 2013) estimated the cross-population F_{ST} (see for derivation) for the core HapMap continentally sampled populations. The estimates were compiled over all sequenced variants and accounted for bias due to sample size.

Estimates of F_{ST} from cross-continent population pairs.

Nei/Hudson estimators with sample-size correction applied to whole-genome sequencing data from the 1000 Genomes continental populations (CEU: European; CHB: Chinese; IBS: Spanish; YRI; Nigerian). [*] indicates variants were ascertained in the IBS population to evaluate the influence of ascertainment. Data from (Bhatia et al. 2013).

Groups	# SNPs	Nei F_{ST}	Hudson F_{ST}
CEU - CHB	7,799,780	0.112	0.106
CEU - YRI	17,814,120	0.149	0.139
CHB - YRI	17,814,120	0.175	0.161
IBS - YRI	17,814,120	0.145	0.131
IBS - YRI[*]	7,709,984	0.141	0.134

The average pairwise (Nei) F_{ST} was 0.15, implying that 15% of cross-continental genetic variation is due to "between-population" differences. In other words, **if we take the individual-level genetic variation at a typical locus and *condition out* every individual's population label, we will still be left with 85% of the original variance**. This value is remarkably consistent with Lewontin's classic 1972 analysis of blood groups and the finding that "*Less than 15% of all human genetic diversity is accounted for by differences between human groups!*" (R. C. Lewontin 1972). This result may seem obvious today, but it was in stark contrast to early racial theories that groups were under extensive divergent selection leading to most variants being largely homozygous within-race and highly divergent between-race; where one would expect F_{ST} values close to 1.0. Echoes of this erroneous race-based thinking about genetic variation continue to reverberate today, even as Lewontin's findings have been extensively and repeatedly replicated.

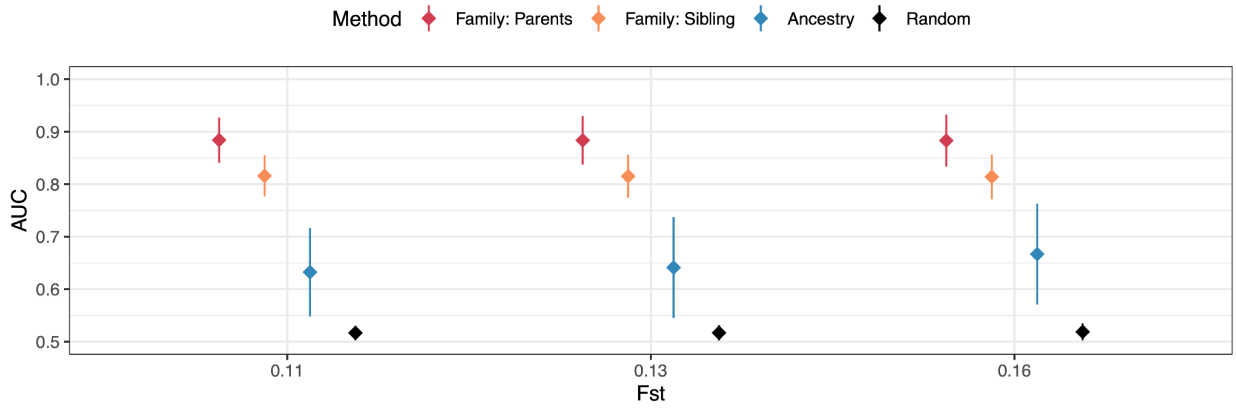
Ancestry-based classification

Another way to think about genetic ancestry is as a *classifier*. For example, let's say we want to identify individuals who are homozygous for the minor allele of a polymorphism for clinical purposes (e.g. it's a recessive variant). Knowing that a given polymorphism is more common in one population than another, we could use an ancestry population label as our classifier. What kind of accuracy would we expect if we used genetic ancestry as the classifier? The figure below shows classification accuracy in simulations with levels of F_{ST} of 0.11 (CEU/CHB), 0.13 (IBS/YRI), and 0.16 (CHB/YRI), as observed for the extreme continental populations above. In all three cases,

classification accuracy (AUC) is approximately ~0.65 for a sample with equal size from each subpopulation; which is to say, not much better than random (0.5). For comparison, using the carrier status of one sibling produces a classification accuracy of ~0.82 and the carrier status of both parents produces a classification accuracy of ~0.88. Indeed, it would take an F_{ST} of 0.5 – equivalent to ~50,000 generations of drift (1.5 million years) or the time of Homo erectus – for ancestry to achieve comparable predictive accuracy to that of a sibling; and and F_{ST} of ~0.7 (~300,000 generations) to reach the accuracy of both parents. Thus, even in cases where the true underlying population label is used and populations are completely distinct (no migration/admixture), ancestry is only a very weak indicator of genetic variation. This example highlights the ongoing debate over using race/ancestry modifiers in clinical screens, which can sometimes provide a small (but non-random) improvement in classification (Borrell et al. 2021).

Accuracy of determining genetic variant carrier status using genetic ancestry.

*The accuracy (AUC) for detecting a minor allele carrier is shown for genetic ancestry at increasing levels of F_{ST}, averaged across multiple simulated sites. For comparison, the accuracy of classification based on sibling or parent carrier status is also shown (orange, red) as well as random (black). Random deviates slightly from AUC of 0.5 because the population with higher frequency of the minor allele is presumed to be known. [**code**]*



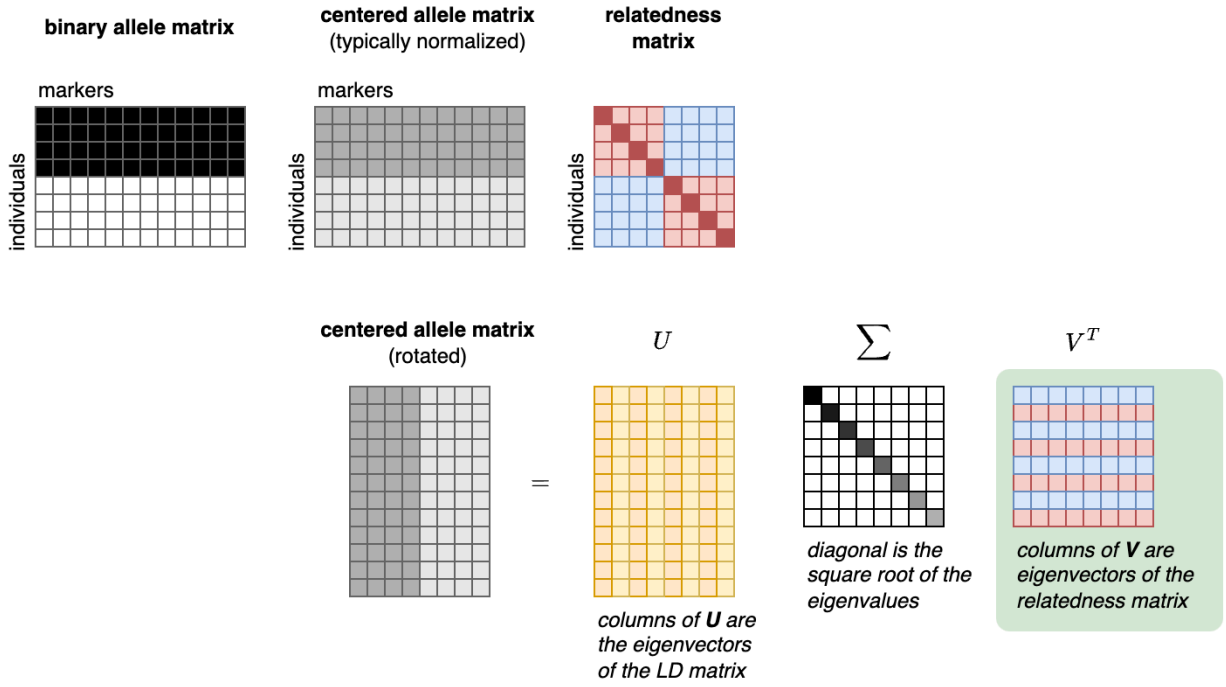
9.4 | Continuous ancestry / Principal Components Analysis (PCA)

Theory

Principal Component Analysis (PCA) is a widely used mathematical technique that often produces an informative low dimensional representation (i.e. a reduced version of the input data that retains more of the original "signal" than just a random subset of the data). Given a data matrix, PCA intends to identify a projection of the data into a smaller number of dimensions/components that either **(a) maximizes the variance in each projected dimension or (b) minimizes the mean squared difference between the data and the projected dimension (these are equivalent) while also ensuring that each component is uncorrelated** (this is necessary to make the problem solvable since many equivalent correlated components could otherwise be identified). These components are also called eigenvectors (from the German prefix "*eigen*" or own/inherent). In population genetics, PCA is typically applied to the centered sample-by-marker

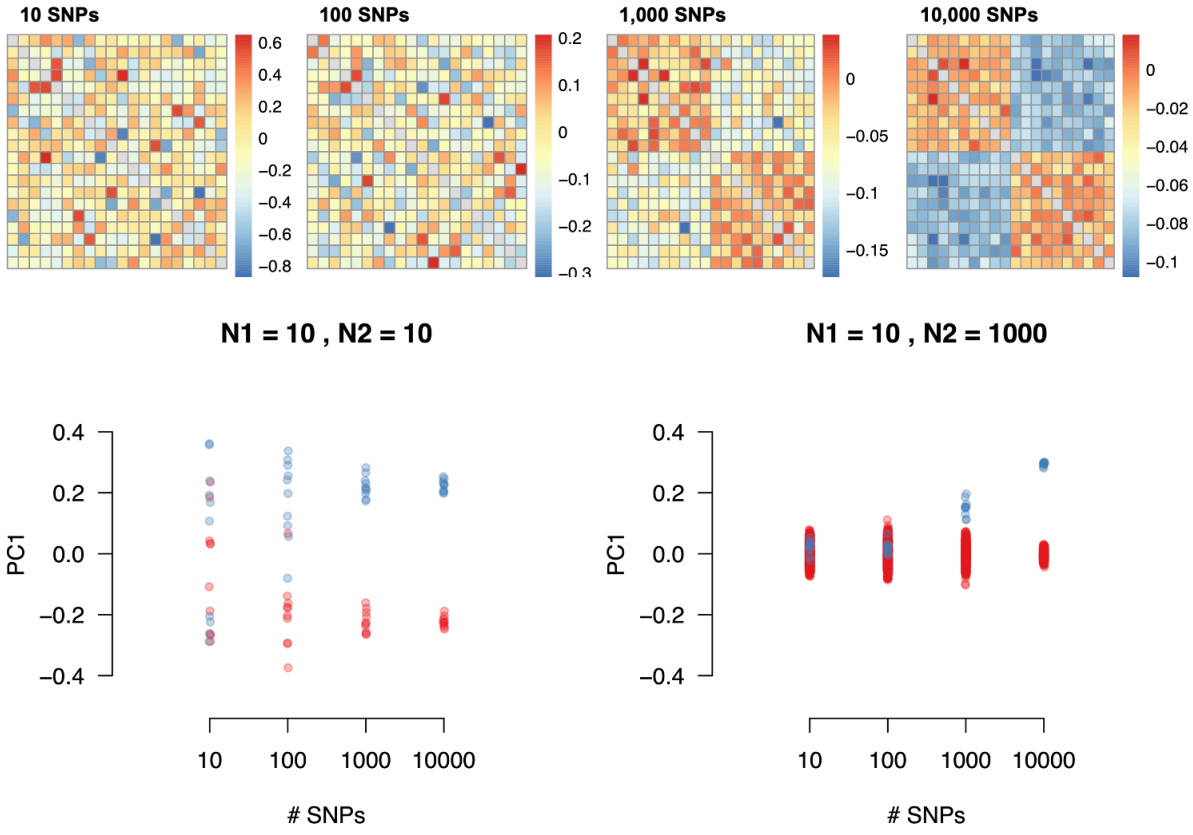
genotype matrix of alleles (with markers assumed or selected to be uncorrelated). Computationally, this typically involves applying Singular Value Decomposition to the same sample relatedness matrix used in molecular heritability estimation (see [2.2]) as shown:

Matrices involved in PCA of genetic data as obtained by Singular Value Decomposition
*(**top**) The binary (or 0/1/2) allele matrix across individuals and markers taken as input (black/white); in this cartoon one population has all black alleles and the other has all white alleles. The centered, and typically normalized, version of the same matrix (grays); and the resulting relatedness matrix across individuals (red/blue). (**bottom**) The SVD of the relatedness matrix defining: eigenvectors of the relatedness matrix in V (red/blue), eigenvalues in Sigma (gray), and eigenvectors of the LD/variant correlation matrix (not shown) in U. Colored bands are used to indicate orthogonality. The individual-level PCs are the columns of V (highlighted in green).*



What does a low dimensional projection of this matrix represent? We can think about the context of data generated from two equally sized populations being reduced to a single dimension (i.e. the leading *eigenvector*). Intuitively, allele frequencies will be more similar within the populations than between them, and so the single eigenvector that maximizes the projected variance (or minimizes the difference to the centered data) is one where the values are positive for one population and negative for the other (Patterson, Price, and Reich 2006). When there are multiple distinct populations, PCA is expected to continue to identify uncorrelated eigenvectors that separate each of the successive populations. We can visualize this behavior for two distinct populations in simulations in the figure below. The more variants we include in our data the more precisely we can estimate the genetic correlation within/between populations, more of the variance in the kinship is driven by population differences than by noise, and more of PC1 corresponds to a separation of the underlying population labels. Interestingly, if we increase the sample size of one of the populations we see a shift in the location; this behavior is characterized in detail in the next section.

Behavior of PCA with increasing number of markers for two discrete populations. *Simulations with two discrete populations with 10 samples each and an F_{ST} of ~0.04. (**top**) The kinship matrix computed from an increasing number of markers. The diagonal was set to be missing for visualization (**bottom left**) The inferred first principal component (PC1) from an increasing number of markers where both populations have 10 samples. (**bottom right**) Same as left but where one population has 1000 samples. Bottom panel based on figure from (McVean 2009). [**code**]*



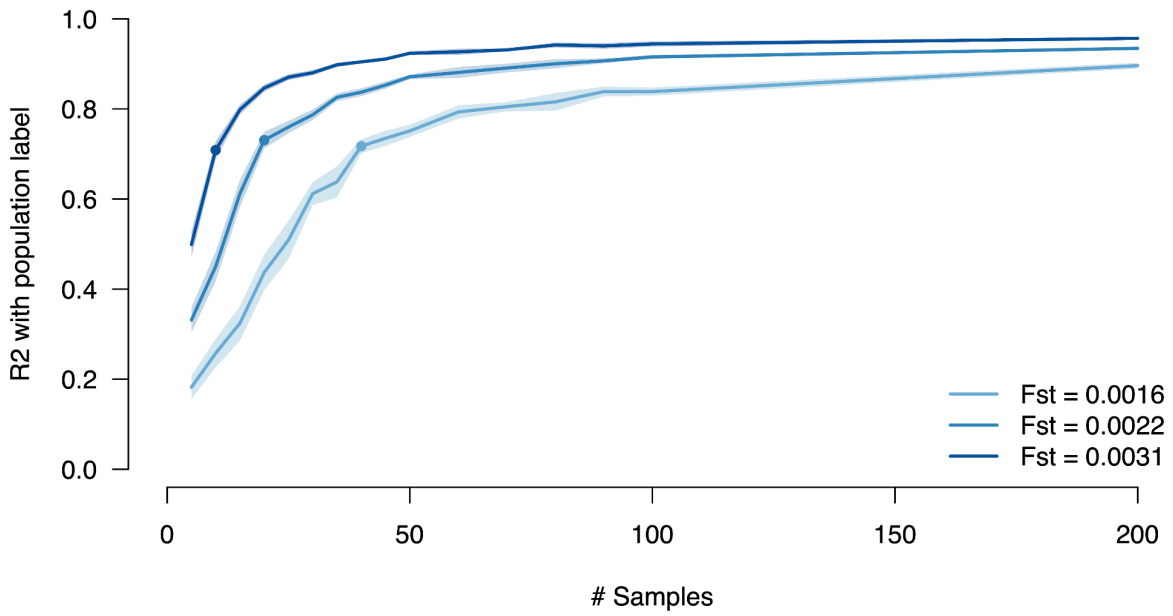
Sensitivity to detect structure / BBP threshold

So far we have discussed the behavior of PCA under the assumption that the underlying genetic structure is observable (i.e. correlated with one or more leading eigenvectors) but how much genetic structure can be detected? Notably, we previously saw (in the figure above) how a small number of markers leads to relatedness correlations that are too noisy to produce PCs that correlate with structure. The relationship between population structure and the sample size needed to detect it was quantified in (Patterson, Price, and Reich 2006). Specifically, theory suggests that for a matrix with a small number of large eigenvalues (as expected for genetic data with relatively simple population structure) the leading eigenvector becomes significantly detectable as a function of the true eigenvalue and number of individuals and markers in the matrix. For two populations, where the variance explained by the first eigenvector is approximately equal to F_{ST}, this eigenvector is significantly detectable as long as [$F_{ST} > 1/\sqrt{N*M}$] where [N] is the number of individuals and [M] is the number of markers; this is referred to as the BBP threshold (for (Baik, Ben Arous, and Peche 2004), who described the relationship for normally distributed data). Additionally, a “phase shift” is observed where structure below the

BBP threshold is essentially undetectable and structure above the threshold quickly becomes very easy to detect (especially if [N], the number of individuals is increased). We can observe this threshold effect in simulations of two discrete populations in the figure below: with markers fixed at 5,000 the first principal component / eigenvector exhibits a high squared correlation with the true population label right at the expected BBP threshold as a function of sample size and F_{ST} (with F_{ST} intentionally selected to be very low).

Detection of population structure at the BBP threshold in simulation.

*The squared correlation between true population label and leading eigenvector (y-axis) shown for a simulation with 5,000 independent markers and two populations of equal size (x-axis). The BBP threshold for each population scenario is indicated with dots. Drift was induced to yield a BBP threshold value at approximately 40, 20, and 10 samples corresponding to approximately 60-120 generations from an ancestral population. [**code**]*



A key takeaway from these findings, as emphasized by (Patterson, Price, and Reich 2006) **is that: "*most large genetic datasets with human data will show some detectable population structure*."**. As we see in the simulations above, PCA is extremely sensitive and BBP theory indicates that, for example, the ~60,000 independent variants in the genome and biobanks of 100,000s of individuals would be powered to detect F_{ST} values of $<10^{-5}$. That corresponds to just 1-2 generations for a typical randomly mating population with Ne=10,000 (see [**8.7**]); in other words **at large sample sizes, PCA can detect essentially *any* level of population structure** (if sufficiently late components are considered). *As an aside: the reason PCA alone may not be sufficient to control for population stratification in GWAS and heritability analyses is that which components capture trait-relevant stratification is not known and the relationship to the trait may be non-linear, whereas PCA only identifies linear projections of the genotypes*.

Finally, why is it that one can separate populations so easily with larger numbers of markers but heritable trait variation across populations (Q_{ST}) is expected to be low regardless of the number of causal variants (see [**8.8**])? This distinction was explained in (Edge and Rosenberg 2015a):

"*Suppose we have a single locus at which the allele that is more common in population A contributes to larger values of the trait. The influence of this locus on the trait gives us a hint about population membership; that hint, however, is likely to be masked by the influence of another locus at which the allele more common in population A reduces trait values.*" In other words, PCA is effectively adding up the squared differences between populations across polymorphisms (i.e. the differences that drive variance between populations), so that many small differences accumulate to eigenvectors that capture very subtle differences; whereas the trait mean is adding up *signed* differences, so that many small differences do not accumulate into large mean differences or Q_{ST} values.

Interpreting PCA location and the impact of sampling bias

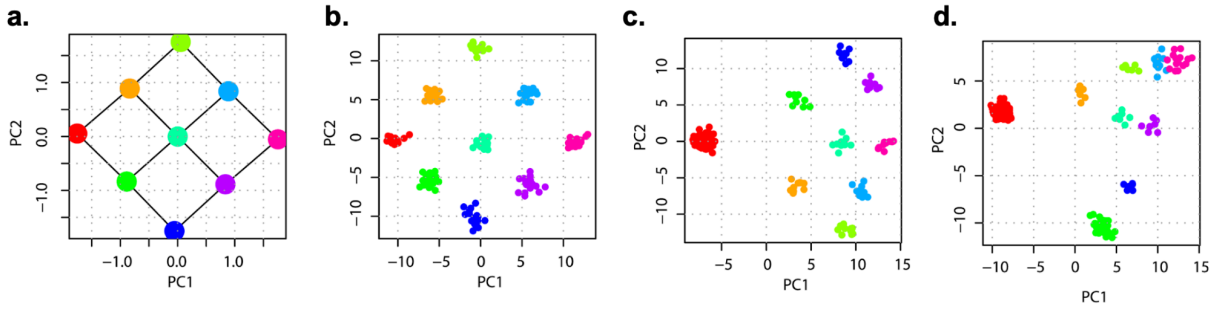
An alternative interpretation of PCA in the context of genetic genealogies was provided by (McVean 2009). McVean showed that the terms in the kinship matrix correspond to the expected coalescence time for the corresponding pairs of samples (i.e. the number of generations to the most recent common ancestor) and the resulting SVD could then be interpreted in terms of genealogical processes. This connection revealed several useful properties of PCA in structured populations:

- When applied to two populations that diverged [d] generations ago from an ancestral source, the euclidean distance between the populations along PC1 is equal to [sqrt(2d/T)] where [T] is the average coalescence time in the total population.
- The positioning of the populations along PC1 relative to the origin is proportional to their sample sizes (this explains the location shift in the figure above).
- The total variance explained by PC1 asymptotes at the F_{ST} between the populations. The influence of SNP ascertainment on F_{ST} estimates will thus also influence PCA-based inference (see [**8.7**]).
- If an admixed individual is projected into the PC space between the two source populations, their location between the source populations is defined by their global ancestry proportion (which is itself a realization of the relative coalescent time to each source population).
- However, non-admixed individuals can still be projected into a location between the two populations (for example, if they are derived from the ancestral population or a related third population).
- As a consequence, **PCA can not distinguish between different populations with the same mean coalescent time** (i.e. the leading eigenvectors will be the same up to some arbitrary rotation).

The impact of genetic distance and sample size on the PCA location is demonstrated in the figure below. For equally sized, randomly mating populations with a simple migration process the first two PCs localize these populations into a grid as expected based on their divergences (panel **a** and **b**). As the sample size of one population is increased (panel **c** and **d**) the larger populations are localized closer to the origin and the overall relationship between populations is distorted. This distortion can be substantial, for example in panel **d** the light blue and pink populations appear much more similar than the pink and purple populations purely as an artifact of the

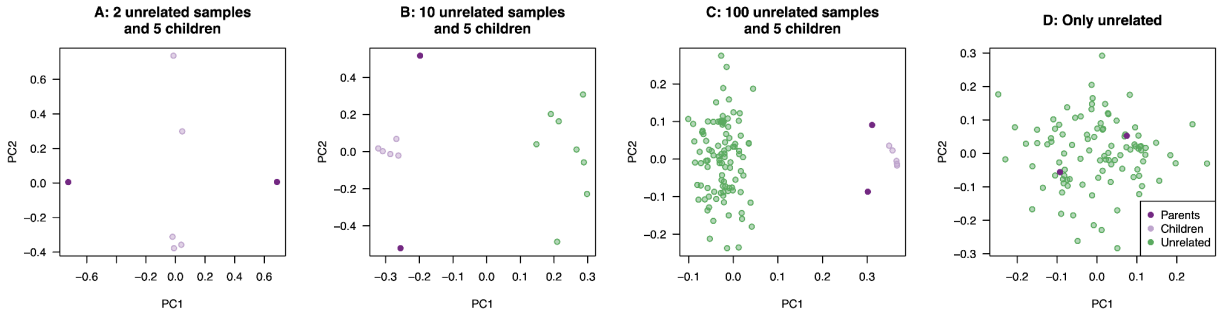
oversampling of the green population. Likewise, the red and green populations also appear much more distant than they are in the true model.

Expected and apparent location of populations with migration and uneven sampling.
*(**a**) The true space for nine populations with lines showing the migrations. (**b**) The inferred PCs with even sampling. (**c**) The distortion of inferred PCs with uneven sampling of the red population. (**d**) Further distortion with additional uneven sampling of the green population. Figure from (McVean 2009)*



This distortion by sampling becomes more extreme when the subpopulations are **not sampled randomly and also not mating randomly**. In the figure below, data is simulated from a single homogenous population and then oversampled from one "family" with many offspring. When PCA is applied to only the family, PC1 distinguishes the parents (and the children as "admixtures") and PC2 positions the children based on their arbitrary genetic similarity (panel **a**). When additional unrelated individuals are included, PC1 distinguishes the family from the unrelated individuals and then PC2 again distinguishes the parents from the children (panel **b** and **c**). This is quite un-intuitive given that the parents are random draws from the homogenous population, but because they are so genetically similar to their children, positioning them close to the family members maximizes the variance along PC1. A naive analysis of this visualization might even conclude that the purple and green samples are genetically distinct populations. Finally, when we remove the children entirely, the entire population is then positioned in a random field as would have been expected.

Inferred PCA components when oversampled with relatedness.
*Visualizations of PC1 and PC2 from: (**a**) two parents from a homogenous population and five children; (b) same with 10 unrelated individuals from the same population; (c) same with 100 unrelated individuals from the same population; (d) only the unrelated individuals. [**code**]*

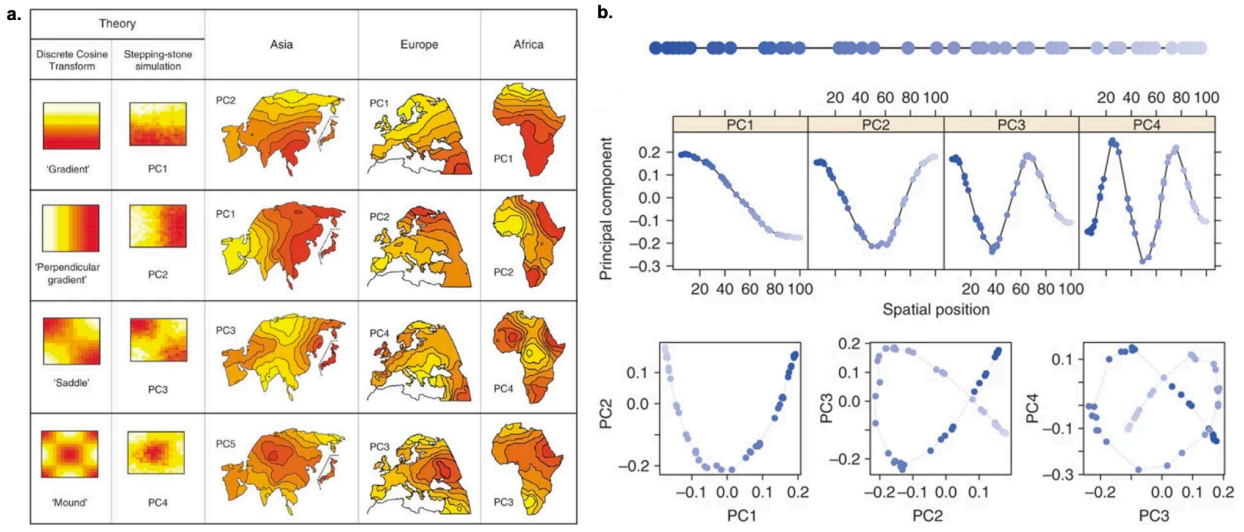


Interpreting PCA shape and local structure

So far we have primarily looked at the expected behavior of PCs for well defined structured populations, but PCA also produces unexpected behavior for more complex populations with small-scale local structure. Early analyses of PCA with relatively small sample sizes often used allele frequencies as the input data instead of individuals/alleles and then projected the eigenvector positions onto geographic maps (some examples shown in the figure below). The shape of these "PC maps" would then be interpreted as evidence of historic population migration and expansion, with radial gradients interpreted as the likely source/ancestral populations spreading outwards over time.

Artifactual PCA spatial gradients under local structure

*(**a**) Theory and simulations under a stepping-stone model (left) compared to equivalent gradients observed in PCA maps from real data (right). (**b**) Simulations under a linear isolation-by-distance model (top) compared to gradients observed in individual-level PCA projections (bottom). Figures from (Novembre and Stephens 2008).*



However, key work by (Novembre and Stephens 2008) eventually showed that nearly identical patterns can be observed artifactually from much simpler demographic models, as a basic mathematical consequence of analyzing data with local spatial structure. Specifically, Novembre simulated data under a "stepping stone" generative model, where a population gradually migrates along a grid. As expected PC1 showed a gradient with respect to the simulated geography. However, the subsequent PCs showed shapes expected from matrix theory: a perpendicular gradient in PC2, a "saddle" in PC3, and a "mound" in PC4 (grids in panel **a** above); even though no such patterns were present in the underlying topology. Likewise, when simulating data from an even simpler one dimensional isolation-by-distance simulation and applying PCA at the level of individuals (as described above), increasing variations of sinusoidal gradients were again observed in PC2-PC4 (panel **b**, above). As it turns out, these shapes are expected from any data where the inputs/populations are locally similar and have linear, circular, or grid-like spatial structure and this behavior has been observed in many other fields. The exact same patterns of spatial PC gradients had been observed in analyses of real genetic data from spatially distributed populations and interpreted as historically meaningful (maps in panel **a**, above). More troubling, these patterns were observed across data from multiple continents,

which were highly unlikely to experience the same exact spatial patterns of migration in the same exact order. Thus, while simulations alone cannot definitely rule out that the PC maps were incorrect, **it is clear that spatially distributed data analyzed with PCA will produce complex spatial gradients even when no complex spatial migration has occurred**.

9.5 | A word on nonlinear dimensionality reduction / UMAP

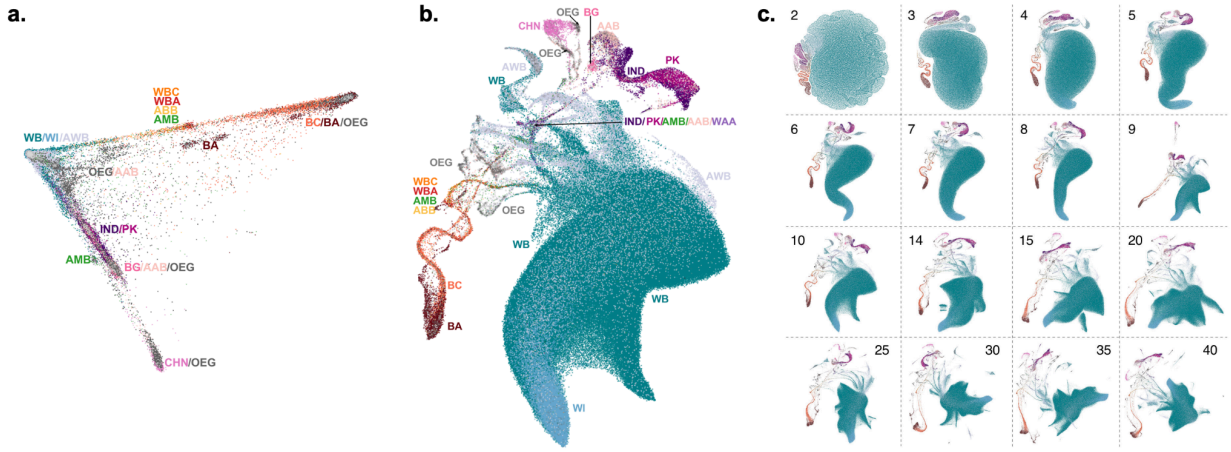
A number of alternative dimensionality reduction methods have been applied to genomic data, including nonlinear methods such as UMAP/t-SNE. Typically, these approaches use a non-deterministic algorithm to optimize some measure of local/global sample distance while projecting the samples into a two-dimensional space. A potential advantage is the ability to efficiently visualize higher dimensional structure in two dimensions: whereas PCA is expected to separate two major populations per PC and lump other individuals where they are most genetically similar, UMAP might place population clusters observed in higher dimensions into "islands" in the 2-dimensional space. Thus UMAP can be useful for exploratory data analysis, identification of data artifacts (which can be non-linear), or structure that only appears in very high dimensions (Diaz-Papkovich, Anderson-Trocmé, and Gravel 2021). However, most natural population relationships, such as admixture and migration, are additive combinations that are well modeled by existing methods. **And unlike PCA, non-linear methods generally do not have genealogical or phylogenetic interpretations (even for idealized populations) and tend to produce arbitrarily nonlinear layouts and clusters**. Thus, for visualization of broad population relationships, nonlinear methods provide limited benefit while running the risk of grossly distorting the results.

An example of this type of distortion can be seen in the figure below, from an analysis of the large population-level sample in theUK Biobank by (Diaz-Papkovich et al. 2019). Panel **a** shows the first two principal components from PCA, which lays out individuals along orthogonal axes (a requirement of PCA) in proximity to the three most divergent populations in the dataset, which are enriched for individuals recorded as (i) White British (WB, blue); (ii) Black African (BA, brown); (iii) Chinese (CHN, pink). Panel **b** shows the same data analyzed with UMAP (in this case also run on top of PCA); similar ethnicity enrichments are observed but they form loose swirls and tails that are mostly meaningless. For example, a cluster enriched for Black African (BA) and Black Caribbean (BC) identification exhibits a snaking pattern that eventually connects with the White British (WB) group; this almost certainly reflects individuals with different levels of admixture from primarily African and European populations, which UMAP then arbitrarily projects onto meaningless curves. How do we know these swirls are meaningless? Panel **c** shows the same data analyzed with an increasing number of starting components: as more components are included the swirls change, arbitrarily contracting or expanding with little relationship to underlying genealogical patterns. In short, while non-linear reduction may be useful for data exploration, there are typically better ways of visualizing population structure.

PCA and UMAP analyses in the UK Biobank

*In every figure an individual is plotted as a point and color-coded by self-reported ethnicity. (**a**) Standard PCA analysis of the UK Biobank plotting PC1 vs PC2 color-coded by ancestry clusters. (**b**) The same data*

*visualized with UMAP. (**c**) UMAP analysis initialized from an increasing number of principal components produces arbitrary nonlinear representations. [Figures from (Diaz-Papkovich et al. 2019)]*



9.6 | Model-based clustering of ancestry / STRUCTURE

An alternative approach to dimensionality reduction is “model-based clustering” as implemented in the widely used STRUCTURE software (Pritchard, Stephens, and Donnelly 2000). The approach is analogous to Latent Dirichlet Allocation (LDA) or “topic modeling”, common in machine learning and natural language processing. The underlying model is intuitive: individuals are defined as mixtures from a predefined number of populations and populations are defined by allele frequencies (i.e. mixtures of alleles); the assignments of frequencies to populations and probabilistic assignments of populations to individuals are then optimized through a (typically) iterative sampling algorithm. The parameters of the model are the number of clusters (***k***) and a Dirichlet distribution parameter (***α***) which reflects the number of populations each sample is expected to be drawn from (high versus low values implying that each individual is a mixture of many versus few populations). In practice, the model-based outputs from STRUCTURE are often highly correlated to the variance-based outputs from PCA and expected to share similar sensitivity characteristics (Patterson, Price, and Reich 2006). Like PCA, STRUCTURE suffers from issues of distortion due to the sampling process and identifiability of population genealogies, as well as the need to specify ***k*** and ***α***.

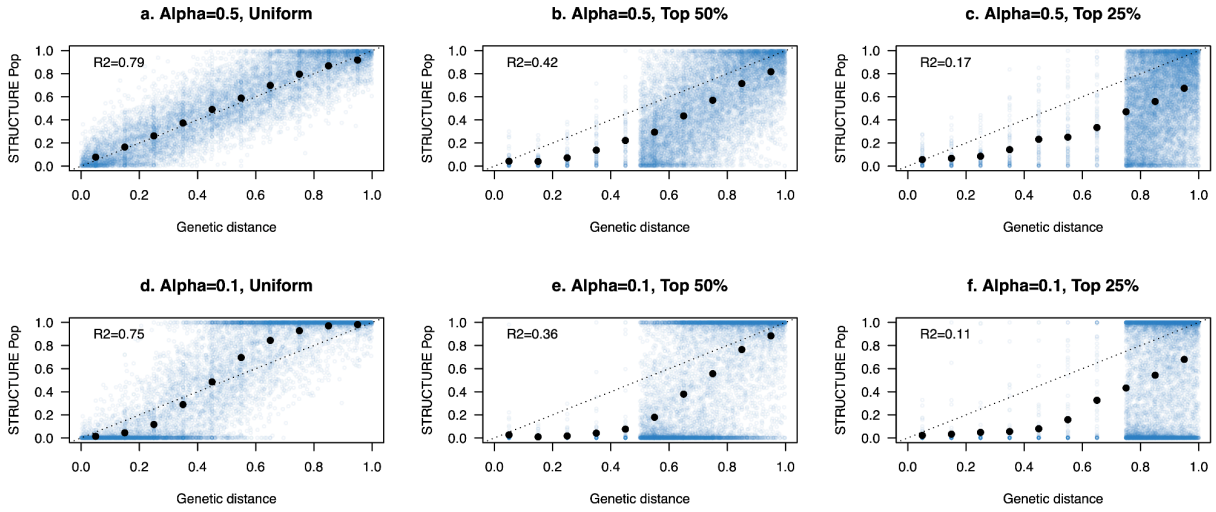
Sensitivity to sampling and *α*

STRUCTURE assigns individuals probabilistic population labels and is therefore distorted by sampling in a slightly different way than PCA. Rather than distorting the *location* of individuals in some continuous space, STRUCTURE distorts the *probability distribution* of belonging to a given population. We can see this in a simple simulation where individuals are drawn along a linear ancestry continuum and analyzed with STRUCTURE at **k**=2 (see figure below). When individuals are sampled uniformly, the inferred admixture proportions roughly correspond to the true genetic distance from the source population. However, as individuals are oversampled from one end of the spectrum (for example, as would happen when comparing modern and ancient data) they

become severely underrepresented in the cluster calling. For example, an individual that is from a population 50% along the continuum is inferred as 0-20% when the sampling is skewed. This distortion occurs even though individuals from the entire continuum are present in the data. This effect is amplified if we decrease the **α** parameter such that individuals are expected to be sampled from fewer populations a priori, with individuals frequently assigned to be 100% from their closest population. **In short, the population assignments that STRUCTURE makes are highly dependent on the population sampling scheme and, to some extent, the prior probability on population diversity.**

The impact of sampling on population labels from STRUCTURE

*Simulated individuals drawn from a population continuum (with Fst of ~0.14 at the extremes), followed by sampling and ancestry inference with a STRUCTURE-like algorithm (LDA) specified to k=2. In each instance, 8% of the individuals are sampled uniformly and the rest are either sampled uniformly (**a,d**), from the top 50% of the continuum (**b,e**), or from the top 25% of the continuum (**c,f**). Individual-level calls are shown as blue points with grouped means shown in black points. Top row shows results with α (population mixing) of 0.5 and bottom row shows α of 0.1 (lower values imply individuals are less likely to belong to multiple populations). [**code**]*

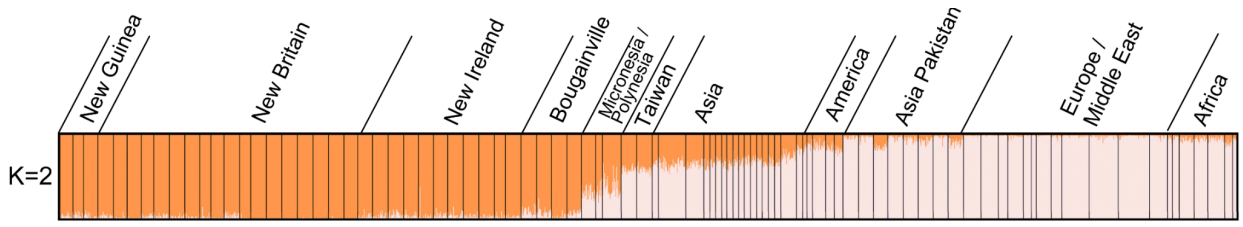


Sensitivity to *k*

Bias due to sampling can be further amplified in the context of multiple underlying populations, which can hinge on the choice of ***k*** clusters. (Lawson, van Dorp, and Falush 2018) highlight this issue by re-analyzing data from (Friedlaender et al. 2008) which studied a large cohort of individuals from Melanesia along with reference populations from other continents. Even though the dominant driver of genetic variation across these populations is the migration out of Africa, STRUCTURE with ***k***=2 infers one homogenous population for the Melanesian cohorts and a second homogenous population for all of Africa, Europe, the Middle East, and the Americas, with an admixture cline through Asian/Polynesian cohorts. This mirrors the simulations above, where sampling populations at one end of a continuum clusters together much more diverged populations from the other end. Notably, increasing ***k*** initially made the bias worse, with European individuals appearing to be a mix of Melansian and Asian populations through ***k***=9 and only assigned their own cluster at ***k***=10.

STRUCTURE clusters together broad continental populations while distinguishing Melanesian sub-groups

Melanesian cohorts (New Guinea, New Britain, New Ireland, Bougainville) were heavily sampled and thus assigned to one of the primary clusters by STRUCTURE with k=2. Figure from (Friedlaender et al. 2008) and (Lawson, van Dorp, and Falush 2018).

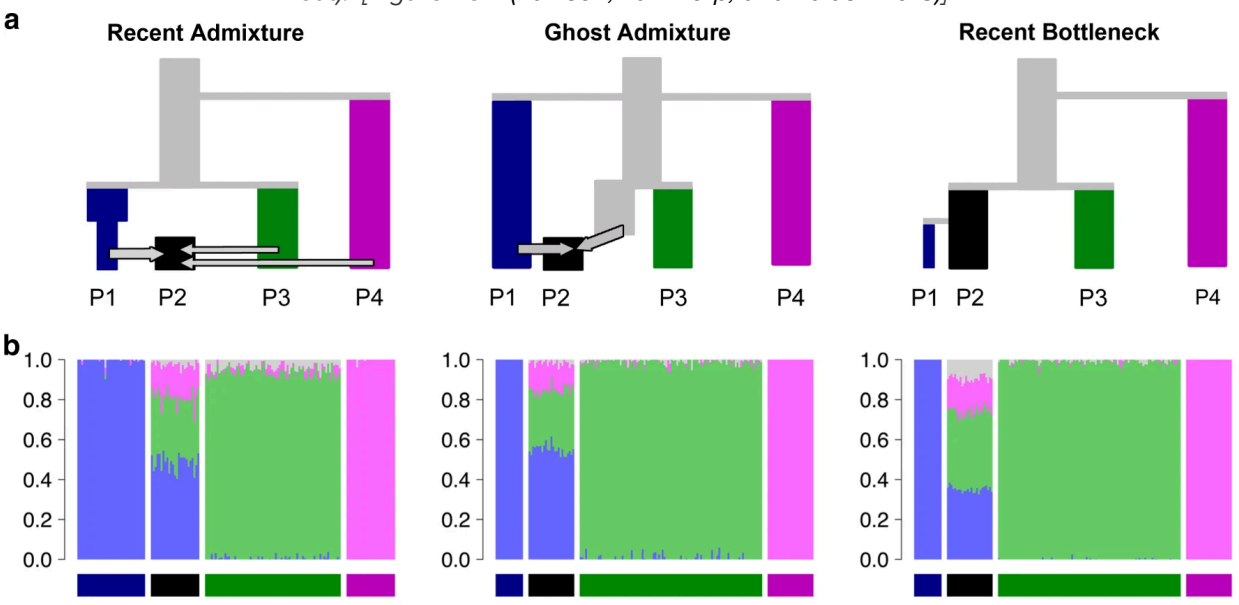


Identifiability

Like PCA, STRUCTURE may be unable to distinguish between populations with different phylogenies, particularly when their genetic history deviates from the clean divergence and admixture the model assumes. (Lawson, van Dorp, and Falush 2018) highlight three fundamentally different demographic scenarios that produce identical STRUCTURE results:

Three different populations that yield identical STRUCTURE outputs

*(**a**) The simulated population relationships for the four focal populations. (**b**) The output population proportions from STRUCTURE with k=10, for a simulation with 13 populations (all other outgroups grayed out). [Figure from (Lawson, van Dorp, and Falush 2018)]*

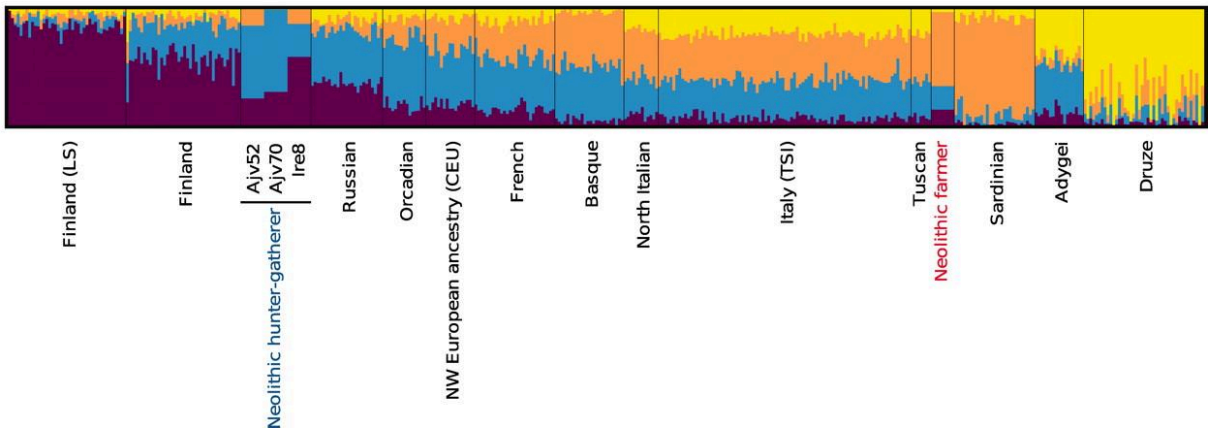


First, an idealized population is simulated with very recent admixture from three highly divergent ancestral populations. As expected, STRUCTURE infers three (nearly) unadmixed populations and one mixture population (P2) with accurate admixture proportions. Next, a “ghost admixture” population is simulated, with recent admixture from two populations, one of which is observed and the other (the “ghost”) which is unobserved but related to two observed populations. STRUCTURE infers the same three-way admixture as in the first scenario because it does not

observe the intermediate admixture source, instead **interpreting distant phylogenetic relationships as if they were admixture events**. Finally, four unadmixed populations are simulated, with accelerated drift in one population (P1) due to a population bottleneck. STRUCTURE again infers the three-way admixture output **even though no admixture has occurred at all**. Due to the excess drift in P1 making it genetically distinct, STRUCTURE defines it as a homogenous population and then fits P2 as a "mixture" from its closest populations in the phylogeny. This form of model misspecification has become particularly apparent with the analysis of ancient DNA, where the linear passage of time guarantees that ancient individuals are not admixtures of modern ones and yet STRUCTURE analyses often infer exactly such admixtures (see figure below):

Ancient samples are estimated by STRUCTURE to be admixtures of modern individuals

*Ancient neolithic (blue and red) and modern European samples were analyzed together, with the former identified as admixtures of modern Northern/Southern European populations. Results shown for **k**=4 but admixture in ancient samples was estimated at all **k** values. [Figure from (Skoglund et al. 2012)]*



In each of these examples, a population is incorrectly inferred as admixed, **but the opposite can also be true: admixed populations will be incorrectly inferred as homogenous if all samples exhibit similar levels of admixture**. For example, European individuals exhibiting similar levels of Neanderthal admixture will be treated as a homogenous population by STRUCTURE, with Neanderthal alleles simply integrated into the population allele frequency estimates, because there is no inter-individual variation to exploit. As (Lawson, van Dorp, and Falush 2018) summarize: "*the algorithm attempts to fit the data as best it can by finding the combination of admixture proportions and ancestral frequencies that best explain the observed patterns.*"

9.7 | A word on parametric models / admixture graphs

A third class of models attempt to identify the parameters of a generative process that provide the best fit to the data, typically along a tree or an "admixture graph". Such models typically operate in units of genetic drift (see [**8.3**]), which enables useful cross-population comparisons without requiring knowledge of the population sizes or generational time relationships (for which other estimators exist). Admixture graphs, in particular, rely on tests of allele sharing called "f-statistics" which can (a) estimate the genetic drift between populations assuming no migration, (b) test for the presence of admixture, and (c) infer admixture proportions. With these building

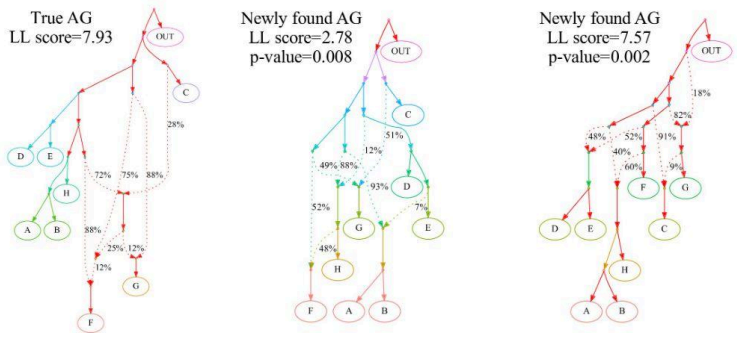
blocks, one can then search for parameters of a tree or directed graph that maximize the fit to the data (Peter 2016; Lipson 2020). Many other parametric approaches exist that incorporate other aspects of genetic variation but they all typically operate along the same principles: searching for parameters of a graph that maximize the "fit" to the data under some graph-to-data generative model. These parametric models can provide highly complex population relationships that are more informative than the simple dimensions or clusters produced by PCA and STRUCTURE. **But a key challenge for these approaches is ensuring that the data does not fit just as well under completely different parameters**. As the number of populations and parameters expands, it becomes impossible to simply enumerate all possible graphs, and so such methods also need to ensure that they are maximizing the fit relative to graphs that they have not observed.

This issue of admixture graph identifiability was extensively analyzed in (Maier et al. 2023), empowered by an efficient software implementation that allowed them to efficiently traverse a much larger number of graphs than prior methods. In simulations of random (but realistic) topologies where the true graph was known, the authors found that at least one alternative graph provided a significantly better fit 60% of the time (when fixing the number of admixture events to the true value) or 100% of the time (when allowing an additional admixture event) (see example in panel **a** below). They then reanalyzed data from prior published studies that had inferred admixture graphs. In 19/22 instances a better fitting graph could be identified with a broader parameter search, and in roughly half the instances the graph was significantly better fitting. Moreover, in many cases a large fraction of graphs were not significantly worse than the published graph, implying that many alternative topologies could be just as representative of the data as the one that was ultimately selected.

Admixture graph identifiability in simulation and real data

*(**a**) Erroneous admixture graphs (middle, right) can provide a better fit to genetic data than the true underlying structure (left). (**b**) The percentage of graphs that provided a Better/Worse fit to data than the published graph, in re-analysis of published studies. [*] indicating statistically significant differences. In some studies, only a minority of alternative graphs are significantly worse. [Figure and Table from (Maier et al. 2023)]*

(a) Incorrect admixture graphs can have better fit to the data



(b) Re-analyzed data	Better [*]	Better	Worse	Worse [*]
Wang et al., 2021	13%	84%	3%	0%
Lazaridis et al., 2014	1%	12%	81%	6%
Lipson et al., 2020b	0%	12%	77%	10%
Hajdinjak et al., 2021	16%	56%	7%	22%
Sikora et al., 2019	0%	17%	35%	48%
Librado et al., 2021	7%	16%	24%	53%
Librado et al., 2021	0%	0%	28%	71%
Bergström et al., 2020	1%	2%	17%	81%
Sikora et al., 2019	0%	1%	10%	89%
Shinde et al., 2019	0%	3%	4%	94%
Librado et al., 2021	0%	0%	5%	96%

(Maier et al. 2023) discuss a number of specific examples where the alternative topologies have meaningful differences from the published graph, including identifying population relationships and admixture that were thought to be non-existent or providing alternative topologies where identified admixture events did not exist. A particularly striking example was the re-analysis of ancient DNA from an African genome found in a rockshelter in Cameroon (Lipson et al. 2020). The original study identified ancestry from two distinct populations, as well as a "ghost" ancestor population, and a highly divergent "archaic" ancestor. Yet alternative and equally likely admixture graphs were identified that contravened all four of these observations. The true history and origins of this genome thus remain an open question (see more on model identifiability in Africa in [**9.9**]). **In short, parametric models can be a powerful tool for inferring interpretable population topologies, but this flexibility comes at the cost of identifiability**. As is often the case in data modeling, drawing confident conclusions requires triangulating across prior knowledge, orthogonal (typically archeological) evidence, and a variety of alternative methods.

9.8 | A final word on ancestry "realism"

It is tempting to take the outputs from dimensionality reduction (PCA) or model-based clustering (STRUCTURE) and treat them as if they reveal a data-driven truth or reality. To state the obvious: **PCA (or STRUCTURE or an admixture graph) is not an oracle and it does not reveal "true" ancestry, population labels, or `k` values**. These methods have some appealing properties and expectations in idealized populations, **but the specific layout and distances in real data are consistent with many population models and also highly dependent on the sampling and complexities of real data**. It is trivial for these methods to produce nonsensical results: (i) projecting un-admixed individuals from an out-group into the same ancestry location as an admixed individual; (ii) locating two populations close together simply due to oversampling of a third population; (iii) simultaneously under-estimating and over-estimating population probabilities due to oversampling of individuals from a population continuum, etc. **And as emphasized in (Lawson, van Dorp, and Falush 2018), it is not possible to know the "true" sample!** Population sizes today do not reflect their historic genetic contribution due to the influence of non-genetic events such as wars, famines, natural disasters, population expansions, etc. Distortion due to sampling would thus be present even if one were able to run PCA on the entire global population. Likewise, BBP theory shows that there is no "true" number of leading PCs or **`k`** clusters: inclusion of more data enables the inference of more refined components or clusters all the way down to individual families.

For this reason, **while PCA/STRUCTURE are frequently used to visualize and explore genetic data, other tests are typically employed to make concrete quantifications about population relationships**: by using metrics that are unbiased with respect to sample size (e.g. "F-statistics" as summarized in (Peter 2016)), or by defining/fixing populations based on external information (such as geography or time) and manipulating the sampling/parameters to match these assumptions (Novembre et al. 2008).

9.9 | Genetic ancestry in real data

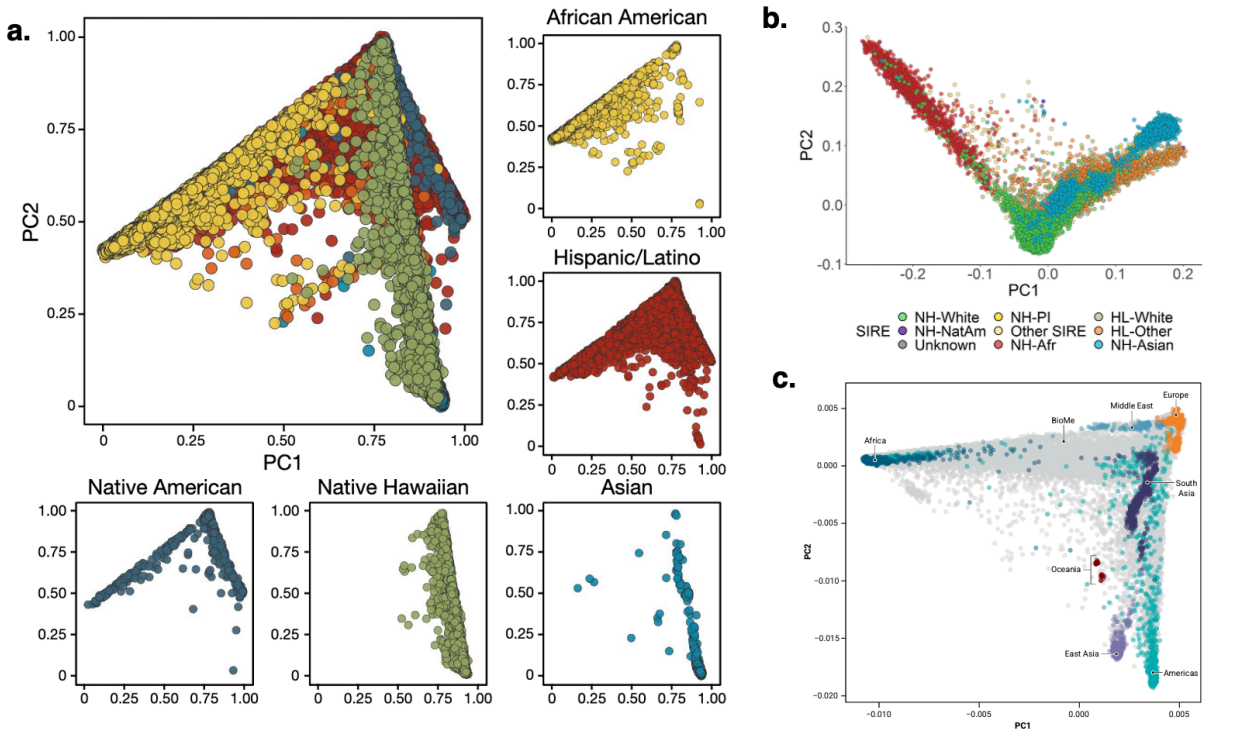
While the above analyses of genetic distances were focused on populations intentionally ascertained to be racially and geographically distinct, what patterns of genetic ancestry do we see with large-scale, modern data from larger, representative studies?

Ancestry versus race

First, the discordance between race and genetic ancestry is apparent in just about every large genetic cohort that has been analyzed. The PAGE study (Wojcik et al. 2019) aggregated data from three large population-based cohorts that focused on recruiting primarily participants who self-identified as non-white, thus offering an opportunity to directly contrast race and genetic ancestry. When overlaying genetic ancestry on self-reported race, it is clear that every racial group exhibits broad continuums of ancestry and contains individuals from all continental ancestries (recall that under simplifying assumptions, the location in PCA space is a proxy for global ancestry proportions). For example, self-reported African Americans exhibit a gradient of ancestry between populations ascertained from the African and European continents, but also include individuals that map entirely to the continental European or Asian locations of the PCA space. Likewise, Hispanic/Latino individuals exhibit extensive three-way admixture from continental European, Asian, and African source populations. **In other words, race neither identifies a clean cluster of genetic ancestry, nor even a clean bifurcation of the ancestry continuum. Although race is *correlated* with ancestry, it is useless in dividing the ancestry space**.

PCA of genetic ancestry in three large population-based cohorts.

(a) The PAGE cohort of primarily non-white participants separated by self-reported race shows continuous genetic ancestry in all groups [Figure from (Wojcik et al. 2019)]. (b) The ATLAS cohort from the UCLA health system, color-coded by race recorded in the electronic medical record [Figure from (R. Johnson et al. 2022)]. (c) The BioMe biobank collected in New York City (gray points) overlapped with data from HapMap/1000 Genomes reference populations (color coded) [Figure from (Lewis et al. 2022)].



The PAGE study is hardly unique and similar patterns are observed in nearly every major biobank collected to date. In the figure above, PCA plots are shown from the ATLAS (UCLA Health System) and BioVu (Mount Sinai Hospital) studies and contrasted with self-reported race or continental reference populations In all instances, continuous genetic variation and ancestry drawn from multiple continental sources was ubiquitous.

Finally, the most direct practical implication of the distinction between race and genetic ancestry is that **race is hardly ever used in purely genetic analyses**: the conventional workflow for a Genome-Wide Association Study, for example, is to identify many (10's or even 100's) of continuous Principal Components from the data itself and include them as covariates (Tian, Gregersen, and Seldin 2008). Where race is analyzed, it is explicitly to contrast with or understand environmental and social factors, or as a crude proxy when genetic data is not available (see much more discussion on the use of race and ancestry in (Borrell et al. 2021) and the report from the National Academies (National Academies of Sciences, Engineering, and Medicine et al. 2023)).

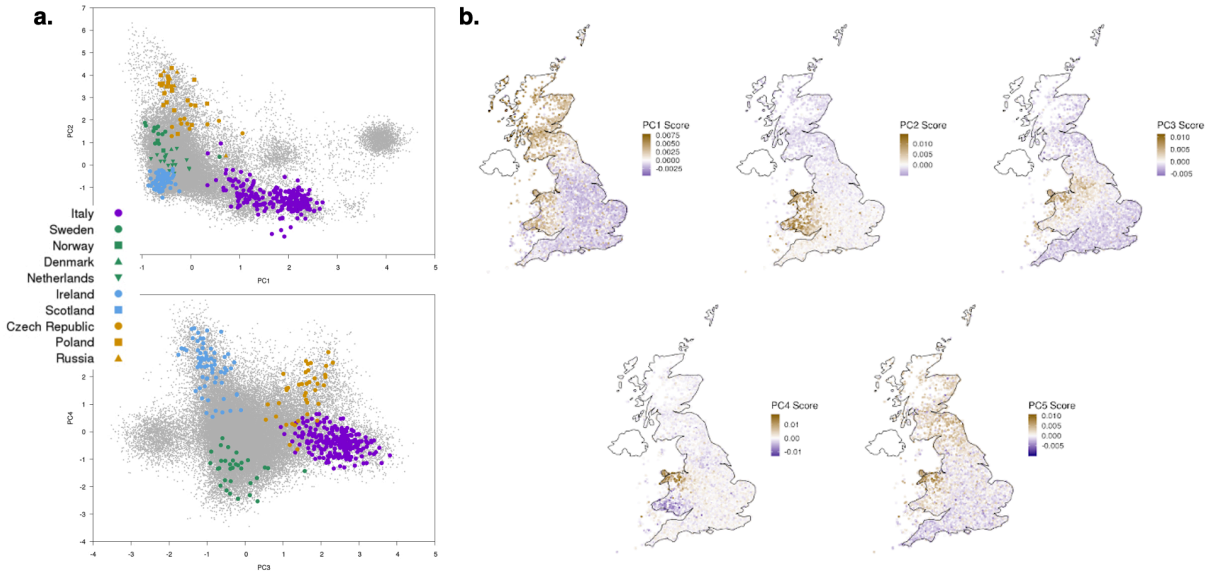
Fine-scale structure

As we move beyond cosmopolitan populations we should expect PCA to continue identifying fine-scale structure at every level of ascertainment as long as the sample size is sufficiently large, as forecast by BBP theory (see [**9.3**]). **Indeed, fine scale population structure is clearly observed even when restricting to seemingly racially "homogenous" populations**. Two large scale studies of "White" individuals in the US and UK are highlighted in the figure below. (Galinsky et al. 2016) applied PCA to ~55k individuals from the GERA cohort (primarily collected in Northern California) after restricting to those with minimal genetic similarity with non-European reference

populations. This analysis revealed the expected clines of population structure reflecting recent geography. When combined with individuals sampled from specific regions of Europe, the leading PCs showed correlation with North/South and East/West European countries, with substantial continuous ancestry between these groups (see panel **a** below). (Agrawal et al. 2020) applied PCA to ~280k unrelated "White British" individuals (identified based on self-reported race and genetic similarity with European reference populations) with known geographic birth coordinates. The leading PCs showed substantial structure and correlation with geography of the United Kingdom, including multiple North/South and East/West clines (see panel **b** below).

PCA reveals fine-scale structure in white US and UK populations.

(a) PCA in the US GERA cohort overlaid with populations sampled from parts of Europe (color coded) [Figure from (Galinsky et al. 2016)]. (b) PCA in the UK Biobank plotted along geographic birth coordinates [Figure from (Agrawal et al. 2020)].

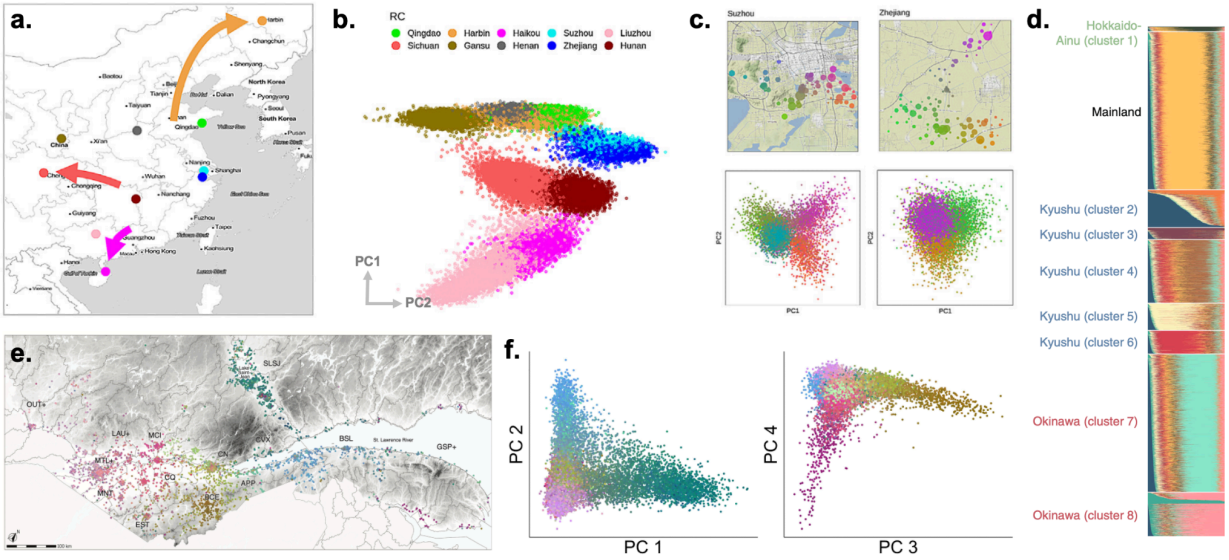


Similar patterns continue to be observed in global biobank studies of seemingly homogenous populations (detailed in the figure below). PCA applied to the China Kadoorie biobank revealed population structure corresponding to regions and major cities in China (Walters et al. 2023). Even when restricting to data collected from individual cities, the leading Principal Components exhibited continuous correlation with local, neighborhood-level geography (see panels **a,b,c** below). STRUCTURE applied to ~170k Japanese ancestry participants in the Biobank Japan identified 11 clusters corresponding to Japanese regions, cities, and islands (Sakaue et al. 2020) (see panel **d** below). Many of these ancestry gradations were not previously known because data from Japan had been limited and presumed to be highly homogenous given the relatively isolated history of the country. PCA applied to ~20,000 French Canadian participants across multiple biobanks revealed fine-scale geographic structure along the communities, lakes/rivers, and mountains of Quebec (Anderson-Trocmé et al. 2023) (see panels **e,f** below).

PCA reveals extensive fine-scale structure in global populations.

*(**a, b, c**) Geographic sampling, leading Principal Components, and fine-scale Principal Components within individual neighborhoods for individuals in the China Kadoorie biobank [Figures from (Walters et al. 2023)].*

*(**d**) STRUCTURE analysis revealing 11 clusters in the Biobank Japan [Figure from (Sakaue et al. 2020)]. (**e, f**) Geographic sampling and leading Principal Components for individuals from Quebec, Canada [Figures from (Anderson-Trocmé et al. 2023)]*



In short, continuous ancestry clines are observed within racial groups (Asia), within "sub-racial" groups (China/Japan), within "sub-sub-racial" groups (cities in China), within "sub-sub-sub-racial" groups (neighborhoods in cities in China) and so on. These findings are entirely consistent with matrix theory and the extremely sensitive nature of PCA to detect structure as recent as 1-2 generations given sufficient sample size. **Ubiquitous and easily detectable continuous ancestry underscores the lack of evolutionary validity for conventional and population-based "race" models**: variation in contemporary individuals is largely unexplained by racial labels, is highly continuous and admixed, and exhibits correlation with geographic and social structure *ad infinitum*.

9.10 | Human history through the lens of modern and ancient DNA

The sequencing of ancient DNA, typically reconstructed from historic specimens such as bones, has provided a window into historic ancestry components that were otherwise unobserved or unidentifiable from modern data. It is now common to integrate large-scale data from contemporary populations together with ancient genomes to infer population structure. While the topic of ancient DNA could fill a book, this section is meant to provide a very brief overview of the major advances and outstanding challenges in the field and how they relate to the contemporary questions regarding race, ancestry, and geography.

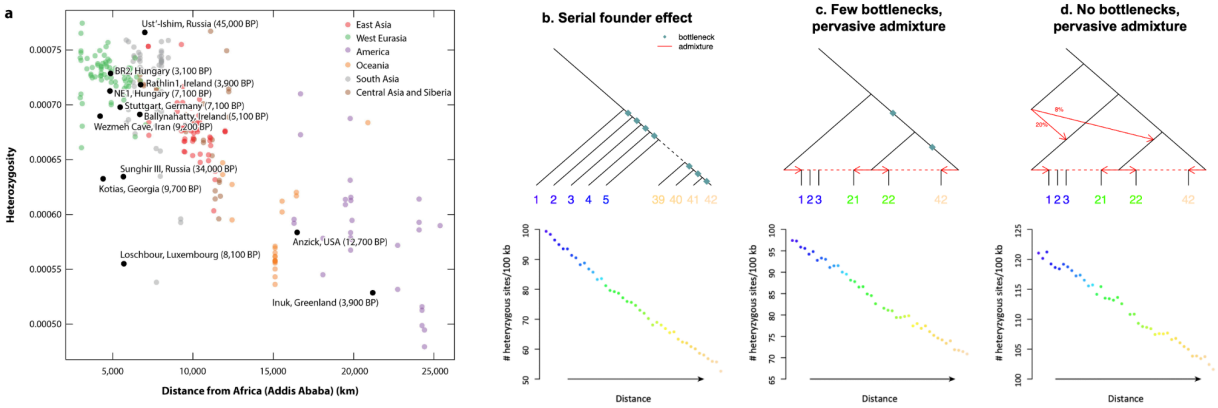
Theory: modeling human expansion and diversity

A long-standing observation in human genetics has been the decrease in genetic diversity with geographic distance from Africa. This gradient was often interpreted under a "serial founder"

model, whereby humans migrated from Africa and experienced repeated bottlenecks followed by locally isolated mating. This combination of bottlenecks and isolation would have reduced diversity within each population along the migratory route and was thought to explain the patterns observed in modern genetic data. This simple model was conceptually aligned with the "population-based" models of race, which also presumed that populations were highly divergent and would easily form natural genetic clusters. **However, recent studies of ancient DNA have shown that the serial founder model of human history is almost certainly wrong**. Notably, ancient genomes often exhibit much lower genetic diversity than more contemporary individuals, consistent with recent admixture and migration (Skoglund and Mathieson 2018).

Genetic diversity out of Africa in real data and in models

*(**a**) Heterozygosity (y-axis) as a function of geographic distance from Africa in real genomic data. Ancient genomes are marked in black and often show lower heterozygosity than modern data, consistent with admixture. [Figure from (Skoglund and Mathieson 2018)]. (**b-d**) Three different models of migration and admixture that produce equivalent heterozygosity/distance gradients in simulations [Figure from (Pickrell and Reich 2014)].*



How could alternative models produce the pattern of decreasing diversity we see in modern data? (Pickrell and Reich 2014) showed through simulations that an identical gradient of decreasing diversity can indeed be observed under multiple different demographies (see figure above). A model with two "severe bottlenecks" followed by semi-local population admixture would produce such a gradient, with the bottlenecks severely reducing diversity in two sub-populations followed by admixture replenishing it along the cline. Even a model with no bottlenecks whatsoever but multiple ancient admixture events (from a highly diverged population such as Neanderthal) followed by extensive recent admixture can also produce such a gradient. In this scenario, rather than bottlenecks decreasing diversity, the ancient admixture increases diversity and extensive admixture events distribute it into a cline. These simulations are, of course, only illustrative. **In principle, the observed geographic cline can be explained by many different combinations of events**: bottlenecks (decreasing diversity), archaic admixture (increasing within-population diversity), and recent admixture (distributing diversity across nearby populations). An interesting corollary is that only the serial founder model requires geographic expansion from Africa. For example, the "*few bottlenecks*" model is consistent with a history where humans originate in Europe and migrate to Africa, experiencing bottlenecks in Europe (decreasing diversity) and expansion in Africa (increasing diversity) followed by migration/admixture. Because contemporary genetic data is variable in ancestry and geography

but fixed in time, it cannot identify these different models. Ancient DNA is additionally variable in time, and can thus impose novel constraints on the data-generating process and space of possible human histories.

Pervasive admixture and migration in Eurasia and the Americas

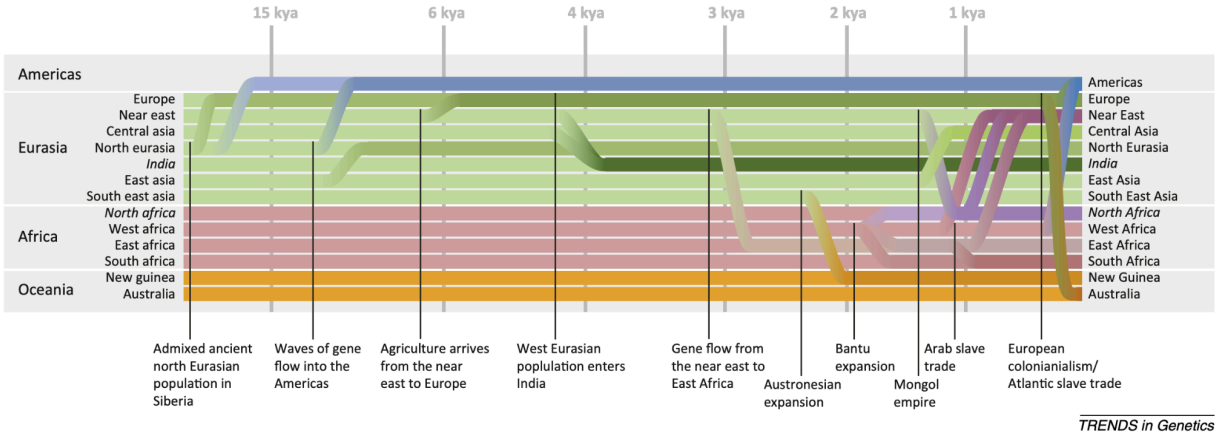
Surveying the ancient DNA studies of the time, (Pickrell and Reich 2014) conclude that simple evolutionary models of serial founder events and isolation are no longer supported by genetic data:

“

It is now clear that the data contradict any model in which the genetic structure of the world today is approximately the same as it was immediately following the out-of-Africa expansion. Instead, the last 50,000 years of human history have witnessed major upheavals, such that much of the geographic information about the first human migrations has been overwritten by subsequent population movements.

Rough timeline of major migrations and admixtures since the African migration

[Figure from (Pickrell and Reich 2014)]

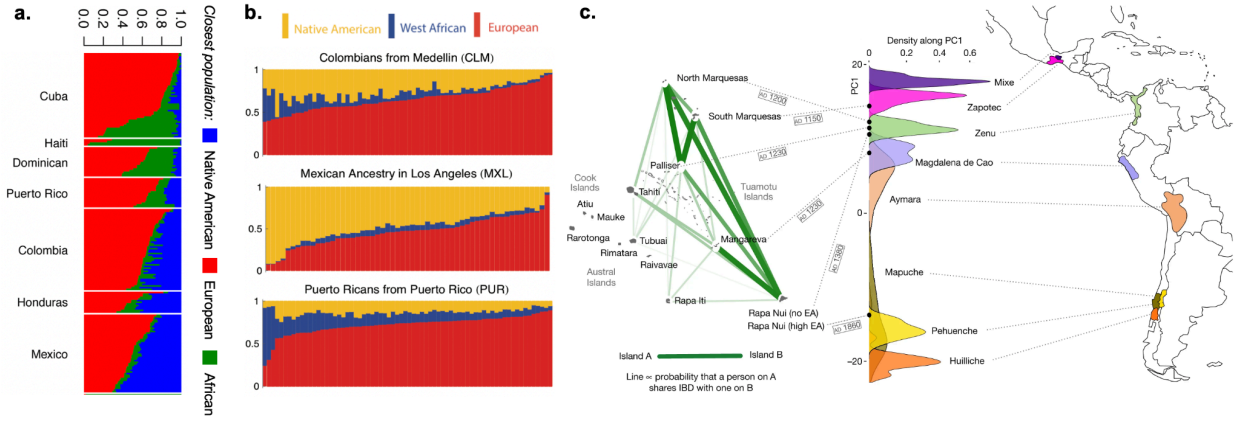


In the decade since, this conclusion has only become more firmly supported by data from global populations. In the Americas, (Moreno-Estrada et al. 2013) and (Gravel et al. 2013) showed that contemporary individuals from Latin America exhibit substantial fractions of European admixture and are often more similar to European than to Native American reference samples. For example, STRUCTURE analysis of whole genomes from Mexican, Columbian, and Puerto Rican individuals estimated their similarity to Native American reference samples at just 48%, 25%, and 13% respectively (Gravel et al. 2013). What about the origins of those Native American reference samples? (Ioannidis et al. 2020) identified genetic sharing between Polynesian individuals and Native American samples consistent with pre-Columbian contact across the Pacific; though the precise directionality of the admixture is compatible with multiple histories. And those Polynesian samples? Analyses of ancient DNA from Oceania suggest that the settlers of Polynesia likely came directly from East Asia rather than nearby Papua New Guinea, only mixing with Papuan individuals at a later point (Skoglund et al. 2016). In short, ancient movements to the Americas

were highly dynamic and often detached from simple geographic proximity, followed by aggressive European colonization that fundamentally transformed the genetic mixtures of modern people.

Extensive admixture in the people of the Americas

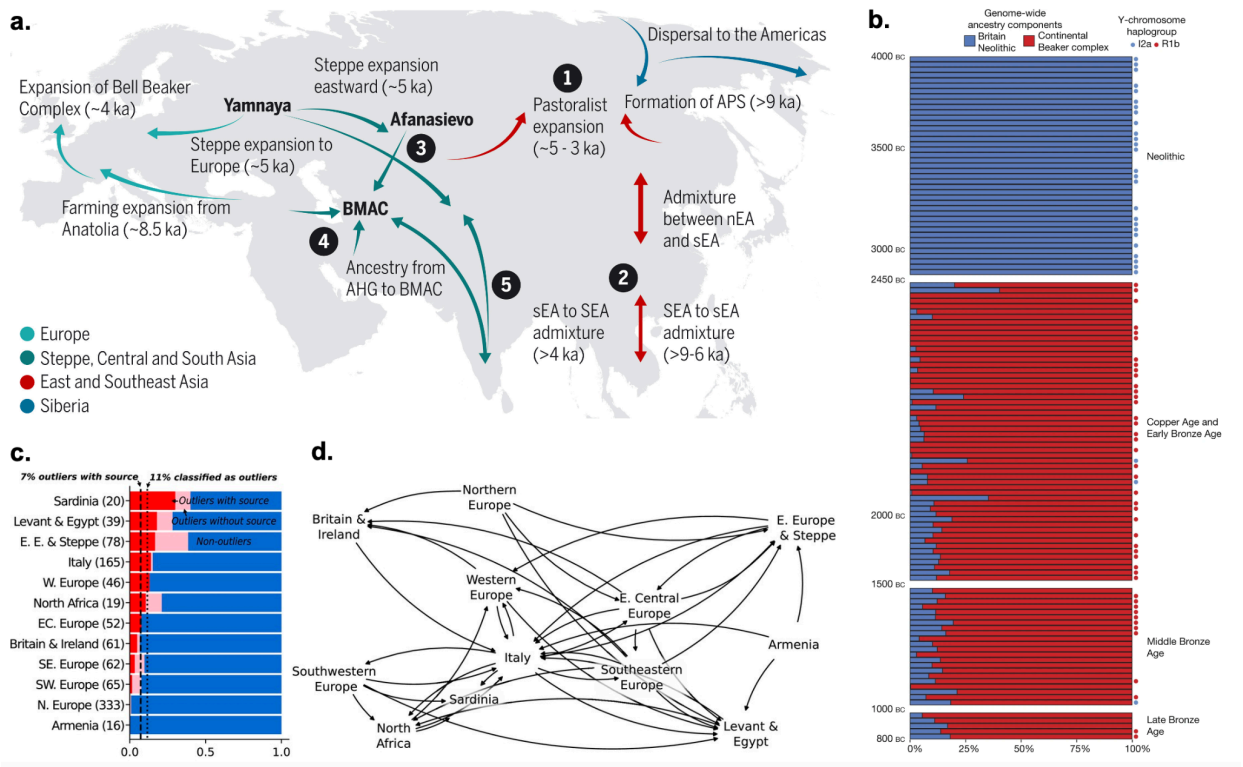
*(**a**) Admixture analysis of contemporary Caribbean populations [Figure from (Moreno-Estrada et al. 2013)]. (**b**) Admixture analysis of Colombian, Mexican, and Puerto Rican populations [Figure from (Gravel et al. 2013)]. (**c**) Recent genetic sharing (green segments) among Polynesian islands and admixture with Native American populations and approximate dates (dotted segments) [Figure from (Ioannidis et al. 2020)].*



In Eurasia, ancient data supports multiple waves of mixture and expansion though the precise timescales and source populations are still contested. In ancient DNA samples from Siberia, Native American ancestry pinpointed a population that likely mixed with both the ancestors of modern-day Europeans and populations that subsequently expanded into Native Americans (Lazaridis et al. 2014; Sikora et al. 2019). In contrast, modern Siberian populations share more of the genetic ancestry with East Asian individuals than with these ancient Siberian samples, highlighting a third historic migration event that defines the contemporary genetic landscape. The fact that ancient individuals often appear to derive ancestry from populations that are no longer un-admixed today is both remarkable and poses a major challenge for simple cluster-based interpretation of ancient and modern data.

Waves of migration and admixture in Eurasia inferred from ancient DNA.

*(**a**) Map of major admixture and migration events in Eurasia reconstructed from ancient DNA; [Figure from (Y. Liu et al. 2021)]. (**b**) Rapid replacement of >90% of neolithic British ancestry through expansion of the Beaker complex ~4-5kya [Figure from (Olalde et al. 2018)]. (**c**) Ancestry "outliers" in ancient DNA from European regions in the past 3,000 years and (**d**) reconstructed migration paths for outliers. (**c,d**) [Figure from (Antonio et al. 2024)].*



In some cases, population shifts appear to be extremely rapid, such as the apparent replacement of 90% of ancestry in Britain with steppe-related ancestry through expansion of the Bell Beaker cultural complex through the Bronze age (~2.5kya) (Olalde et al. 2018) (panel **b** above). In other cases, the data support a complex relationship between migration and long-term structure. Recent analyses of DNA specimens from Europe during the Bronze age (up to 3kya) revealed a substantial fraction of ancestry "outliers" in most of the sampled geographic sites (Antonio et al. 2024) (pane **c,d** above). At least 7% of the sequenced individuals showed significant ancestry from a region other than where they were sampled, with some spanning major geographic barriers. Interestingly, the high fraction of ancestry outliers nevertheless co-occurred with sustained population structure in these regions over time, suggesting that migrating individuals either did not settle in the regions they were buried or exhibited spatial migration/mating patterns that are not consistent with simple random mating. In short, much like today, ancient people appear to have traveled across Europe for work or trade, while simultaneously maintaining stratified societies.

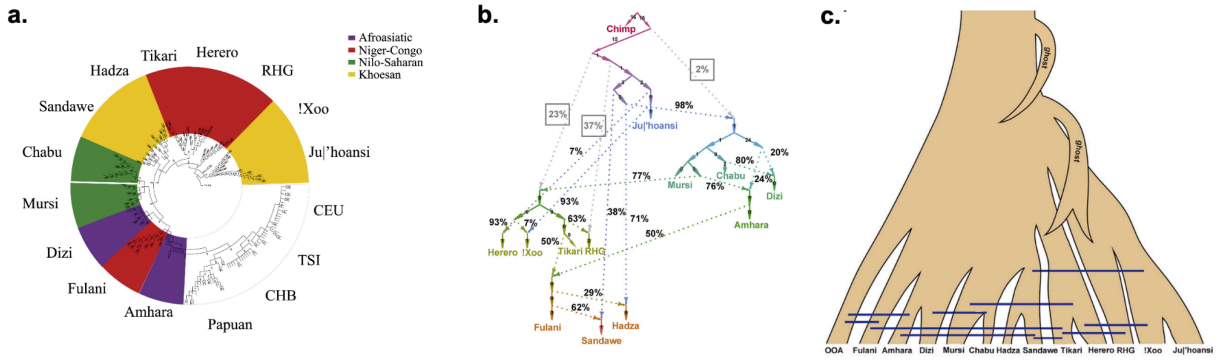
Model identifiability in Africa

Remarkably, while we know that there is much more genetic variation in Africa than in other parts of the world, we still do not fully understand the migration patterns within and out of Africa during the modern human period. Recent analyses of contemporary African genomes show many populations that appear to have diverged tens of thousands of years ago, followed by recent migration and gene flow that sometimes spanned the continent (Fan et al. 2023). When modeling African populations with a simple phylogenetic structure that does not allow admixture, most populations were clustered within their current geographic locations and consistent with their language groups (panel **a** below). **In contrast, when admixture and migration was allowed in**

the model, the recovered topologies were significantly different: "*the Hadza and Sandawe, respectively derive 71% and 38% ancestry from a population ancestral to the southern African Khoesan population … These populations, particularly the Sandawe, also derive ancestries from an Afroasiatic-like population, likely reflecting recent Afroasiatic gene flow … the Ethiopian populations (Amhara, Dizi, Mursi, and Chabu) derived 98% and 2% of their ancestries from a population ancestral to the Hadza and a population ancestral to all modern human populations, respectively … 80% of the Omotic-speaking Dizi ancestry can be traced back to a Chabu-related population and 20% to an Amhara-related population … the RHG derive 37% of their ancestry from a population ancestral to the San and 63% of their ancestry from a Niger Congo-speaking population*" (Fan et al. 2023) (visualized in panel **b,c** below). While the precise relationships remain ambiguous, there is clear evidence of extensive gene flow between African populations.

The traces of admixture and migration in modern Africa genomes

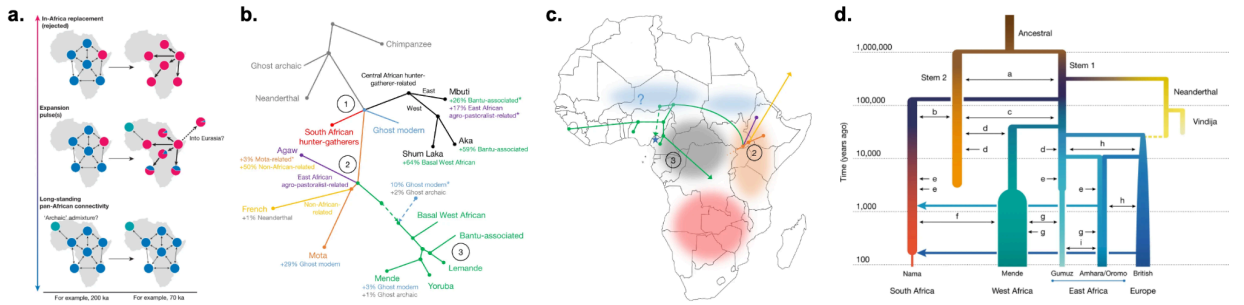
*(**a**) Simple neighbor-joining tree of genomic data without admixture/migration. (**b**) Admixture graph reconstruction of genomic data allowing for 10 admixture events; putative ancient admixtures shown in gray. (**c**) Schematic of demographic reconstruction from modern African genomic data with blue bars indicating gene flow. Upper roots indicate genetic material from multiple "ghost" populations into the ancestors of modern humans. OOA: Out of Africa populations. [Figures from (Fan et al. 2023)].*



Studies of ancient African genomes have begun to orient these divergences and mixtures in time. This includes the identification of deep population structure and admixture throughout Africa (Lipson et al. 2020) (panel **b,c** below; but see (Maier et al. 2023) for alternative models), mixture between pastoralist and forager groups during the spread of food production (K. Wang et al. 2020), and substantial change in population structure as a likely consequence of the spread of food production (Skoglund et al. 2017).

Model identifiability in ancient Africa

*(**a**) Multiple putative models of African replacement/expansion [Figure from (Bergström et al. 2021)]. (**b,c**) Admixture graph and corresponding geographic locations inferred using ancient African genomes. [Figure from (Lipson et al. 2020), but see (Maier et al. 2023) for alternative models]. (**d**) Best-fitting model of African population structure when allowing for continuous and reciprocal migration (bi-directional arrows) [Figure from (Ragsdale et al. 2023)]*



Coming back to models of human expansion, the complex structure, divergence, and mixture in Africa has left this fundamental question largely unresolved (panel **a** above) (Bergström et al. 2021). A simple model of complete population replacement can be rejected based on the presence of small fractions of very ancient ancestry in modern and contemporary individuals. However, highly divergent ancestry is observed in many parts of Africa (Skoglund et al. 2017; Lipson et al. 2020), making it difficult to anchor more complex models of expansion. Indeed, even these initial findings of deep structure now appear to be compatible with multiple alternative phylogenies (Maier et al. 2023) (see [**9.7**]). In one proposed "pan-African" model, African groups lived in multiple "structured but connected" subpopulations forming a "metapopulation" with continuous and complex gene flow (Scerri, Chikhi, and Thomas 2019; Ragsdale et al. 2023) (panel **d** above). This model could potentially explain the mosaic of genetic and archaeological findings, but is also difficult to verify with current statistical methods which generally assume trees and defined mixtures. Such a "structured but connected" model may also mirror the structured migration that was recently observed – albeit at a much shorter time scale – in Bronze Age Europe (see above). Alternatively, a "back to Africa" model proposes that the same population that migrated out of Africa also expanded back across Africa from the East, substantially (but not completely) replacing a structured historic population (Cole et al. 2020). Finally, lurking amidst these possible histories is the indeterminate evidence of multiple admixture events with a population that diverged millions of years ago from humans (evidence that has also been recently contested (Ragsdale et al. 2023)).

In sum, it is remarkable that while ancient DNA has informed the history of many populations, there is still so much ambiguity about human history in Africa. This is in part due to the basic technical challenges of extracting ancient DNA out of remains in a hot and humid climate, as well as the broader conceptual challenge of modeling a long and complex history with statistical methods that are relatively crude. **It is clear that models of simple population divergence or complete replacement do not fit the observed data.** However, it is still an open question if the marginally more realistic phylogenetic and admixture models currently being employed are sufficient to characterize such complex population histories. It should go without saying that conventional models of race provide no meaningful information on human evolutionary history.

9.11 | Further reading

Race and ancestry:

- (Edge, Ramachandran, and Rosenberg 2022): Special theme issue celebrating 50 years since Lewontin's seminal work on "The Apportionment of Human Diversity", including the historic context, modern criticism, and ongoing challenges in the field.
- (J. M. Kaplan and Winther 2014): Commentary on Lewontin's study and subsequent responses.
- (Borrell et al. 2021): Perspective on the use of race and ancestry in clinical practice.
- (Lewis et al. 2022): Perspective on the use of continuous ancestry in genetic analyses.
- (Carlson et al. 2022): Perspective on effective visualizations of genetic ancestry.
- *Visualizing Human Genetic Diversity*: Interactive visualization of allele sharing across populations.

Genetic ancestry methods:

- (Patterson, Price, and Reich 2006): Introduction to PCA/eigenanalysis of genetic data.
- (McVean 2009): Genealogical interpretation of PCA and implications for sampling and simple admixed populations.
- (Lawson, van Dorp, and Falush 2018): Tutorial on model-based clustering / STRUCTURE and examples of challenging identifiability.
- (Maier et al. 2023): Analyses of identifiability for parametric / admixture graph methods and re-analysis of published graphs.

Ancient DNA:

- (Pickrell and Reich 2014): Early review and outlook on ancient DNA studies and human migration/admixture.
- (Skoglund and Mathieson 2018): Review of the first decade of findings from ancient DNA.
- (Bergström et al. 2021): Review and perspective on the origins of humans.

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