Reproduction of socioeconomic differences and mental health across generations

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If you are never wrong, then you work in a field that is too easy for you

Linus Pauling

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Hans Fredrik Sunde
Oslo, June 2023

Summary

The premise of this thesis can be summarized in three statements: (1) Socioeconomic position runs in families; (2) Mental health runs in families; and (3) Mental health and socioeconomic position are correlated. The goal of this thesis is to advance our understanding of *why* these variables are associated. Three scientific papers spring from this work, each addressing a particular facet of the overarching research question.

In the first paper, titled "The ADHD deficit in school performance across sex and parental education", I investigated the relationship between ADHD and school performance. I analysed register data on practically every Norwegian junior high school student born between 1997 and 2002 (N = 344,152) and found a large difference in school performance between children with and without ADHD. This difference was partly due to ADHD being more prevalent in groups that typically perform worse in school, such as boys and children of less educated parents. When I adjusted for potential confounders, including unobserved familial confounders by comparing siblings, the difference was reduced but remained relatively large. Performance differences related to ADHD was not stable across social background: The differences was larger among children with highly educated parents, despite ADHD being less common in these groups. Finally, I also found that ADHD was associated with large performance differences across all school subjects, indicating that ADHD is associated with general factors shared across these subjects.

In the second paper, titled "Parental income and mental disorders from age 10 to 35", I studied the relationship between parental income rank and prevalence of mental disorders using register data on practically every Norwegian resident aged 10 to 35 between 2006 and 2018 (N = 2,112,355). I found large differences in the prevalence of mental disorders across parental income quartiles, with higher prevalences in the lower income quartiles throughout the entire age-range. Applying an extended children-of-twins model, I found evidence suggesting a small, direct effect of parental income among adolescents, but genetic similarity accounted for most of the correlation. In terms of variance explained, high heritability was evident for both income rank (30–40%) and mental disorders (47–70%), with minimal variance explained by shared environmental factors.

Finally, in the third paper, titled "Genetic similarity between relatives provides evidence on the presence and history of assortative mating", I used path analysis to investigate the expected impact of assortative mating (i.e., non-random matching of partners with similar traits) on genetic similarity within families. I found that assortative mating will have a greater impact on similarity between distant relatives compared to close relatives, indicating that genetic variants associated with assorted traits will concentrate in extended families, potentially increasing inequality. I then correlated polygenic scores between 47,135 partner pairs and 1,213,258 dyads of related individuals in the Norwegian Mother, Father, and Child Cohort Study (MoBa) cohort study, and found empirical evidence of assortative mating for several traits including educational attainment, height, intelligence, and body mass index. Surprisingly, I did not find genetic evidence of assortative mating for mental disorders, which could either suggest other causes of phenotypic partner similarity or that the polygenic scores are severely limited. For some of the traits that showed evidence of assortative mating, such as educational attainment, my analysis suggested that genetic variance and similarity in families are still increasing across generations, leading to increasing differences. However, most of the genetic consequences of assortment had already manifested.

In the thesis introduction, I discuss the nature of causality, differences between genetic and environmental influences, and the challenges posed by inferring causality from observational data. This exploration sets the groundwork for the analyses carried out in the research. In the concluding chapters, I further address methodological considerations and potential biases, and provide a general discussion on the potential implications of these findings.

Overall, the findings across these papers reiterates that there is a strong association between socioeconomic position and mental disorders. As to whether this association is causal, the answer depends on whether we are looking at this across generations or within individuals. Across generations, it appears that the association cannot entirely be blamed on confounding factors, but a large part of the association seems attributable to a genetic correlation. Within individuals, the answer remains uncertain, but when my findings are seen in the light of other studies, bidirectional influences between mental health and socioeconomic position seem plausible. Finally, assortative mating seems to increase and maintain the differences caused by intergenerational transmission of socioeconomic differences.

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Paper 1:

Sunde, H. F., Kleppestø, T. H., Gustavson, K., Nordmo, M., Reme, B. A., & Torvik, F. A. (2022). The ADHD deficit in school performance across sex and parental education: A prospective sibling-comparison register study of 344,152 Norwegian adolescents. *JCPP Advances*. https://doi.org/10.1002/jcv2.12064

Paper 2:

Sunde, H. F., Eilertsen, E. M., Kinge, J. M., Kleppestø, T. H., Nordmo, M., Caspi, A., Moffitt, T., & Torvik, F. A. Parental income and mental disorders from age 10 to 35: a genetically informative population study (*Submitted*)

Paper 3:

Sunde, H. F., Eftedal, N. H., Cheesman, R., Corfield, E. C., Kleppestø, T. H., Seierstad, A. C., Ystrøm, E., Eilertsen, E. M., & Torvik, F. A. Genetic similarity between relatives provides evidence on the presence and history of assortative mating (*Submitted*)

Chapter 1: Introduction

The premise of this thesis can be summarized in three statements: (1) Socioeconomic position runs in families; (2) Mental health runs in families; and (3) Mental health and socioeconomic position are correlated. These statements can be illustrated as in Figure 1.1, where bidirectional arrows indicate associations between mental health and socioeconomic position in both the parental generation and the offspring generation. The close relationship between socioeconomic position and mental health signals that mental health could be a key for understanding how socioeconomic position are transmitted through generations. Likewise, socioeconomic position could be a key for understanding mental health. The goal of this thesis is therefore to advance our understanding of *why* these four variables are associated within and across generations.

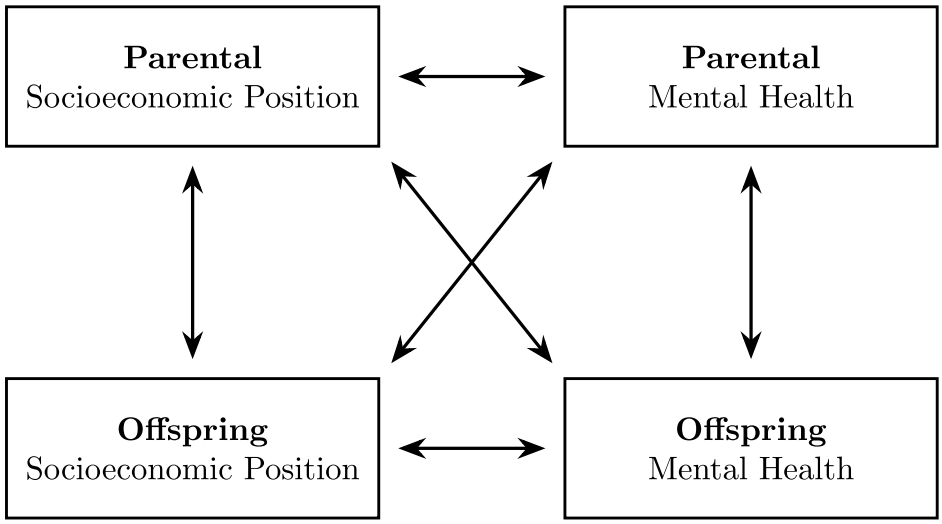

Figure 1.1: Intergenerational associations between socioeconomic position and mental health

The rest of this chapter is devoted to laying out the premises for this thesis. Chapter 2 explores causality and what previous research says about causal associations between mental health and social differences. In chapter 3, I describe the aims of this thesis, which will be limited to excerpts of Figure 1.1 in a Norwegian context. This is followed by a descriptions of the data and materials (chapter 4) followed by a thorough explanation of the statistical approaches with particular emphasis on the underlying logic and assumptions (chapter 5). In chapter 6, I summarize the main findings, before discussing the implications of this work along with more assumptions and complications in chapter 7.

1.1 What is socioeconomic position?

Socioeconomic position (aka. socioeconomic status) refers to an individuals' access to or accumulation of various social and economic resources, including income, education, occupational opportunities, and subjective perceptions of social status and class (Diemer et al., 2013; Muntaner et al., 2004). The different dimensions of socioeconomic position are highly correlated, meaning factors associated with income are typically also associated with education, and vice versa. This can make it hard to distinguish which dimension of socioeconomic position are most important, a task that is beyond the scope of this thesis (but see section 7.6). This also makes socioeconomic position an ontologically fuzzy concept, because it is not clear what we are measuring (Braveman et al., 2005). The individual papers in this thesis will use and discuss specific

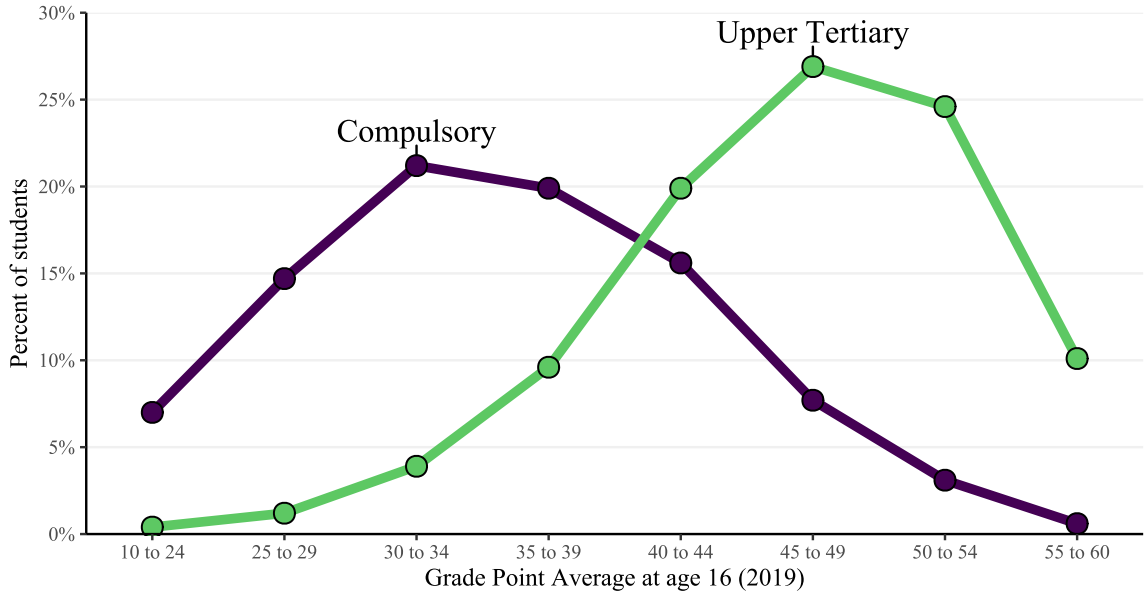

Figure 1.2: Offspring GPA and parental education.
Distribution of GPAs among offspring of parents where neither has completed more than compulsory education (purple line) and among offspring of parents where at least one has a Master's degree or equivalent (green line). Figure is based on numbers from table 11689 from Statistics Norway (2020)

measures of socioeconomic position, like education or income, but because it will be unclear which dimension is important in the grand scheme of things, I will use the term socioeconomic position in general discussions.

The socioeconomic position of offspring is not separate from the socioeconomic position of their parents when the offspring are still children. One useful indicator of the child's later socioeconomic position is their early school performance: Children who perform well in school often grow up to be well-educated, employed, and healthy, whereas children who do poorly risk unemployment and social exclusion (Bachman & O'Malley, 1977; Borghans et al., 2016; Moffitt et al., 2011). A Norwegian report estimated that each additional grade point on a scale from 1 to 6 was associated with 55 000 NOK (roughly 5000 USD) higher annual income at age 30 (Markussen et al., 2020).

1.2 Socioeconomic position runs in families.

School performance is highly correlated with parental socioeconomic position: Children of highly educated parents typically outperform children of less educated parents (OECD, 2016; Sirin, 2005; Statistics Norway, 2020). Figure 1.2 shows the distribution of grade point averages (GPA) among Norwegian 16-year-olds by the highest achieved education of either parent. Whereas 34.7% of children of highly educated parents (green line) achieved a grade point average of 50 or more, only 3.7% of children of parents with compulsory education (purple line) achieved similarly high results. Conversely, whereas 42.9% of children of parents with compulsory education achieved a grade point average less than 34 points, only 5.5% of children of highly educated parents had similarly low performance.

A similar pattern emerges when we look at the socioeconomic position of offspring as adults (Figure 1.3). Children of less educated parents are far less likely to complete tertiary education: Among parents where neither has more than compulsory education, only 16% of their offspring completed tertiary education,

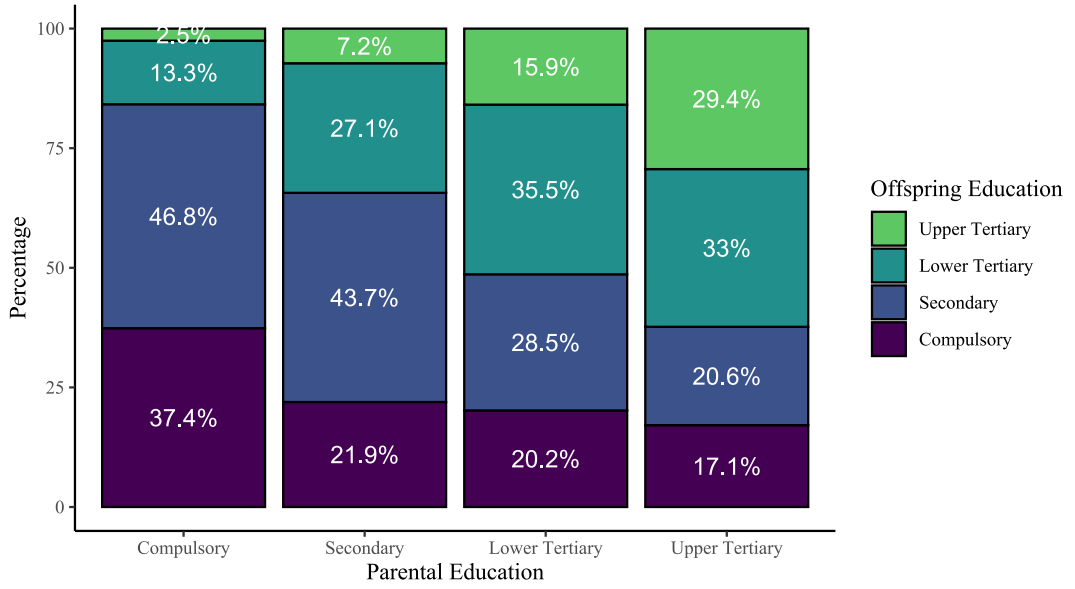

Figure 1.3: Educational attainment by parental educational attainment.
Numbers are based on table 12935 from Statistics Norway (2022), and is a cross-sectional view of the entire population in 2019.

compared to 62% among parents where at least one parent had a master's degree or equivalent (Statistics Norway, 2022). The report mentioned earlier found that offspring of highly educated parents had on average 30% higher annual income (~120 000 NOK) at age 30 than offspring of less educated parents (Markussen et al., 2020). This association largely disappeared when they adjusted for the offspring's own school performance, suggesting that parental socioeconomic position's effect on offspring socioeconomic position is mediated through offspring school performance.

1.3 What is mental health?

Mental health is a broad term that encompasses numerous dimensions of psychological well-being (WHO, 2022). The dimension I will focus on here is mental disorders. Mental disorders (aka. mental illnesses, aka. psychiatric conditions) are significant disturbances in cognition, emotion, or behaviour that reflect a dysfunction in the processes underlying mental functioning. Crucially, they are usually associated with significant distress or disability in daily life (APA, 2013)

Mental disorders come in many forms with different severities and symptoms and are typically classified according to diagnostic manuals such as DSM-V (APA, 2013) or ICD-10 (WHO, 1992). Some of the more common disorders include (1) attention-deficit hyperactivity disorders (ADHD), which are characterized by a lack of control over attention and impulses; (2) depressive disorders, which are characterised by persistent feelings of sadness and hopelessness accompanied by a general lack of interest in activities; and (3) anxiety disorders, which are characterised by excessive fear or worries that debilitates daily life.

Mental disorders are treated as categorical for practical reasons. In reality, most mental disorders likely represent the ends of continuous distributions (Cuthbert, 2014; Haslam et al., 2012; Plomin et al., 2009; Verhoef et al., 2019). According to this view, the mental state of every individual lies on a continuum of, for example, "depressivity", and depressive disorder is the name we give to mental states at the end of this

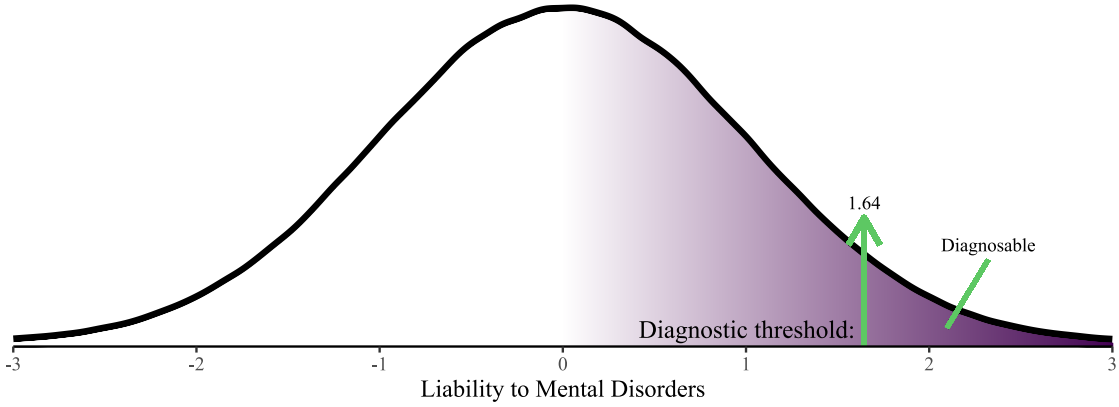

Figure 1.4: Illustration of the continuous nature of mental disorders

continuum (Figure 1.4). A useful analogy is whom we consider to be "very tall". To parallel the definition of mental disorders, we could define it as being so tall that it becomes a problem in daily life. Where is the cut-off? It is obvious that there is no absolute height at which someone goes from being tall to being very tall, but it still makes perfect sense to describe someone as very tall. The same goes for mental disorders. An individual may be easily distracted, but not so much that it warrants an ADHD diagnosis. Others may have an anxious character, creating a slight hindrance in daily life but not a debilitating hindrance. There is no set point where an anxious character struggles so much that it becomes a major problem, but rather a gradual change.

There are three important corollaries: First, the differences between cases that are just below or just above a threshold for a given disorder will be insignificant. Second, any changes in the threshold (across age, sex, social group, or time) may give the impression that the disorder is becoming more or less common despite a constant underlying distribution. Third, there may be large variation in severity among those we consider as having the disorder. Someone could be barely above the threshold, others could be far above it. Despite this, it is sometimes practical to speak of mental disorders as categorical. This should not hide the underlying continuous nature of mental disorders. Whenever I refer to a diagnostic category, I therefore urge you to think about it as if I had said "very tall". This is also reflected in how mental disorders are modelled in Paper 2, which uses a liability threshold model. More on that later (section 5.5.7).

The historical origin of the current diagnostic categories was mostly motivated by the administrative needs of health care systems, and not by a rigorous scientific consensus (Horwitz, 2021). It is therefore not surprising that there are many concerns about the validity and reliability of the categories despite its use (Hyman, 2010). For example, mental disorders often lack external heterogeneity and internal homogeneity: the same diagnosis is indicated by a wide range of symptoms and severities, while symptoms can overlap significantly among different diagnoses. Furthermore, it is common for different disorders to co-occur, with shared risk factors and overlapping treatment options (Fried et al., 2022; Kessler et al., 2005; Kotov et al., 2017; Krueger & Eaton, 2015; Mcgrath et al., 2020; Newson et al., 2020; Plana-Ripoll et al., 2019). This is not to deny the reality or diversity of mental disorders, but we need to remain agnostic on how to best understand the different manifestations of mental disorders. There are several proposals that address these issues, such as the hierarchical taxonomy of psychopathology (Kotov et al., 2017), the p-factor (Caspi & Moffitt, 2018), or the network theory of mental disorders (Borsboom, 2017), but for now, the jury is still out (Aristodemou et al., 2023; Lahey et al., 2021). In the meantime, it is generally accepted to group mental disorders into externalizing

and internalizing dimensions, especially when speaking of children (Caspi & Moffitt, 2018). Externalizing disorders include behavioural disorders such as ADHD whereas internalizing disorders include emotional disorders such as depression and anxiety. The goal of this thesis is not to solve these ontological issues, but, as with any scientific work about mental disorders, it must take a position on it. Throughout most of this thesis, I will use conventional diagnostic categories or dimensions where appropriate or practical, but otherwise refer to mental disorders as one heterogeneous phenomenon.

1.4 Mental health runs in families

One of the strongest predictors of mental disorders is a family history of mental disorders (Fristad & Clayton, 1991; Steinhausen et al., 2009). Compared to the general population, individuals with an affected first-degree relative are at significantly higher risk of having the same disorder. Some studies estimate the risk to be increased more than twofold for major depression (Sullivan et al., 2000), fivefold for anxiety disorders (Hettema et al., 2001), fivefold for ADHD (Musser et al., 2014), and sixfold for schizophrenia (Chou et al., 2016; Hilker et al., 2018). Notably, this heightened risk is not confined to the specific disorder diagnosed in the family member but extends to other disorders as well (Steinhausen et al., 2009). For example, a study that investigated first-degree relatives of people with schizophrenia found they also had a threefold increase in the risk for mood disorders like depression (Chou et al., 2016). Another line of evidence comes from behaviour genetic studies, which indicate that most mental disorders are highly correlated between family members (Polderman et al., 2015).

1.5 Mental health and socioeconomic position are correlated.

Socioeconomic position and health are robustly associated both within and across generations (Bor et al., 2017; Davies et al., 2018; Evensen et al., 2021; Kinge et al., 2019; Kinge et al., 2021). This health gradient is apparent for mortality (Kinge et al., 2019), COVID-19 infections (Liao & De Maio, 2021), somatic health (Evensen et al., 2021), and, crucially, mental health. (Fryers et al., 2003; Hackman et al., 2010; Jenkins et al., 2008; Kinge et al., 2021; Lorant et al., 2003; Luo & Waite, 2005; Macintyre et al., 2018; Peverill et al., 2021; Weich et al., 2001). The association between mental health and socioeconomic position is persistent across various facets of socioeconomic position, such as unemployment (Paul & Moser, 2009), debt (Jenkins et al., 2008), income (Meng et al., 2020), parental income (Kinge et al., 2021), and educational attainment (Tambs et al., 2012). Several studies also document a robust association between mental health and educational performance in adolescence. A Norwegian study concluded that, among all health conditions, mental disorders had the largest educational burden of disease (Nordmo et al., 2022). Other studies from Denmark (Dalsgaard et al., 2020) and Sweden (Shen et al., 2016) also show a large association between mental health and school performance. ADHD in particular seems important in this regard (see Paper 1): Having ADHD is negatively associated with several later socioeconomic outcomes (Jangmo et al., 2021).

Why do these associations exist? This is actually two subtly different questions: (1) Why do socioeconomic position and mental health correlate *within the same individuals*, and (2) why do socioeconomic position and mental health correlate *between family members*, such as between parent and offspring. The difference between intergenerational correlations and within-individual correlations can be easy to miss, but they may end up having completely different explanations. In the next chapter, I discuss what *could* cause these associations.

Chapter 2: Causality

The premise of this thesis is that there are associations between socioeconomic position and mental health across generations. The goal of this thesis can therefore not be to simply reiterate that such associations exist but must instead be to illuminate the underlying causal structure. A thorough discussion of causality is therefore warranted. In this chapter, I will discuss (1) what it means for something to cause something else, (2) what could explain the observed associations that form the premises of this thesis, and (3) what prior research says about causality on this matter. Before that, however, I must introduce a useful tool that I will use throughout this thesis, namely path diagrams.

2.1 How to illustrate causality?

Path diagrams, first introduced over a century ago by Sewall Wright (1921, 1934), illustrates hypothesised causal relationships between a set of variables. They exist in a variety of forms, each with slightly different applications, limitations, and strengths. These include directed acyclic graphs (DAGs), which are usually used to find out the consequences of conditioning on certain variables, and structural equation models (SEMs), which are used to estimate parameters in path diagrams (Pearl & Mackenzie, 2018; Rohrer, 2018). For now, we will simply use path diagrams to visualise different ways two variables can be associated. Later, in section 5.2, I will explain path analysis more thoroughly.

All path diagrams are composed of nodes and edges, where nodes represent variables and edges (arrows) represent the causal relationships between those variables. Figure 2.1 shows a very simple path diagram that illustrates that we think one variable called X causes another variable we call Y. The diagram does not consider other causes of X or Y; it merely posits that the association between X and Y is exclusively because X causes Y. Using these building blocks, it is possible to build intricate causal diagrams that would illustrate hypothetical explanations for observed associations.

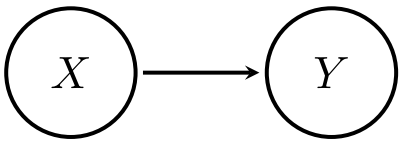

Figure 2.1: Example of a simple path diagram

2.2 What is causality?

Now that we have a way of illustrating causal relationships, we can ask what it means that X causes Y. We are now on the precipice of a deep philosophical pit which we will do our utmost not to fall into. Suffice to say that any meaningful definition of a cause must involve making a difference. In this context, we say that a causal variable is a *difference maker*, meaning that a change in the causal variable brings about a change in the outcome variable (e.g., Waters, 2007; Wright, 1921). This distinguishes the idea of *causality* – where making a difference in X makes a difference in Y – from mere *association* – where observing a difference in X is associated with an observed difference in Y. This definition also neatly captures different aspects of causality that we might encounter if we had fallen into the philosophical pit, such as concerns about interventions, time

directionality, and counterfactuals (Pearl & Mackenzie, 2018). To assert that X causes Y means that a truly random change in X would result in a change in Y as well.

At least on average. In complex systems, causation is intrinsically probabilistic (e.g., Kaplan & Turkheimer, 2021), and we must abandon concepts such as necessary and sufficient conditions. For example, socioeconomic position of parents could heighten the risk of mental disorders in their offspring, but we would not expect it to be necessary (not everyone with mental disorders comes from a low socioeconomic background) nor sufficient (not everyone from a low socioeconomic background develops mental disorders). Multiple factors act together to create outcomes, often through mediators and conditional on moderators, rendering relationships between causes and effects probabilistic, not deterministic. This is inherent in complex systems, not just a product of our ignorance (Gleick, 1987; Palmer, 2022). This means when we assert that X causes Y, we're asserting that changing X shifts the probabilities for various outcomes of Y, not that it guarantees a particular outcome.

2.3 The consequences of causation depend on variation

A goal of this thesis is to illuminate causes of *observed* variation and associations. As such, we must distinguish between potential causes and actual causes of differences (Waters, 2007). It could be the case that changing X sufficiently would bring about a change in Y (thus satisfying our criteria for causation) but that the change in X needed would be far greater than the existing variation in X (i.e., the cause is practically invariant). In other words, the observable consequences of causation depend on *variation* in the difference makers. Consider a mundane hypothetical example where gravity during development influences adult height (Gravity → Height). While this may be true, everyone experiences similar gravity. Gravity's effect on height can therefore not explain why people differ in height or why height correlates with other variables. In other words, claiming that X is or isn't a cause of observable differences in Y is not the same as claiming that X would invariably or never cause observable differences in Y. In this thesis, I am using the former interpretation of "cause".

With this in mind, it is important to note that the current population under study has comparatively little inequality (OECD, 2022; The World Bank, 2022). The findings may not generalize to contexts with more variance in the putative causes. I discuss these issues further in section 7.3 and 7.4.

2.4 What can cause an association?

Now that we understand what causality means, we can ask: What *could* cause the observed associations illustrated in Figure 1.1?

The first reason is that there really is no association at all. This could come about through random sampling variation or if the sample is constructed in a way that inadvertently conditions on a collider variable (see section 7.5). This is not likely to be an important explanation, although the specific point estimates are likely to be influenced somewhat.

Correlation does not imply causation directly, but if there really is a true association in the population, some form of causal process is implied. Let us narrow down to just one association in Figure 1.1, namely that between parental socioeconomic position and offspring mental health. What could give rise to an association here? There are three explanations (visualised in Figure 2.2): First, parental socioeconomic position could directly cause an increased risk of mental disorders in offspring (i.e., *direct causation,* or X → Y). For now, it

does not matter whether this is mediated or not as it would still be correct to call it a causal effect (see section 2.5). Second, mental disorders in offspring could cause differences in parental socioeconomic position (i.e., *reverse causation,* or X ← Y). Finally, the association could be *confounded* by other variables, such as shared genetic factors, which influence both parental socioeconomic position and offspring mental health (i.e., X ← U → Y). Note that confounding still implies a causal process, just not between the variables of interest, and therefore require similar care and rigour as when concluding direct causation.

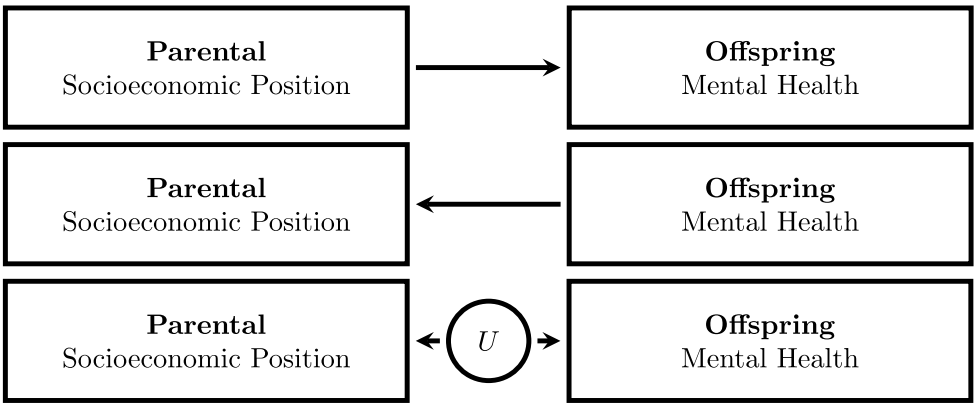

Figure 2.2: Possible causes of an association

Correlations could also arise through extrinsic processes, such as when students are sorted into classes based on performance or when prospective partners match based on similar traits, but those are not likely to explain within-individual correlations or intergenerational correlations. It will become important when attempting to understand assortative mating, though (see section 5.6.1).

Even though the list of causal processes that could give rise to an association between any two variables is short, the causal processes may be operating simultaneously, dynamically, and to varying degree on the six associations in Figure 1.1. This also applies to each separate indicator of socioeconomic position and mental health. These complexities make a comprehensive disentanglement of the associations between socioeconomic position and mental health within individuals and across generations an extremely challenging task. This task is beyond the scope of this thesis. I will therefore limit the scope to illuminate selected aspects of these associations, with varying degree of causal inference. More on that in chapter 3.

2.5 Mediation is causation

A special version of causation is *mediation*, where the causal effect of one variable on another variable is mediated – that is, it "goes through" – a third variable (i.e., X → Z → Y). For example, it could be that parental socioeconomic position causally influences offspring socioeconomic position, and offspring socioeconomic position influences the risk of offspring mental disorders. In this example, it would be correct to say that parental socioeconomic position causes an increased risk of offspring mental disorders, because a random change in the cause would bring about a change in the outcome. There is initially no substantive difference between a direct effect and a mediated effect.

This has three corollaries: First, it is possible to speak of causation without knowing the underlying mechanism, meaning we can claim that X causes Y without knowing how. Most causal claims are probably versions of X → ? → ? → ? → Y. Second, the question of how a causal effect is mediated only becomes relevant after the causal effect has already been established. The mechanism, while relevant for future research, is not relevant to the initial question of whether X causes Y, and the initial causal claim that X causes Y is agnostic to mechanism. Third, one should be careful adjusting for plausible mediators as this would adjust away part of the true causal effect (Rohrer, 2018). It is often unclear whether a variable is a confounder or a mediator (or both), but this distinction has important implications for how the result should be interpreted. One example, discussed in Paper 1, is whether poor early school performance (Z) is a confounder or mediator in the association between ADHD (X) and later school performance (Y). If it is the case that early school performance increases the risk of being diagnosed with ADHD (X ← Z → Y), then it acts as a confounder, and should be adjusted for. On the other hand, if ADHD also influences early school performance (X → Z → Y), then it acts as a mediator, and adjusting would remove part of the causal effect.

2.6 Social causation versus social selection

Is socioeconomic position a cause or an effect? These two fundamental hypotheses are referred to as social causation and social selection, respectively (Kröger et al., 2015). Here, we must contrast the subtle differences between within-individual correlations and intergenerational correlations. For within-individual correlations, social causation would be that an individual's *own* socioeconomic position caused differences in their mental health, whereas social selection would be either a causal effect of their mental health on their socioeconomic position or that there were third variables that caused both. Note that social selection includes both reverse causation and confounding. For intergenerational associations, social causation would be that their *parents'* socioeconomic position caused differences in their own mental health, whereas social selection would be that there were *shared* third variables – either genetic or environmental – that independently caused both the parent's and offspring's phenotype, or that the offspring's mental health influenced their parents' socioeconomic position. For intergenerational correlations, it would also be possible to talk about effects on offspring's own socioeconomic position, with similar possible explanations.

These subtle differences mean that intergenerational correlations and within-individual correlations could have different explanations. For example, it could be that parental socioeconomic position don't cause differences in mental health among their children (intergenerational social selection), but that the children's own socioeconomic position cause differences in their mental health (within-individual social causation). A crucial implication of this is that finding evidence of within-individual social causation cannot be taken as evidence for social causation across generations. Likewise, evidence of social selection across generations cannot be taken as evidence for social selection within individuals.

2.7 Matthew effects

Named after a biblical passage about how the spiritually rich get richer and the poor get poorer, *Matthew effects* describe situations of double (dis)advantage (Merton, 1968). These include feedback loops where current advantage influences future advantage, or situations where good (or bad) things tend to co-occur. Here, I use the term to describe situations where there are correlations between different causes. When causes are correlated, the differences caused by both causes will be more than the sum of their individual effects. (see also section 5.5.1).

One such process is assortative mating, which is the non-random matching of partners with respect to their traits. If one parent is, for example, highly educated, then the other parent is likely to be highly educated too (Torvik et al., 2022). To the extent that high parental education benefits children, assortative mating creates a Matthew effect whereby children who benefit from having one highly educated parent are likely to benefit from having two highly educated parents (and vice versa). This will occur regardless of whether the intergenerational association is due to social causation or social selection. Considering that partners tend to be similar when it comes to socioeconomic position and mental health (Horwitz et al., 2023; Nordsletten et al., 2016), this process is highly plausible. Assortative mating is the topic of Paper 3 and indirectly in Paper 2.

A correlation between causes can also arise if intergenerational social causation and social selection operate simultaneously. They are, after all, not mutually exclusive. If this is the case, then it is likely that children exposed to beneficial (or detrimental) causal effects tend to also be exposed to beneficial (or detrimental) confounding factors. For example, it could be that children benefitting directly from their parents (social causation) simultaneously benefit from inherited genetic variants that lead to traits that benefit them in the current society (i.e., social selection). Such gene-environment correlations cause Matthew effects because the differences caused by the two causal pathways will be more than the sum of their individual effects.

Assortative mating and gene-environment correlations could also be operating simultaneously, which would increase differences even further. Within individuals, the co-occurrence of social selection and social causation could form a feedback-loop, which would also lead to a form of Matthew effect.

2.8 Previous studies on causal effects between socioeconomic position and mental health

Causal inference is very difficult. Not in a way where a sufficiently skilled researcher could do it, but in a way that makes it near impossible simply because of all the obstacles that are being faced (Eronen & Bringmann, 2021; Rohrer, 2018). This is especially true for the issues raised in this thesis, where experimental designs are neither practical nor ethical. In the absence of good methods for inferring causality, many observational studies use theoretical justifications of varying soundness to infer causality. One often cited study, published in *Science*, purported to separate social causation and social selection by comparing rates of disorders in different ethnic groups, claiming that a consistently higher rate of mental disorders in disadvantaged ethnic groups across all socioeconomic strata would suggest social causation, whereas a concentration of disorders in the lower socioeconomic strata of advantaged groups would indicate selection (Dohrenwend et al., 1992). While the logic is not entirely unreasonable, the paper "appear to fall far short of the standards necessary for even cautious causal inference" (Goldman, 1994, p. 1255). Several other studies have attempted to tackle the causation-selection question with longitudinal designs, but with varying quality and mixed results (Lorant et al., 2007; Meng et al., 2020; Ritsher et al., 2001).

The evidence is also mixed among studies using more innovative designs. A regression discontinuity design on participants in the UK biobank found evidence for a causal effect of longer schooling on various health outcomes, but not mental health (Davies et al., 2018). Two studies comparing discordant identical twins found no evidence of causal associations (Fujiwara & Kawachi, 2009; Halpern-Manners et al., 2016). On the other hand, a recent Dutch study using sibling comparisons and mendelian randomization concluded that educational attainment appears to causally decrease the risk of several psychiatric disorders, but also that ADHD seems to causally affect educational attainment (Demange et al., 2023).

A systematic review of studies on the causation-selection issue for health in general found no preference for either hypothesis, but noted that more statistically rigorous studies tended to favour the social selection hypothesis (Kröger et al., 2015). A large meta-analysis of longitudinal associations between unemployment and mental health, on the other hand, concluded that there was evidence of both social causation (Job Loss → Distress) and social selection (Distress → Job Loss) (Paul & Moser, 2009). Finally, a recent meta-analysis concluded that income changes likely has a modest causal effect on mental health, but there were considerable study heterogeneity and the largest effects were observed in studies most susceptible to bias (Thomson et al., 2022). Overall, the results suggest that social causation may play a role, but that the alternative hypothesis, social selection, likely accounts for a large proportion of the associations.

The studies discussed so far has all concerned the within-individual correlation. What about the intergenerational correlation? Here, the evidence is also mixed. One of the more convincing studies used a natural experiment where a casino opened in an American Indian reservation which gave income supplements to the local population. Based on structured interviews, they found that children whose family moved out of poverty had significantly fewer symptoms of externalizing disorders, but not internalizing disorders (Costello et al., 2003). Using questionnaires in a follow-study up on the same cohort, they found positive changes in both behavioural and emotional problems (Akee et al., 2018).

A Norwegian study investigated the association between parental income and adolescent mental disorders in a subsample of adoptees. They found that the association was substantially smaller than in the overall population, but still statistically significant (Kinge et al., 2021). This would suggest that social selection plays a large role, although social causation also plays a part. Other studies with diverse methods also find evidence of non-zero social causation for ADHD, for example by comparing siblings (Larsson et al., 2014), comparing children of twins (Torvik et al., 2020), and comparing parental and offspring polygenic scores to the offspring phenotype (Eilertsen et al., 2022).

However, there are also studies failing to find evidence of intergenerational social causation, especially among adults. A Norwegian twin study on young adults found the association between educational attainment and mental disorders to be primarily caused by a genetic correlation, which would suggest limited influence of familial characteristics beyond genetics (Tambs et al., 2012). Most twin studies of mental disorders also find them to be highly heritable with no or limited familial environmental influences (Polderman et al., 2015). A Swedish register study exploiting longitudinal variation in income compared siblings and concluded that family income during childhood had no causal effect on adult mental health issues (Sariaslan et al., 2021). This last study has sparked fervent discussions about what sibling designs can and cannot tell us (Biele et al., 2022; Keyes & Susser, 2022; Ledberg et al., 2022; Rod et al., 2021; Sariaslan et al., 2022).

In short, the question of causality in the reproduction of social differences and mental health across generations remains open. Additionally, causal processes connecting mental health and socioeconomic position are likely to be culturally dependent, making generalizability to the Norwegian population uncertain. We are far from being able to conclude “no more research is needed”.

Chapter 3: Research Aims

As mentioned in section 2.4, a full disentanglement of the causal structure underlying the reproduction of mental health and social differences across generations would be an unrealistic aim of a single thesis. I will instead limit my task to illuminate selected "excerpts" from Figure 1.1. I will also limit the scope to illuminating these association as they appear in Norway.

3.1 Paper 1: ADHD and school performance

The first paper investigated school performance among adolescents with and without ADHD (Figure 3.1). Even though ADHD and school performance was known to be associated, the precise nature of this association across sex, parental education, and school subjects remained unclear. In paper 1, I attempt to remedy this with an accurate description of the ADHD deficit in school performance across these variables. A secondary aim was to investigate this association while adjusting for plausible confounders such as unobserved family characteristics and earlier school performance.

3.2 Paper 2: Parental income and mental disorders

The second paper investigated the association between parental income and mental disorders (Figure 3.2). The aim was to accurately describe how the association persists into adulthood, and to attempt to disentangle direct effects of parental income (social causation) from the confounding factor of shared genetic influences (social selection) using children of twins.

3.3 Paper 3: Assortative mating and genetic similarity in families

The third paper investigated assortative mating for numerous traits and its consequences for familial resemblance (Figure 3.3). As mentioned in section 2.7, assortative mating could increase the differences caused by intergenerational transmission regardless of whether it is social causation or social selection. The aim of this paper was therefore to clarify the theoretical consequences of assortative mating on resemblance within families and investigate which traits, such as socioeconomic position and mental health, show genetic evidence of assortative mating (via correlations between partner's polygenic scores). Another aim was to use genetic similarity in families to infer whether assortative mating have been stable for many generations, as this would decide whether assortative mating increases or maintains increased differences.

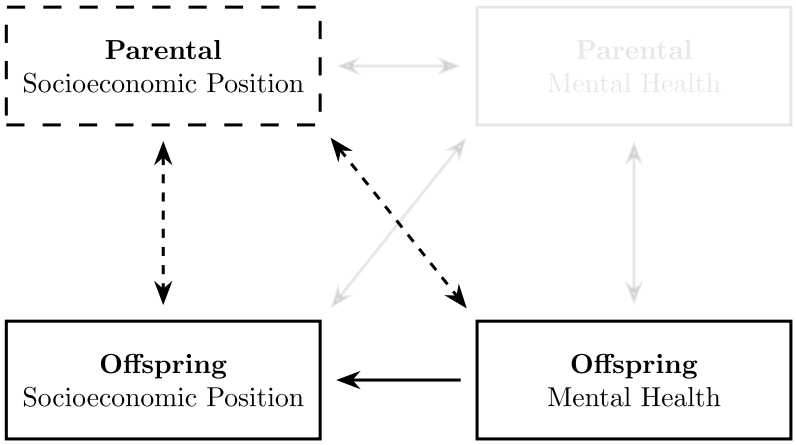

Figure 3.1: Paper 1 is about ADHD and school performance.

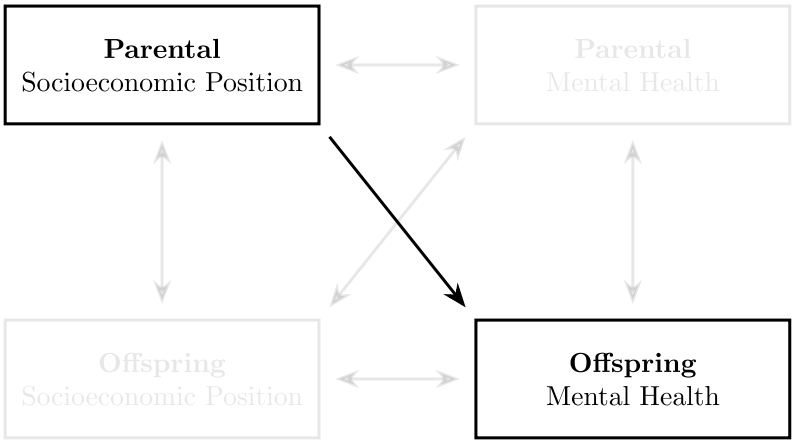

Figure 3.2: Paper 2 is about parental income and mental disorders in offspring.

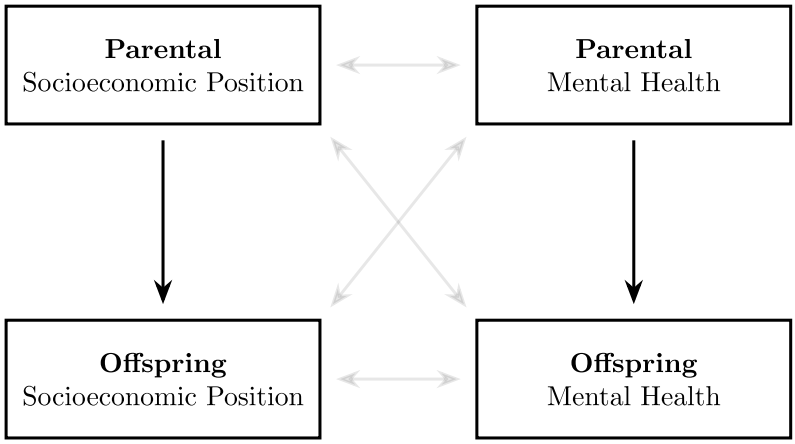

Figure 3.3: Paper 3 is about assortative mating's consequences for familial resemblance.

Chapter 4: Data and Materials

The three papers in this thesis use two data sources: The first two papers use data from Norwegian administrative registers and the final paper uses data from the Norwegian Mother, Father and Child Cohort Study (MoBa). The measures are described in more detail within the relevant papers. Here, I will briefly summarize the parts relevant for the overall thesis.

4.1 The Norwegian population register

The Norwegian national population register was started in 1967 and contains basic information such as births, deaths, and parentage on all Norwegian citizens and residents since then (some 8 million individuals). Because it also includes a unique ID-number for every individual, it forms the backbone of many other administrative registries, such as tax registries and health registries. This ID-number (or rather, a de-identified version of it) allowed me to accurately link information on the same individual from different registries. Because the register also contains information on who's whose parents, it is straightforward to link together siblings and other family members.

I had access to complete data up to and including 2018.

4.2 Socioeconomic indicators from Statistics Norway (SSB)

Socioeconomic indicators used in this thesis were provided by Statistics Norway (SSB), and include educational attainment, educational performance in primary education, and yearly taxable income.

The first paper used two of the indicators: educational performance during childhood and educational attainment as adults. Educational performance was assessed using grade point average (GPA) from the end of junior high school when children were approximately 16 years old, converted to z-scores to ease communicability for international readers. Parental educational attainment was assessed using the highest achieved education of either parent at time of graduation. It was recoded into four levels and treated as a categorical variable.

The second paper used yearly taxable income. Parental income was assessed from offspring age 10 to 18. As income varies by parental age and sex, not to mention from tax year to tax year, the income of either parent was ranked within the parent's sex and birth year, as well as within tax year. The yearly income ranks from offspring ages 10 to 18 was then averaged.

4.3 Health indicators from the Norwegian Control and Payment of Health Reimbursements Database (KUHR)

Paper 1 and Paper 2 use a health register called the KUHR-database. The KUHR-database is an administrative database set up to facilitate subsidies to primary care (e.g., general practitioners). Health services are heavily subsidized in Norway, but the health care providers still need to cover their expenses. Anytime someone uses primary care services, the service provider sends a bill to the Norwegian Directorate of Health, who in turn reimburses the provider according to fixed rates. These bills are indexed in the KUHR-database. Because both public and private service providers are covered by this scheme, cases are unlikely to go unreported. The database contains several pieces of information, including patient ID number, date, and *reason for encounter*. The *reason for encounter* is coded according to the International Classification of Primary Care, version 2

(ICPC-2, WONCA, 2005). The ICPC-2 consists of many chapters that in turn consist of different types of codes, including process codes, symptom codes, and diagnostic codes. In this thesis, the diagnostic codes from the psychological chapter (i.e., the "P"-chapter) were the most relevant (i.e., code P70 to P99). This includes codes such as P74 Anxiety Disorder, P76 Depressive Disorder, and P81 Hyperkinetic Disorder (i.e., ADHD). The first paper in this thesis primarily used P81, whereas the second paper used all the psychological diagnostic codes. See the supplementary figures in Paper 2 for prevalences.

The KUHR-database includes entries from 2006 and onwards, meaning I had access to 13 years of data from 2006 to 2018. In both papers, I coded diagnoses dichotomously, where individuals were coded as having the diagnosis if they had at least one entry with the relevant diagnostic code within a given time frame. In the first paper (Figure 4.1, left), the time frame was between age 10 and 16. In the second paper (Figure 4.1, right), the time frame was each calendar year (and later, for five-year intervals).

The second paper investigated mental health from age 10 to 35. Even though it would be preferable to follow the same individuals for 35 years, the multiple years of available health data allowed me to create something akin to an accelerated longitudinal design whereby each birth cohort was observed for up to 12 years starting in either 2006 or at age 10. This also maximised the sample size, which was needed for the children-of-twins models described later.

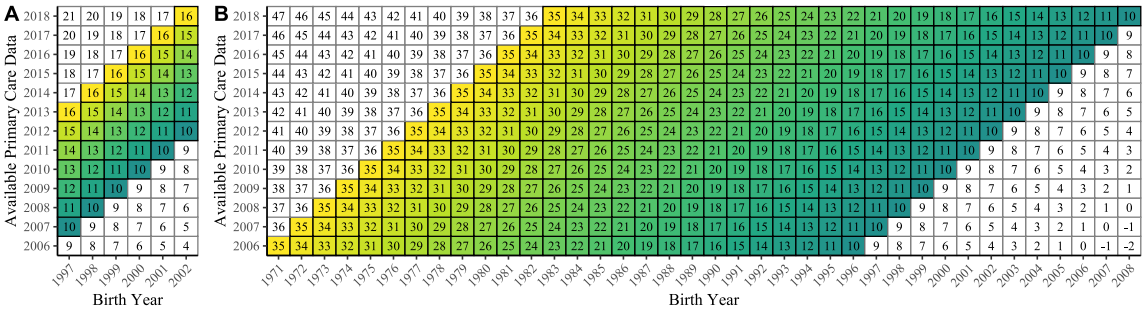

Figure 4.1: The subject's ages during the observation period.

4.4 Zygosity information from the Norwegian Twin Register (NTR)

The second paper used an extended children-of-twins model that exploits that monozygotic twins are genetically identical (described in section 5.5). Finding twins in the population register is straightforward (shared mother and same birth month), but the register does not contain information about whether the twins are monozygotic or dizygotic. To find out which pairs were monozygotic twin pairs, we linked the data to zygosity information obtained from the Norwegian Twin Registry (Nilsen et al., 2012).

The Norwegian Twin Registry is not really a register per se, but the result of a merging of three consent-based twin panels. The sample size is therefore somewhat limited compared to the total number of twins in Norway. Furthermore, the panels are limited by the birth years of the recruited cohorts, with no twins born between 1960 and 1967, as well as no twins born after 1992.

4.5 Genetic data from the Norwegian Mother, Father, and Child Cohort Study (MoBa)

The third paper used genetic data from MoBa, which is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). Pregnant women from all over Norway were invited to participate between 1999 and 2008. The women consented to participation in 41% of the pregnancies. The cohort includes approximately 114,500 children, 95,200 mothers and 75,200 fathers. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. For less technical information about the cohort, see the cohort website: fhi.no/en/studies/moba/.

Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth, which allowed most of the sample to be genotyped (Corfield et al., 2022). This allows figuring out who is related to whom, as well as the calculation of polygenic indices.

4.5.1 What are polygenic indices?

Polygenic indices (aka., polygenic risk score, aka., polygenic score) measure individuals' genetic propensity for a given phenotype. They are constructed using summary statistics from published Genome-Wide Association Studies (GWAS), which attempt to estimate how variation at different loci (meaning positions within the genome) relate to phenotypic differences (Abdellaoui & Verweij, 2021; Abdellaoui et al., 2023; Uffelmann et al., 2021). Individuals have 0, 1 or 2 copies of a particular genetic variant at any given locus. By comparing the phenotypes – for example, height – of individuals with 0, 1 or 2 copies, researchers may find that individuals tend to be 0.5 mm taller for each additional copy they possess. A GWAS repeats this process for hundreds of thousands of loci, sometimes with a sample size in the millions. Once this is done, the resulting associations can be used to construct a measure of genetic propensity in a new sample, such as MoBa, by measuring the same loci, weighing them by their estimated association with the phenotype, and summing across the genome. This measure is called a polygenic index. Polygenic indices are crude and noisy measures – especially if the GWAS is small or the phenotype poorly defined – but they nevertheless give an indication of genetic propensity. Technical details about how the polygenic indices used in paper 3 were constructed are available in that paper's methods section.

Chapter 5: Methodology and Statistical Approaches

All three papers have large sections devoted to describing the associations (mean differences, prevalences, and correlations, respectively). These descriptions are complemented with different statistical approaches of varying complexity and with varying degrees of causal inference. The methods are thoroughly described within the papers themselves, and the technical details do not bear repeating here. In this chapter, I will (1) briefly discuss challenges related to causal inference in observational designs, (2) provide a thorough explanation of path analysis, and (3) use path analysis to describe the logic behind the methods applied in the three papers and to discuss complications, solutions, and limitations with these methods. Specifically, for the first paper, I discuss how regular statistical adjustments and sibling designs can and can't inform us about causality. For the second paper, I explain how twins and children of twins can inform us about causal pathways linking parental and offspring phenotypes. For the third paper, I explain how assortative mating induces correlations among causes and how to apply path analysis correctly to account for this.

I will assume the reader is familiar with elementary concepts commonly introduced in first-year methods courses, such as covariance and what it means to control for something. I will also temporarily set aside concerns about sampling variation, ascertainment bias, and similar sources of spurious correlations that might arise in a specific sample while not being true for the overall population (I discuss this in section 7.5). In this chapter, I will take for granted that associations are true for the population.

5.1 Causality in observational designs

The research questions discussed in this thesis do not lend themselves to experimental designs, as that would be both impractical and unethical. We must therefore rely on observational designs. It is often said that causality can only be inferred in experiments, but this is incorrect. Regardless of approach, causal inference always relies on underlying assumptions: There is no such thing as assumption-free causal inferences (Rohrer, 2018). If the assumptions are well founded, then one can be reasonably confident in the causal conclusion regardless of whether the study is experimental or observational.

Experimental designs are called the gold standard of causal inference, not because it has magical properties, but because researchers can make well founded assumptions. This is possible because researchers have complete control over at least one source of variation in the study and can take measures such as randomization to ensure this variation is entirely independent from other sources of variation. Given this independence, there are no alternative sources of covariance except for direct causation, thus allowing a causal conclusion. However, not even experiments are bulletproof. They must still make additional assumptions about factors such as representativeness, compliance, and ecological validity, which may or may not be well-founded. The distinction from observational designs is therefore not as stark as it appears: It is assumptions all the way down.

Causal inference in observational designs rest on the same fundamental principle as in experimental designs: Find and employ methods to account for alternative causes of covariance (i.e., confounding factors or reverse causation), for example by exploiting natural sources of random variation or by adjusting for covariates. If this is done in a way that only makes well-founded assumptions, then a causal conclusion is warranted. It may be more difficult to do in an observational design, especially in social science (Eronen & Bringmann, 2021), but it is not impossible. The important thing is to be explicit about the assumptions so that the reader can judge

the conclusions for themselves (Grosz et al., 2020). It should never be necessary to simply trust the authors of a study. Large parts of this thesis are therefore devoted to clarifying explicit and implicit assumptions. To do that, the first thing to do is to get an overview of what different worlds could look like, and what the various implications for observed associations should be. That is, we need to know the consequences of different assumptions. Enter: path analysis.

5.2 Introduction to path analysis and path tracing rules

In Chapter 2, I briefly introduced path diagrams to visualise potential causal relationships. While useful for such simple purposes, the true power of path diagrams comes from the ability to derive equations that describe the expected covariance between any two variables, thus providing a deeper understanding of what various causal relationships imply (Wright, 1921). As this will greatly help illustrate the strengths and weaknesses of various ways to do causal inference, a thorough explanation of path analysis is warranted. It is common to confuse path analysis with structural equation models (SEMs), but they are not the same thing: Path analyses are purely theoretical, whereas SEMs are applied to data. I will explain SEMs in more detail in section 5.5.3 below.

As a reminder, path diagrams are drawn to reflect the assumed causal relationships between variables of interest and are used to understand the implications of various hypotheses. They consist of nodes (representing variables) and edges with path coefficients (representing associations between variables). Single-headed arrows represent causal effects and double-headed arrows represent exogenous sources of variance (if it connects a variable with itself) or covariance (if it connects two variables). By convention, it is common to illustrate observed variables using rectangles and unobserved variables using circles, but unlike in SEMs, this is just for aesthetic purposes. Assuming the associations are linear, the expected covariance between any two variables can be derived by applying path tracing rules to identify all valid chains of path coefficients. The covariance attributable to a single chain is the product of all path coefficients in the chain, and the total covariance is the sum of all valid chains connecting the two variables. Variance can be thought of as a variable's covariance with itself and can be derived by similar rules (i.e., sum of all valid chains that lead back to itself).

For a chain to be valid, it *must* start by traveling against the direction of the arrows (←), and it *must* include exactly one double headed arrow (↔). Once a double-headed arrow has been traversed, the direction changes so that – if one wishes to continue tracing – one must trace with the direction of arrows (→). (These rules imply that a chain consisting of a double-headed arrow only is a valid chain). A double-headed arrow must be included because it provides the scaling for the remaining path coefficients in the chain. One way to think of it is that the causal effect of a variable is weighted by its variance (ref. section 2.3). There is no limit to the number of arrows that can be included on either side of the double headed arrow as long as they do not change direction. That is, all arrows "before" the double-headed arrow must go backwards against the direction of arrows and all arrows "after" the double-headed arrow must go forwards with the direction of arrows.

Figure 5.1 (left) shows an example of a path diagram where X has a causal effect with magnitude b on Y. Applying path tracing rules, we find the following: $Cov(X,Y) = \sigma_x^2 b$, $Var(X) = \sigma_x^2$, and $Var(Y) = \sigma_x^2 b^2 + \sigma_\epsilon^2$. If we prefer thinking about correlations, we can divide the covariance by the geometric mean of the two variances. Alternatively, we can redraw the path diagram to have unit variances (i.e., all variables have a variance equal to 1), which means the covariances can be interpreted as correlations. In these situations, it is

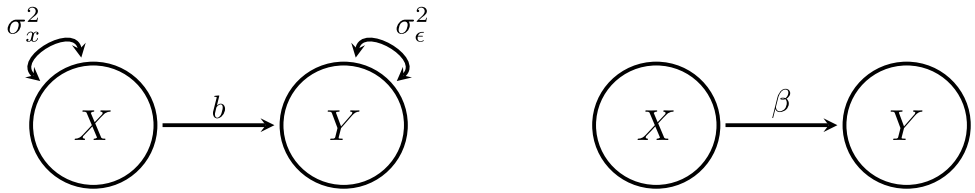

Figure 5.1: Unstandardized and standardized path diagrams

common to not draw double-headed arrows to denote sources of variance, and instead exploit a shortcut enabled by standardized variables (Figure 5.1, right).

The shortcut relies on treating variables as double-headed arrows with a coefficient of 1. This makes it possible to change direction at a variable (i.e., trace backwards to that variable, and continue tracing forwards from that variable) as long as there is still only one change of direction in a given chain. By similar logic, it is also possible to begin a chain by tracing forwards with the arrows (which is equivalent to changing direction immediately). This shortcut is possible because changing direction at a variable would normally involve tracing all the valid chains from that variable back to itself, and for unit variance variables, these chains will always sum to 1. In other words, tracing all those chains will just be a convoluted way of multiplying the rest of the chain by 1. Needless to say, one cannot both change direction at a variable *and* include the chains that lead back to that variable, which is why path tracing with standardized variables includes the added rule that one can only trace through a given variable once in each chain. Applying these rules to Figure 5.1 (right) gives us $Corr(X, Y) = \beta$.

The original description of path tracing rules by Sewall Wright (1921) was for this special case of standardized variables, and most later descriptions consider it valid to change direction at a variable. It is important to note, however, that these rules are just taking advantage of a shortcut that becomes possible in the special case of standardized variables and are therefore only applicable for these scenarios. The models I've drawn in this thesis mostly use standardized variables, but see the supplementary information to paper 3 for examples of unstandardized path diagrams.

For assortative mating, there are special path tracing rules described in section 5.6.3 on page 38. For another description of path tracing rules, see Balbona et al., (2021).

5.3 Estimates and estimands

In this chapter, it can be useful to keep in mind the difference between the causal effect we want to estimate – called the *estimand* – from the *estimate* itself. The difficulties of causal inference in observational designs arises from the challenges in developing a procedure (an *estimator*) that provides an unbiased and reliable estimate of the estimand (Lundberg et al., 2021). When we discuss bias and methodological challenges, we're specifically referring to the discrepancies between the estimate and the estimand. Conversely, when we interpret what true causal effects mean, we are focusing on the estimand.

5.4 Paper 1: ADHD and school performance

On reading this paper for the first time, it might not appear that it is doing causal inference. This is deliberate: I don't deem the underlying assumptions to be strong enough, so I downplayed the causal interpretation and highlighted the descriptive aspects instead. Here, I will explain the causal reasoning behind the analytical choices and explain what assumptions must be made to interpret it as causal. The question is whether ADHD affects school performance.

A note on language: In the following paragraphs, I will often use the term ADHD to describe the *variable* ADHD, not the condition. For practical reasons, I will assume that it is normally distributed (which is a reasonable assumption, as discussed in section 1.3), and, although the specific equations might change when treating ADHD as a dichotomous diagnosis, the overall consequences should be the same. In the analyses done in the paper, though, it is treated as dichotomous.

5.4.1 The problem

There is a strong association between ADHD and school performance, as documented in the paper. One explanation could be that ADHD causes children to perform worse in school (*direct causation)*. Another explanation could be that both ADHD and school performance are partly caused by the same things (*confounders*). Finally, children could be diagnosed with ADHD because they perform worse in school (*reverse causation*). All of these processes could be occurring simultaneously. How can we disentangle the estimand from these alternative explanations?

5.4.2 Accounting for reverse causation

Paper 1 uses a prospective design, where ADHD was measured in the years before school performance. Because causality imply a direction in time (the cause must come before the effect), it may be tempting to argue that longitudinal designs automatically account for reverse causation. However, this would be a mistake. Longitudinal designs do not offer a magic bullet to the problem of reverse causation, but it does allow us to reframe the problem: Reverse causation can be seen as confounding in a different guise, where school performance at some earlier stage could have caused ADHD. In other words, by using a longitudinal design, we have reduced the list of three explanations down to just two: direct causation and confounding.

5.4.3 Accounting for confounding factors

ADHD and school performance could be associated because they are caused by overlapping sets of variables. For example, they could both be caused by earlier school performance (as discussed in the previous section), or by other individual characteristics, such as sex or maturity. They could also both be caused by family characteristics, such as rearing environment or parental socioeconomic position. Note that the last example would imply that the within-individual correlation was confounded by intergenerational social causation. Figure 5.2 shows a hypothesised causal structure where ADHD has a causal effect on school performance (GPA), denoted a. This would be the estimand. At the same time, there are two sets of third variables that also has causal effects on both ADHD and GPA, namely individual-specific factors (Z) and familial factors (U). If we apply path tracing rules to the correlation between ADHD and GPA, we find that it should be:

$$Corr(ADHD, GPA) = a + bc + de \tag{5.1}$$

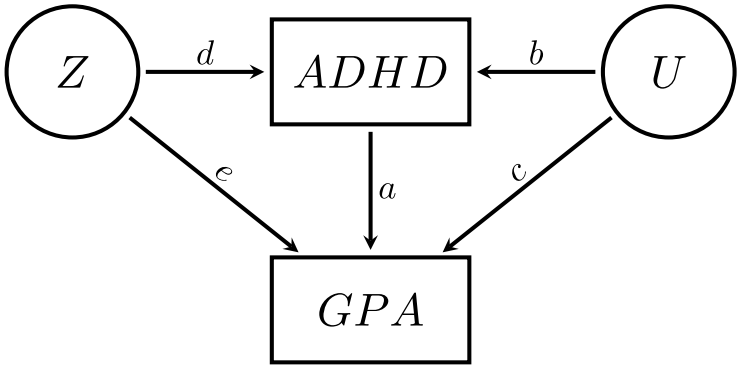

Figure 5.2: The causal effect of ADHD on GPA could be confounded

That is, the correlation should be the sum of (1) the causal effect of ADHD on GPA, (2) the product of the familial confounders' causal effects on ADHD and GPA, and (3) the product of the individual confounders' causal effects on ADHD and GPA. If we are interested in the causal effect of ADHD on GPA, we cannot just estimate the raw association because we would not know how much of it was due to a and how much was due to $bc + de$. This is, mathematically speaking, what confounded means.

Accounting for confounders is in theory straightforward. One simply adjusts for them, for example by including measures of U and Z as covariates in a multiple regression (which would be equivalent to estimating a, c, and e simultaneously, which closes the door for bc and de). In practice, however, it is more complicated. First and foremost, there is always a strong assumption that the path diagram contains all relevant variables and paths (Rohrer, 2018). If there exist confounders that aren't included or causal pathways not drawn, then the inferences may be invalid. Furthermore, adjusting for some confounders can inadvertently adjust for other undrawn variables that one shouldn't adjust for, such as colliders and mediators. For example, it could be that ADHD caused early school performance rather than the other way around. If this is the case, adjusting for it would remove part of the true causal effect of ADHD on later school performance. Drawing the path diagram correctly is one of the major challenges in doing causal inference with observational data because it involves assuming what the causal structure of the world is, and lack of knowledge about the causal structure of the world is precisely what motivates the research in the first place.

Assuming the path diagram is correctly drawn, though, it is straightforward figuring out what adjustments are needed to control for all relevant confounders while avoiding mediators and colliders (Pearl & Mackenzie, 2018). The next problem is that the required covariates may not be available. That is, there could be *unobserved* confounders. Even if they are available in the data, they could have measurement error or otherwise be imperfect proxies for what we are trying to adjust for (Westfall & Yarkoni, 2016). That is, there could be *residual* confounding. (You can think of residual confounding as resulting from partly unobserved confounders).

Figure 5.3 depicts a hypothesised causal structure where we assume that the only thing confounding the association between ADHD and GPA is early school performance (Z) and parental socioeconomic position (U). We have not measured these directly but have instead access to proxy variables such as test scores from fifth grade and parental educational attainment (EA). When we are including these as covariates in a regression

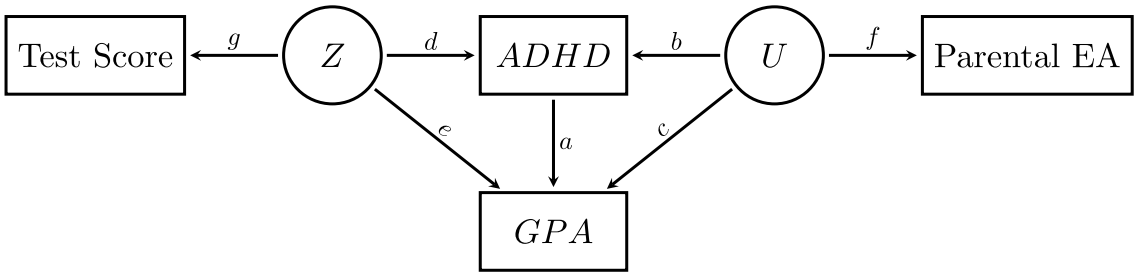

Figure 5.3: Confounders are measured by proxy variables

model to control for the confounders, we are implicitly assuming that these are perfectly correlated with the variables we are trying to adjust for. To the extent this is not the case, then adjusting for those variables will fail to adequately account for the confounding factors. We can see this if we derive the partial covariance between ADHD and GPA in Figure 5.3 conditional on test score and parental educational attainment:

$$Cov(ADHD, GPA \mid Test\ Score, Parental\ EA) = a + (bc - f^2bc) + (de - g^2de) \quad (5.2)$$

Stated plainly, unless both g and f are 1, the partial covariance could still be confounded by these other pathways.

5.4.4 Accounting for unobserved confounders: The sibling design

Unobserved or residual confounders are two of the largest obstacles to causal inference in observational designs. We therefore need a way to completely cut off the confounding pathways without observing the confounders. This can involve exploiting sources of variation that should be independent of these pathways. In the case of familial confounding factors, one such possibility is sibling designs (aka. sibling-fixed effects, aka. sibling comparisons). Here, the idea is that familial confounding factors should influence both siblings equally, while the extent to which siblings differ should be random with respect to these factors. Figure 5.4 illustrates this idea by splitting ADHD into two components: The familial mean, denoted $\overline{X_f}$, and an individual's deviation from that mean, denoted $X_i - \overline{X_f}$. To keep all variables at unit variances, they have each been weighted by the between- (σ_b) and within-family (σ_w) standard deviations, respectively. Because there are no valid chains between $X_i - \overline{X_f}$ and Y that goes through U, we have been able to remove unobserved familial confounding factors without needing to know what those factors are.

Despite being a powerful method, sibling designs have some important limitations. Some of these will become immediately apparent if we write out the correlation between $X_i - \overline{X_f}$ and Y using path analysis:

$$Corr\left(X_i - \overline{X_f}, \mathrm{Y}\right) = \sigma_w a + de \quad (5.3)$$

Obviously, a sibling-fixed effect could still be confounded by individual-specific confounding factors (Z), as indicated by the chain de. This chain will also become a relatively larger part of $Corr\left(X_i - \overline{X_f}, Y\right)$ than $Corr(X, Y)$, which can complicate the interpretation. Individual-specific confounding factors can be conditioned on if they are observed, but it would still be limited by residual confounding as discussed above. I adjusted for early school performance in the sibling model in the paper, which should give our best guess of what the causal effect of ADHD on school performance is, but it is far from perfect.

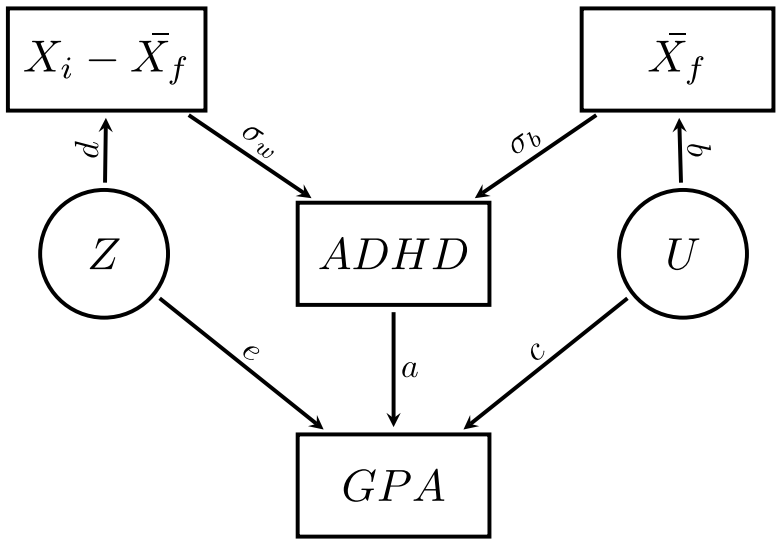

Figure 5.4: Path diagram illustrating the sibling design.

Another problem is that Figure 5.4 could be missing important causal pathways. As discussed above, one of the most difficult problems in using path diagrams is drawing them in a way that reflects reality. The model in Figure 5.4 assumes that the effects of both the sibling mean, $\overline{X_f}$, and the deviation from the sibling mean, $X_i - \overline{X_f}$, are fully mediated by measured $ADHD$ and therefore represent the same causal mechanism. However, it is possible that the aspect captured by the deviation from the sibling mean differs from what is captured by the sibling mean itself, and these differences might exert different causal effects on Y (this would be equivalent to drawing direct arrows from $X_i - \overline{X_f}$ and $\overline{X_f}$ to Y). For example, the deviation from the sibling mean could largely reflect measurement error with no causal effects. The incommensurability of the familial mean and individual deviation is a common critique of sibling designs (Rod et al., 2021). Finally, a third problem could be inadvertent selection bias as such analyses must always condition on multiple offspring and on siblings discordant for the exposure (Biele et al., 2022; Keyes & Susser, 2022). Overall, sibling designs are powerful ways to adjust for unobserved confounders but have their limitations.

In this case, I am not too concerned about the potentially different effects of sibling mean and individual deviations, nor about selection bias. That is, I would consider them well-founded assumptions that would warrant a causal conclusion. However, residual confounding caused by an imperfect measure of early school performance is highly likely, and it could also be the case that early school performance is a mediator that shouldn't be controlled for. These two concerns make a causal conclusion unwarranted, which is why I downplayed this interpretation in the paper.

The limitations of sibling designs render them somewhat unsatisfactory. A key issue is that, while the sibling design does exclude intergenerational social causation for the *remaining* associations, it doesn't quantify the degree and nature of confounding. In contrast, the next paper uses an intergenerational biometric model that allows explicit estimation of intergenerational genetic and environmental influences.

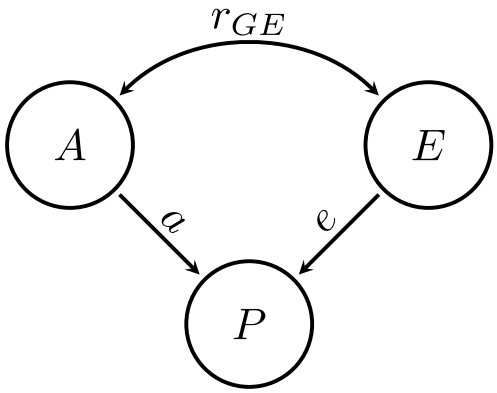

Figure 5.5: A simple model of phenotypic differences

5.5 Paper 2: Parental income and mental disorders

Why is it that parents with lower income have offspring with increased risk of mental disorders? The first part of the paper provides detailed descriptions of this phenomenon by calculating age-by-age prevalences across sex and parental income quartiles. The second part of this paper attempts to explain why this association exist: social causation or social selection. To do this, I have used a variant of the children-of-twins model (Mcadams et al., 2018). As before, the technical details are described in the paper itself. Here I will provide a more thorough explanation of the logic behind this type of analysis.

5.5.1 Introduction to quantitative genetics and twin models

To better understand the model used in Paper 2, it is worth taking a slight detour to introduce key concepts within quantitative genetics and twin models (Knopik et al., 2017). Figure 5.5 illustrates a simple model for understanding causes of individual differences. Here, differences in a phenotype (P) are thought to be caused by additive genetic factors (A) and environmental factors (E). Other genetic factors, such as dominant genetic factors, do not appear to play an important role in complex traits variation, so I have left them out (Pazokitoroudi et al., 2021). Using path tracing, we can describe the phenotypic variance as the sum of genetic causes, environmental causes, and the degree to which these causes tend to co-occur:

$$Var(P) = 1 = a^2 + e^2 + 2aer_{GE} \tag{5.4}$$

where a^2 is the variance attributable to additive genetic differences (a.k.a., the *heritability*), e^2 is the variance attributable to environmental differences, and $2aer_{GE}$ is the variance attributable to the correlation between genetic and environmental differences (see section 2.7 on Matthew effects). The heritability is often denoted h^2 (or H^2 if it includes non-additive genetic factors), and specifically refers to cases where a^2 is standardized (i.e., $h^2 = \frac{a^2}{Var(P)}$). Because we are assuming unit variances, this distinction is not important here and I will use h^2 and a^2 interchangeably.

Note that the model in Figure 5.5 is completely agnostic about what mediates these effects, or what the specific genetic and environmental factors are (see section 7.3 for a discussion about how to interpret heritability). For now, we do not need to worry about that. Note also that we are here only concerned about population average effects. While it could be that environmental factors, such as traumatic events, have made a massive difference

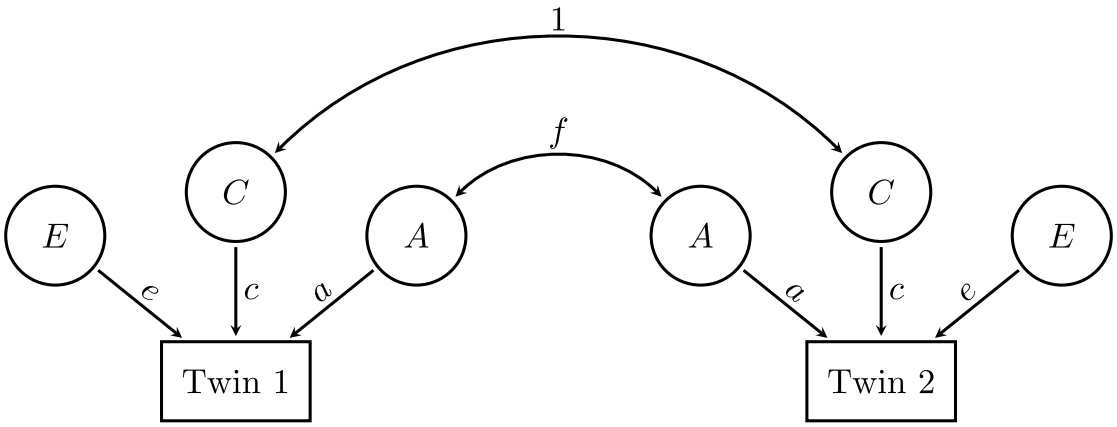

Figure 5.6: The ACE model.
The parameter f denotes the genotypic correlation between twins.

to a few people, it may not affect the variance in the population that much. This nuance is missed in this way of thinking (see also section 7.4).

The question is whether there is a way to estimate the parameters in the model. One way could be to measure genetic and environmental factors and include them in a regression, but this is unlikely to succeed. Polygenic indices, for example, only capture a fraction of the likely genetic effect (Young, 2019). We therefore want to find a way to estimate the parameters using phenotypic observations alone. A good place to start is genetically related individuals. If individuals who are more genetically similar are more phenotypically similar, then this could indicate that genetic factors make a difference. On the other hand, genetically similar people also tend to be exposed to similar environments, meaning related individuals could be similar for both environmental and genetic reasons.

5.5.2 The classic twin design: The ACE model

The classic twin design manages to overcome this by making a few simple assumptions (Knopik et al., 2017). First and foremost, it exploits the fact that twins come in two forms: monozygotic (i.e., genetically identical) and dizygotic (i.e., like regular full siblings). If one is willing to assume that exposure to environmental causes is equally correlated among monozygotic twins as dizygotic twins, then any difference in correlation must be attributable to increased genetic similarity. This is called the *equal environments assumption* (Knopik et al., 2017). If one is further willing to assume that there are no gene-environment correlations ($r_{GE} = 0$), then it is possible to estimate the relative contribution of genetic, shared environmental, and unique environmental factors on phenotypic differences.

Figure 5.7 illustrates the logic by showing how genetic and environmental factors correlate between twins. The environmental factor is split into that shared by twins (C) and that unique to each twin (E), and f represents the correlation between the twins' additive genetic factors (A). The three factors give the model its name: the ACE model. Applying path tracing rules to the ACE model, we find that the phenotypic correlation between twins can be described as:

$$Corr(Twin\ 1, Twin\ 2) = fa^2 + c^2 \tag{5.5}$$

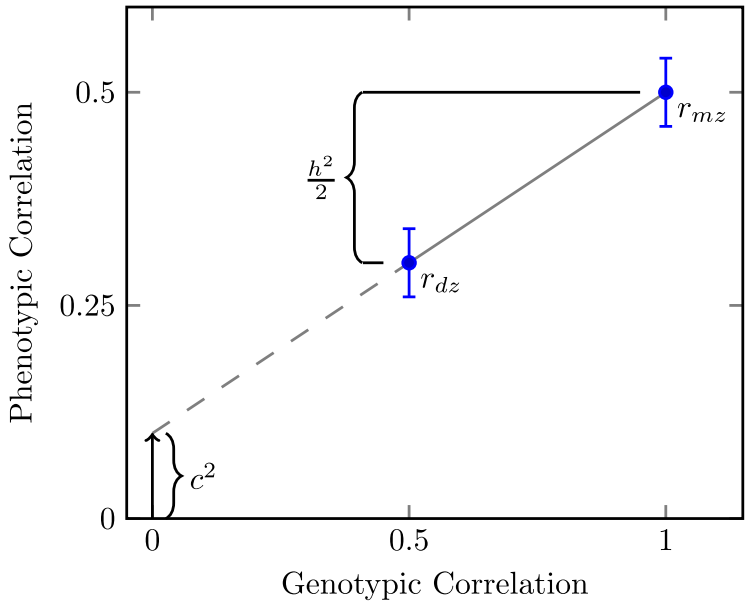

Figure 5.7: The logic of the classic twin design.
Assuming equally correlated environments, then heritability is the slope of genotypic to phenotypic similarity. If the genotypic correlation between dizygotic twins equals 0.5 (meaning random mating), then the difference between r_{mz} and r_{dz} is half the heritability.

Crucially, f is known for monozygotic (*mz*) and dizygotic twins (*dz*): Their genotypic correlation should be 1 and .50, respectively, assuming negligible de-novo mutations and assortative mating (but see Paper 3). This means that $r_{mz} = a^2 + c^2$ and $r_{dz} = \frac{a^2}{2} + c^2$. From this, it follows that the difference in correlation between monozygotic and dizygotic twins should reflect half the effect of genetic factors. The influence of genetic factors must therefore be twice this difference, and shared environmental factors must be whatever is left (see Figure 5.7). This is the logic that underlies Falconer's well-known equations which allow back-of-the-envelope calculations of heritability (h^2), shared environmental effects (c^2), and unique environmental effects (e^2):

$$h^2 = 2(r_{mz} - r_{dz}) \quad (5.6a)$$
$$c^2 = 2r_{dz} - r_{mz} \quad (5.6b)$$
$$e^2 = 1 - r_{mz} \quad (5.6c)$$

5.5.3 Structural equation models (SEMs)

Falconer's equations have been used extensively in twin research, but in the last few decades they have been superseded by SEMs that estimate the ACE model (Polderman et al., 2015). SEMs exploit a feature of a subset of path models, namely that it is possible to solve for all parameters in the model by comparing the observed covariances between the variables. (For some of these models, such as the ACE model, it is not even necessary to observe all the hypothesised variables, thus giving us the distinction between observed and latent variables). In short, SEMs can be applied to path models where all parameters are identified.

Before a SEM can be estimated, the covariance matrix between the observed variables must be defined in terms of equations consisting of the parameters in the model. This is done using the path tracing rules described earlier. For simple models, the computer software can do this automatically, but for more complicated models (such as the children-of-twins model), this must be done manually. One then applies a fit function – usually

maximum likelihood – to find values for the parameters that, when entered into these equations, produce an implied covariance matrix that matches the one we observe between the variables as closely as possible. If the implied covariance matrix matches the observed covariance matrix, then the model is said to have good fit. I used OpenMx (Neale et al., 2016) in R (R Core Team, 2022) to estimate the models used in paper 2.

There are multiple advantages of using SEMs rather than Falconer's equations. First, because SEMs are using maximum likelihood estimation, routine statistical procedures such as calculating confidence intervals, handling missing data, and testing for significance become easier. Second, the assumptions underlying the ACE model are explicit in the path diagram, such as equally correlated environments and no gene-environment correlation. A person who is unfamiliar with the classical twin model but familiar with path analysis should be able to deduce the assumptions I mentioned before using Figure 5.6 alone. Third, and most importantly for Paper 2, they are easily extendable. That is, one can extend the ACE model with additional observed variables to account for some of the limitations or answer different questions. There are numerous possible extensions. In Paper 2, I extended the model by including partners and children, which allows relaxing some of the assumptions while modelling intergenerational transmission.

5.5.4 Extending the ACE model

Extending the ACE model works because increased genetic similarity between monozygotic twins also affects the similarity between other family members. For example, most children are half as related to their uncle or aunt as they are to their parents. Children of monozygotic twins, on the other hand, are equally related to their uncle or aunt as to their own parents. If we include the twin's children in the ACE model, we can use this to decompose the parent-offspring correlation into genetic and environmental pathways. Furthermore, if we include the other parents of these children (i.e., the co-parents), then it is possible to account for assortative mating. Before I explain the details of this model, it can be worth taking a step back and ask: What are the possible causes of a parent-offspring correlation?

5.5.5 Visualising explanations for the parent-offspring correlation

A good place to start is to draw a path diagram that captures the different causal processes that could lead to an intergenerational association. Figure 5.8 visualises some of these possible explanations, with different colours for the different causal pathways. Just as in the ACE model, the parental phenotypes are imagined to be the weighted sum of genetic factors (A_1), shared environmental factors (C_1), and unique environmental factors (E_1). The offspring phenotype is similar, but here, the genetic and familial environmental factors are split into those associated with the parental phenotype (A_1' and F, respectively) and those unique to the offspring phenotype (A_2 and C_2, respectively). Because the latter do not matter for the parent-offspring correlation, they are greyed out.

The most intuitive hypothesis – the social causation hypothesis – would be that parental income directly causes an increased risk of mental disorders (direct phenotypic transmission, indicated in red). An alternative explanation is that there could be a correlation between the set of genes that causes variation in income and the set of genes that causes variation in mental disorders. Because offspring inherit their genes from their parents, an intergenerational association would emerge (passive genetic transmission, blue). By the same logic, if environmental factors that made a difference to parental income also make a difference for mental disorders among offspring, then this would also lead to an intergenerational association (passive environmental

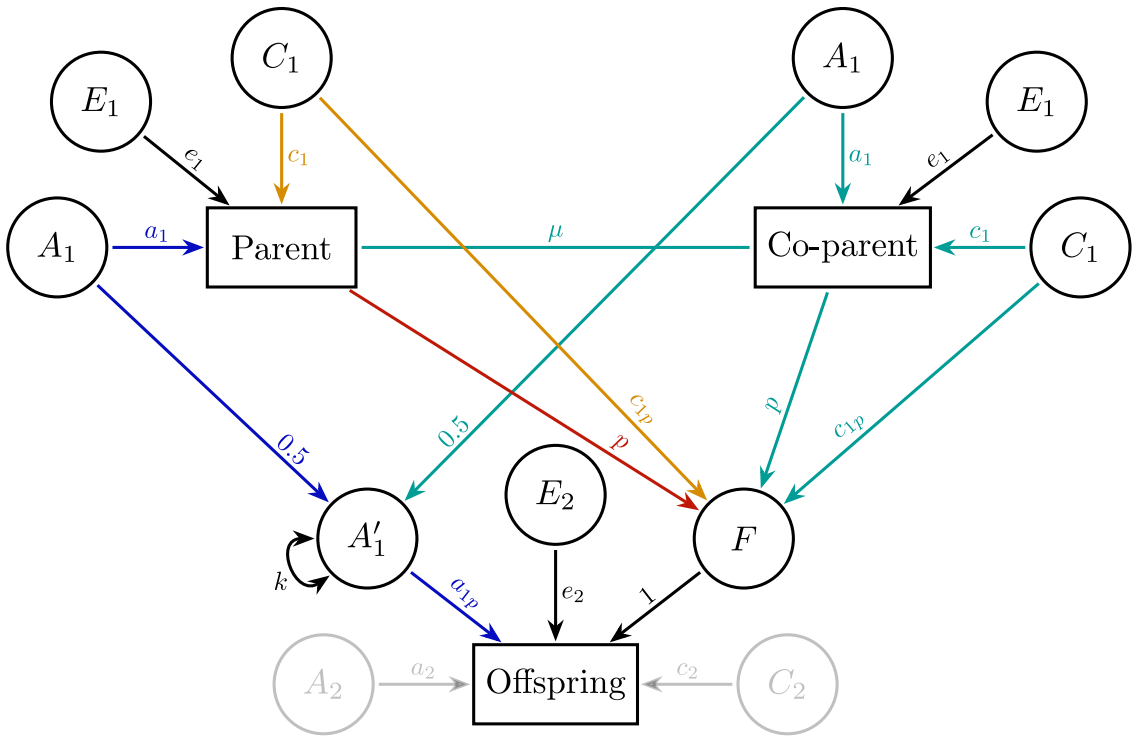

Figure 5.8: Different causal processes that could lead to a parent-offspring correlation.
All variables have unit variances except F, whose variance depends on the coefficients of the incoming paths (hence the unit effect size for outgoing paths instead).

transmission, orange). Finally, if parents resemble each other due to assortative mating, then parents may correlate with their offspring because their partner (i.e., the co-parent) is correlated with their offspring through the aforementioned pathways (teal). In summary, Figure 5.8 visualises four causal pathways that could result in a correlation between parents and offspring. Using path tracing, we can represent the correlation between a parent and their offspring by an equation consisting of the four components discussed in the previous paragraph:

$$Corr(Parent, Offspring) = p + \frac{a_1 a_{1p}}{2} + c_1 c_{1p} + \mu\left(p + \frac{a_1 a_{1p}}{2} + c_1 c_{1p}\right) \quad (5.7)$$

While it's plausible that additional causal processes could be influencing both the parent-offspring and parent-co-parent correlations, there comes a point where we must limit the scope of the investigation. This is not because we deny the existence of other potential processes (e.g., reverse causation), but because we must accept that it is impossible to estimate all conceivable causal processes in one model. Remember, there are assumptions all the way down. If we are satisfied that the model captures likely causes of the correlations (or deem the biases that will arise if this is not the case as acceptable), then the next step is to find a way to estimate these parameters.

5.5.6 The extended children-of-twins-and-siblings model

When the ACE model is extended with partners and children (as in Figure 5.9), it becomes able to identify the parameters in Figure 5.8. Even though Figure 5.9 may look a bit complicated, the only difference between it

and Figure 5.8 is that there are two nuclear families instead of one, each with two children instead of one. If you use path tracing to find the parent-offspring correlation, it will equal equation 5.7.

Although every covariance is used when the parameters are estimated, the key contrast is between the parent-offspring correlation and the avuncular correlation. If we assume a scenario with no assortative mating where the parent-offspring correlation was solely due to genetic similarity, then we would expect the parent-offspring correlation to equal the avuncular correlation in monozygotic twin families, and be exactly twice the avuncular correlation in dizygotic twin families. On the other hand, if parents had a causal effect on their offspring, then we would expect the parent-offspring correlation to be higher than the avuncular correlation in monozygotic twin families, and more than twice the avuncular correlation in dizygotic twin families.

While this verbal description should suffice, I think it will be beneficial to derive the avuncular correlation in Figure 5.9 so that we could compare it to equation 5.7. That way, we could see mathematically what I described verbally above. To simplify the equation a bit, let us denote δ as the phenotypic correlation between the twins (equation 5.5):

$$Corr(Uncle/Aunt, Offspring) = \delta p + \frac{f a_1 a_{1p}}{2} + c_1 c_{1p} + \delta\mu\left(p + \frac{a_1 a_{1p}}{2} + c_1 c_{1p}\right) \quad (5.8)$$

The first thing to notice when comparing equation 5.8 with equation 5.7 is how similar they are. The passive environmental components (orange) are equal and the only thing that differs in the genetic components (blue) are that the avuncular correlation includes the genotypic correlation between twins, f. For monozygotic twins, where $f = 1$, the only things that differ are the direct phenotypic transmission (red) and assortative mating (teal). If we temporarily assume no assortative mating ($\mu = 0$), then any difference between the parent-offspring correlation and the monozygotic avuncular correlation must be attributable to direct phenotypic transmission. Differences between monozygotic and dizygotic avuncular correlations can give similar information about passive environmental transmission. Assortative mating complicates things a fair bit, meaning it is not straightforward to simply solve for genetic and environmental pathways with Falconer-like equations, but estimating the parameters is not a problem in a structural equation model.

Another key quirk is that the genotypic correlation between cousins (denoted q) is different in monozygotic twin families and dizygotic twin families: In monozygotic twin families, cousins in the next generation are genetic half siblings. This gives more statistical power to differentiate genetic and environmental sources of sibling similarity that are independent of the parental phenotype.

5.5.7 The liability threshold model

As discussed in section 1.3, mental disorders are likely the ends of continuous distributions, but they are measured dichotomously in my data. To get around this, I modelled mental disorders with a liability threshold model. In such a model, the dichotomous measure is assumed to represent an unobserved, normally distributed *liability* to be diagnosed with a mental disorder. We then assume that diagnosed individuals are above a threshold and undiagnosed individuals are below the threshold. With these assumptions, we can easily calculate the correlation between the liability and other variables. For continuous variables, it would be a polyserial correlation, and for other dichotomous variables, it would be a tetrachoric correlation. These correlations are then used to estimate the parameters in the model. It is important to note that the correlation

being decomposed is between parental income rank and offspring *liability* to mental disorders, not mental disorders per se.

5.5.8 Including full siblings

Children-of-twins models require a large sample size to identify all parameters accurately, especially for small parent-offspring correlations like that in paper 2 (between –.10 and –.15). This is especially true for liability threshold models, because polyserial and tetrachoric correlations are less precise than regular product-moment correlations given the same sample size. To maximize statistical power, it is therefore common to also include full siblings. Genetically speaking, full siblings and dizygotic twins are the same. I therefore estimated the models with about 100 000 full sibling families (coupled with about 1000 monozygotic twin families). Given that most of the parameters in the model are identified with full sibling families alone, the gains in power are very large. (If you leave out c_{1p}, you would not actually need the children of monozygotic twins).

Full siblings have larger age differences than dizygotic twins, which may reduce our confidence in the equal environment assumption. On the other hand, this may not be a big concern when they are adults. Using full siblings instead of dizygotic twins also relaxes other assumptions: Dizygotic twins may have issues with selection bias because, unlike monozygotic twins, they are not randomly distributed in the population (Bortolus et al., 1999). It is not clear which assumption is best, but given the need for statistical power, using full siblings seems preferable. It is possible to estimate or otherwise vary the environmental correlation between different types of relatives, thereby relaxing this assumption, but that would negate the increase in statistical power.

Another way to increase power would be to include half-siblings in the parental generation, as that would add a third group with different genetic relatedness. This is not uncommon in children-of-twins-models (Torvik et al., 2020), and I initially intended to include them. However, the subset of the population with half-siblings are not representative of the population: In my sample, they had significantly lower income and their offspring had more mental disorders. Because I was not sure how this would impact the model (and because the gains in statistical power would be marginal), I decided to not include half-siblings.

5.5.9 Variable parental phenotypes

Parental income rank was calculated for the years the children were between 10 and 18 years old, meaning parental income rank would not be equal for two siblings. Which parental phenotype should be used in the model? While one could create an average, another approach is to model a variable parental phenotype as depicted in Figure 5.10 (Mcadams et al., 2018). This has the added benefit of increasing the statistical power of the model considerably, thus solving our first problem as well.

Although the model in Figure 5.10 may seem overly complex, the underlying logic is very similar to the one in Figure 5.9 and most implied covariances – including the parent-offspring correlation – will remain the same. The difference is that the parental phenotype is observed at two time points, denoted P_{t1} and P_{t2}, representing the average parental income rank for child 1 and child 2, respectively. These two observations are thought to represent the sum of an underlying, stable phenotype and deviations from that stable phenotype. This is very similar to the logic behind sibling designs discussed in section 5.4.4, only that we are here concerned with within-individual variation rather than within-family variation. One difference is that the stable characteristics

are modelled as a latent variable rather than as the observed mean between the observations. Genetic and shared environmental factors are assumed to influence the stable characteristics, whereas the unique environmental component (E) is split into between-individual sources of variation (E_{1b}) and within-individual sources of variation (E_{1w}).

5.5.10 Advantages of the children-of-twins model over the ACE model

The classical ACE model derives its strength from being agnostic to what the genetic and environmental factors are and how they work. This is also one of the major drawbacks. The children-of-twins model partly remedy this by distinguishing offspring factors that are associated with the parental phenotype – in this case, income rank – and factors that are independent of parental phenotype. It is still agnostic to the specific mechanisms, but not as agnostic as the classic twin model.

There are also other advantages. For example, whereas the classical twin model makes strong assumptions about no assortative mating or gene-environment correlations, the children-of-twins model relaxes these assumptions by modelling them explicitly. Because genetic and environmental transmission are modelled as separate pathways, gene-environment correlations are inherent in the design: It is simply what follows from both genetic and environmental pathways being non-zero. If you model the same phenotype across generations, you could even use this as a best-guess estimate of what the gene-environment correlation is in the parental generation, although that is not possible when the phenotypes differ. Assortative mating is modelled by allowing parents (and their effects on offspring) to correlate. Obviously, modelling these assumptions breeds more assumptions, such as the type of assortative mating – there are assumptions all the way down – but these assumptions are often less severe than the alternative. Don't mistake a more complicated model for a model that makes stronger assumptions.

5.5.11 What other assumptions underlie this model?

Most assumptions are explicit in Figure 5.10 if one knows what to look for. For example, the model assumes no direct causal effects from the offspring to the parent, or from the uncle or aunt to the offspring. However, these assumptions are not as severe as they may sound because they will affect the model in predictable ways. For example, if offspring truly had a causal effect on their parents' phenotype, then this would appear as a causal effect of the parent on the child (Mcadams et al., 2018). If the overarching aim is to distinguish genetic and environmental pathways, then this limitation is of little importance, although the causal effect itself must be interpreted with this in mind. Relatedly, if uncles or aunts truly had a causal effect on offspring mental disorders, then this should look like passive environmental transmission.

Another assumption, still implicit in Figure 5.10, is the comparability of different groups. For example, the model assumes that the only thing that differs between monozygotic twin families and full sibling families are the values of f and q. Inherent in this is an adapted version of the equal environment assumption where children of monozygotic twins do not have more contact with their parent's twin than children of full siblings (at least not in a way that have causal consequences).

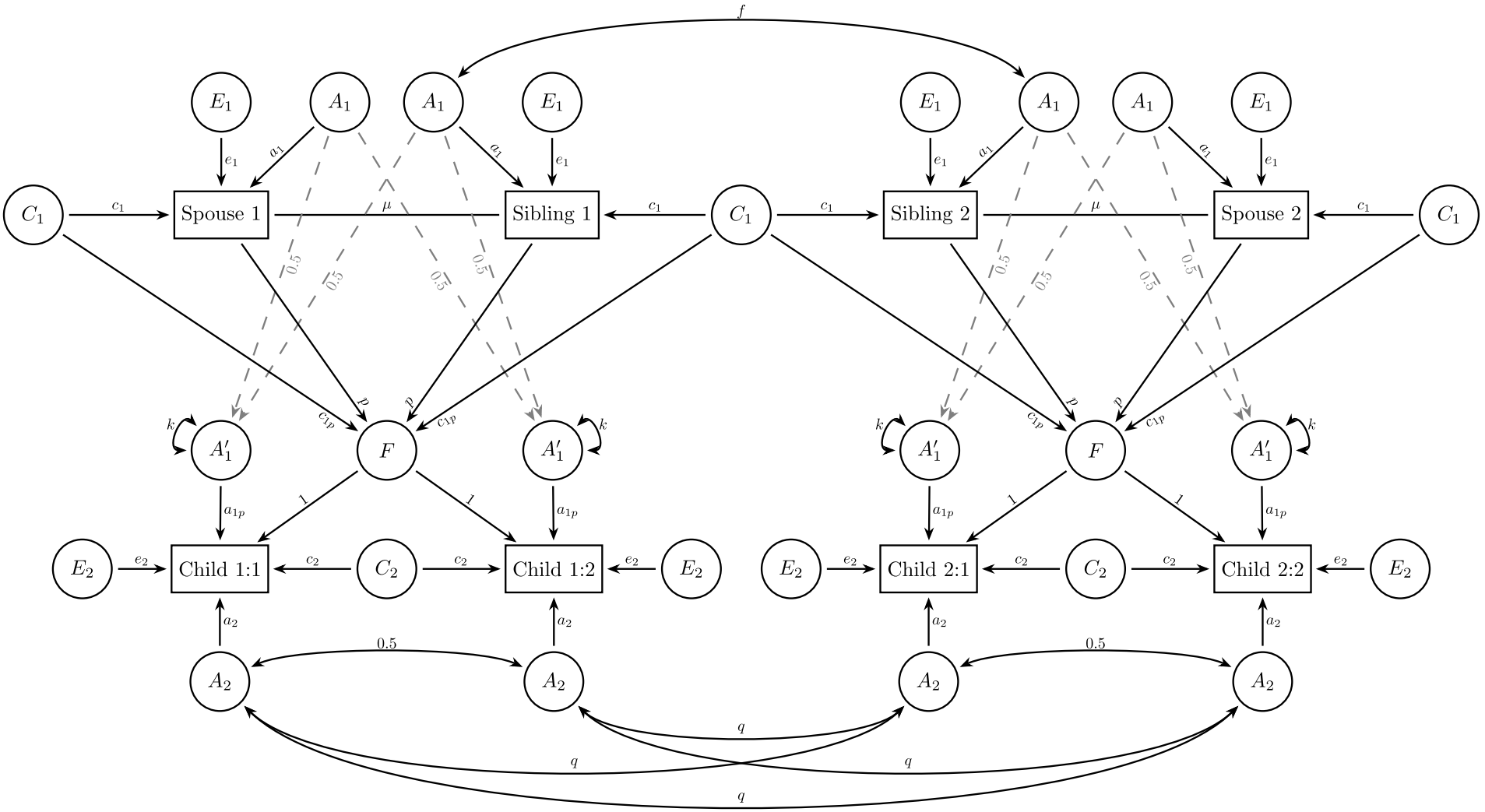

Figure 5.9: The full extended children-of-twins-and-siblings model.

All variables have unit variances except F, whose variance depends on the incoming paths (hence the unit effect size for outgoing paths instead). All sources of variation are explicit for endogenous variables,

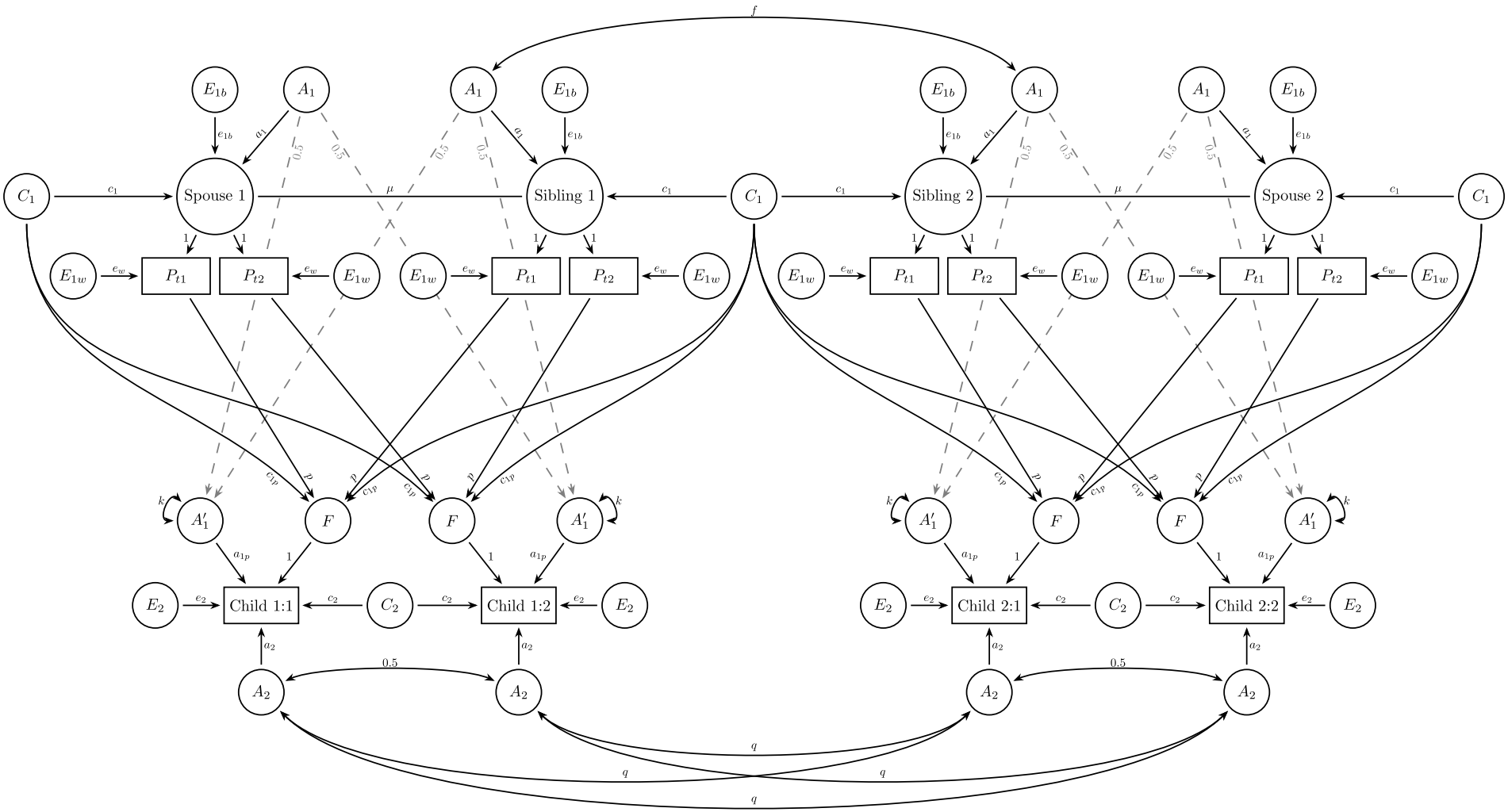

Figure 5.10: An extended children-of-twins model with variable parental phenotypes.
All variables have unit variances except F, Sibling 1/2 , and Spouse 1/2 , whose variance depends on the incoming paths (hence the unit effect size for outgoing paths instead). All sources of variation are explicit for endogenous variables,

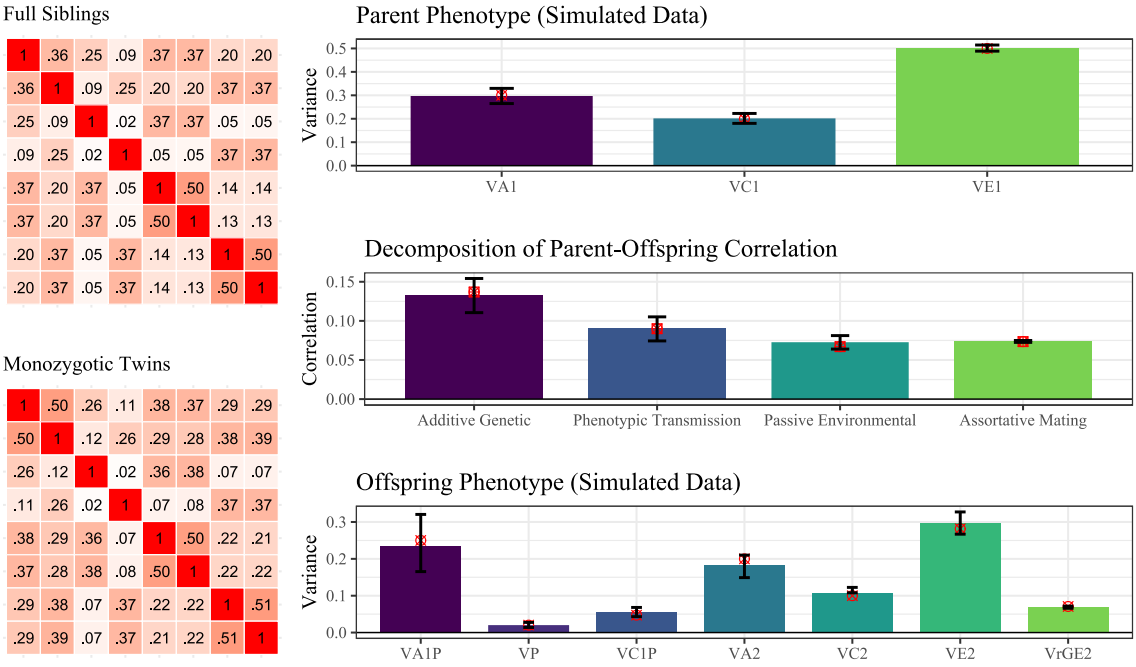

Figure 5.11: Simulating the children-of-twins model.
Based on the correlation structure on the left, the model is able to recreate the simulated parameters (red dots) on the right.

The more severe assumptions concerns the causes of partner similarity. The model assumes that they are matching on the phenotype and that they have done so for many generations (i.e., it is in equilibrium, see Paper 3). However, the partner correlation could have come about through other processes, such as matching on a secondary phenotype or mutual influence (Sjaarda & Kutalik, 2023). It appears that, by attempting to relax the assumption of no assortative mating, we have opened pandora's box and ended up assuming much more. However, we have simply discovered that there are assumptions all the way down. Violating these new assumptions are likely to result in less severe biases than not accounting for partner similarity at all.

A related assumption concerns interactions with sex. The model does not consider sex (although I did not include opposite-sex sibling pairs), but intergenerational effects could be specific to the sex of offspring or the sex of the parent, or the heritability could be sex-specific. Because income rank likely represents different aspects of men and women, such interactions are likely. Most of these will simply be averaged out and is therefore more of a limitation than an assumption. However, all dyads in the parent generation are sex specific: The partner correlations (e.g., Sibling 1 – Spouse 1) and in-law correlations (e.g., Sibling 1 – Spouse 2) always include opposite sex dyads, and the sibling correlation (Sibling 1 – Sibling 2) and co-in-law correlation (Spouse 1 – Spouse 2) always include same sex dyads. It is therefore no longer trivial that the model assumes that the parental phenotype is the same across sex. This problem becomes more complicated with the assumption of primary phenotypic mating because sex-specific phenotypes can (and have) lead to higher correlations among co-in-laws than in-laws. This is impossible given the causal structure in Figure 5.10 and could bias the results in unpredictable ways.

It is possible to model such sex differences and secondary assortative mating, but at some point I had to call it a day. (Wouldn't you agree the model in Figure 5.10 is complicated enough?). While I intend to investigate these possibilities in the future, time constraints forced me to simply parse out sex-specific between-family

variation in income-rank from the model and move forwards (see details in the paper's methods section). Sex differences in the ontology of income rank is for a later project to investigate.

If the causal model in Figure 5.9 or Figure 5.10 accurately reflects the world, then the respective structural equation models will give correct estimates by comparing monozygotic twin families and full sibling families (sampling variation, notwithstanding). To confirm this (and to make sure the model was specified correctly in OpenMx), I simulated data with that causal structure. As we can see in Figure 5.11, the model is able to recreate the simulated parameters based on the observed variables alone. The scripts for simulating data and running the model are available at osf.io/6324g/.

5.6 Paper 3: Assortative mating and genetic similarity in families

Paper 3 is not directly inferring cause and effect, but it builds on a well-established causal relationship: a parental genotype has causal effect equal to .50 on their offspring's genotype (Fisher, 1918). One would then think that the genotypic correlation between a parent and offspring should also equal .50, but this assumes that there are no other reasons for them to correlate. If the offspring inherit similar genetic variants from the other parent, for example because of assortative mating, then the genotypic correlation between parent and offspring will be larger. Paper 3 focuses on assortative mating and its consequences for genetic similarity in extended families. Between the thorough description of path analysis in section 5.2, the methods described in the paper itself, and the paper's supplementary methods, there is not much to add here. The first part of the paper uses path analysis to understand the theoretical consequences of assortative mating, whereas the second part documents empirical correlations for numerous traits using polygenic scores. Here, I will describe why assortative mating creates these complications and how to use path analysis to understand them.

5.6.1 Assortative mating induces correlations between antecedent variables

Unlike with correlations that are due to shared causes of variation, which only induce correlations in descendent variables, sorting processes induce correlations between antecedent variables. It is similar to conditioning on a collider. If partners – consciously or as a side effect of something else – enter partnerships in part because of phenotypic resemblance (i.e., assortative mating), then all the causes of variation in the maternal phenotype will become correlated with all the causes of variation in the paternal phenotype. If the phenotype in question is heritable, then partners will tend to have genetic variants with similar effects on the phenotype.

5.6.2 What are the genetic consequences of assortative mating?

Assortative mating creates a dependency between the genetic variants an individual inherits from their mother and father (Bulmer, 1980; Fisher, 1918; Lynch & Walsh, 1998). Depending on how many generations of assortative mating there have been, numerous consequences follow including two that are important here: First, trait-related genetic variance will increase in the initial generations of assortment and thereafter be maintained at an equilibrium (see section 2.7 on Matthew effects). Second, the genetic variants an individual inherits from their mother is no longer independent from the genetic variants their sibling inherits from their father. This means that siblings and other relatives will be more genetically similar than normal for the trait in question (which is why the ACE model implicitly assumes no assortative mating). Just like for genetic variance, the genetic similarity will increase in the first few generations before stabilizing at an equilibrium. The questions this paper poses are: (1) how genetically similar do various relatives become (in theory), and (2)

how similar have relatives become (in practice)? Note that these consequences only applies to genetic variants that are correlated with the assorted trait, not to the entire genome.

5.6.3 How to model assortment in path analysis

A double-headed arrow implicitly assumes that the modelled correlation is due to a common cause, which is reflected in the path tracing rules described earlier in this chapter. It is therefore inappropriate to use a double-headed arrow if the modelled correlation arose because of extrinsic reasons, such as a sorting process. Doing so would fail to correctly infer the correlations between the causes of the sorted variables. To get around this problem, correlations that arise from sorting processes can be specified with a *co-path* (—), which is an arrowless path indicating correlations that arise from extrinsic processes like assortment (Cloninger, 1980). The co-path was introduced with assortative mating in mind and comes with its own path tracing rules that can handle the special correlation structure that assortment would lead to (Balbona et al., 2021). It works by connecting two valid chains (per the rules described in section 5.2 on page 20), thus creating a single longer chain (e.g., ↔ — ↔). This allows all the chains that connect with one of the sorted variables to traverse the co-path and connect with all the chains that connect with the other sorted variable. An alternative description is that once a chain traverses the co-path, the path tracing rules described above are "reset", so that one again must start tracing against the direction of arrows and include exactly one double-headed arrow. A particular co-path can only be traversed once in each chain, although a chain can include multiple, distinct co-paths.

Because a co-path connects two valid chains, one can technically not end or start a chain with a co-path (with the corollary that the co-path coefficient is neither the covariance nor the correlation between the sorted variables). This is similar to how a valid chain cannot start by following an arrow but must instead always start by going against arrows. However, a similar shortcut exists for standardized variables: If all valid chains from the sorted variable leading back to itself sum to one, it is possible to trace *as if* it was possible to start or end a chain with a co-path. If the variables have unit variances, the co-path coefficient is equivalent to the correlation between the two variables attributable to assortment.

In the supplementary information for this paper, I go into more detail about incorporating polygenic indices into the path diagram, as well as allowing variance to differ across generations (i.e., allow disequilibrium).

Chapter 6: Main Findings

6.1 Paper 1: ADHD and school performance

Using register data on practically every Norwegian junior high school pupil born between 1997 and 2002 (N = 344,152), the first paper documents a large difference in school performance – more than one standard deviation (–1.11) difference in grade point average – between children with and without ADHD. This was partly because ADHD is more common in groups that already tend to do worse in school, such as among boys and children of less educated parents. When I compared siblings while adjusting for within-family confounders, the difference was reduced but remained large (–0.60). Parental factors, including their socioeconomic position, are therefore unlikely to be the main cause of the association between ADHD and school performance. When I also adjusted for early school performance (which I did separately as this could be a mediator), the difference was –0.33 in the sibling models, which is not consistent with ADHD being the consequence rather than cause of poor school performance. (As discussed thoroughly in the previous chapter, I don't think the assumptions underlying this conclusion warrant enough confidence to unapologetically assert that ADHD causes poor school performance, although the results are suggestive).

When I compared the association between ADHD and school performance across parental education, I found that differences were larger among children with highly educated parents than less educated parents. ADHD is less common among children of highly educated parents, raising the question of why the difference was larger. It could be higher thresholds for getting a diagnosis or that unaffected children do relatively better and thereby makes the difference appear larger. Nevertheless, despite relatively larger differences associated with ADHD, children of highly educated parents generally outperformed children of less educated parents regardless of whether they had ADHD or not. Let me repeat that for clarity: Children *without* ADHD but with the least educated parents were outperformed by children *with* ADHD but with highly educated parents. In other words, social background is a much more potent predictor of school performance than mental health. I found similar results (albeit less dramatic) when comparing the association across sex, raising similar questions. The larger differences in groups with lower prevalence compensates for the lower prevalences, limiting the possibility that ADHD mediates the effect of parental education on offspring school performance.

When I investigated school performance in individual school subjects, I found ADHD to be associated with large differences in all school subjects, including what are occasionally thought of as "ADHD-friendly" school subjects like sports (–0.60) and arts and crafts (–0.47). The differences were slightly larger in more theoretical school subjects like mathematics (–0.82) and English (–0.70), but not so large as to suggest that ADHD primarily impacts school performance through these school subjects. Instead, the results indicate that ADHD impacts (or at least is associated with) school performance through general factors that are shared across school subjects.

6.2 Paper 2: Parental income and mental disorders

Using register data on practically every Norwegian aged 10 to 35 between 2006 and 2018 (N = 2,112,355), the second paper documents large differences in the prevalence of mental disorders across parental income. These differences exist across the entire age range and are large for practically every mental disorder, for both men and women, and across both paternal and maternal income. Diagnosed mental disorders were 2.13 times more

common among 10-year-olds with fathers in the bottom income quartile compared with the top quartile. Among 35-year-olds, mental disorders were 1.62 times as common among those with fathers in the bottom quartile.

The polyserial correlation between parental income and offspring mental disorders was –.15 among 10- to 14-year-olds and –.10 among 30- to 34-year-olds. When I applied the children-of-twins model described in section 5.5, I found that genetic similarity accounted for most of the correlation in all age groups. This suggests that social selection plays a large part in explaining why parental socioeconomic position and offspring mental disorders are correlated. However, among adolescents, I also found evidence consistent with a direct effect after genetic similarity was accounted for, making up 21-23% of the correlation. This suggests that social causation may play a minor role in explaining the parent-offspring correlation among adolescents.

In terms of variance explained, high heritability was evident for both income rank (30–40%) and mental disorders (47–70%), with minimal variance explained by shared environmental factors. Shared environmental effects accounted for less than 0.5% of the variance in the offspring generation, which was less than variance explained by the co-occurrence of environmental and genetic effects (up to 1.7% among 15- to 19-year-olds, but negative in the older age-groups). Finally, partners were significantly correlated (.09–.18), which is consistent with assortative mating.

6.3 Paper 3: Assortative mating and genetic similarity in families

Using path analysis, the third paper describes how similar relatives become, genetically, if partners are matching based on similar phenotypes (i.e., assortative mating). I found that assortative mating has a relatively larger impact on similarity between distant relatives compared to close relatives. This would indicate that genetic variants that are associated with traits undergoing assortment, such as educational attainment, will concentrate in extended families, thereby increasing or maintaining inequality.

Using genetic data on 47,135 partner pairs and 1,213,258 dyads of related individuals from the MoBa cohort study, I complemented the theoretical analysis with empirical correlations between the polygenic indices of partners and relatives. Unlike phenotypic correlations, which can arise through multiple other processes, genotypic correlations are much stronger evidence of assortative mating. I found that several traits showed evidence of assortative mating, including educational attainment, height, intelligence, and body mass index. These traits showed correspondingly increased similarity between relatives, as expected. Somewhat surprisingly, I did not find evidence of assortative mating on mental disorders despite prior studies showing substantial phenotypic correlations. This could be because the phenotypic correlations are caused by other processes, or it could be that the polygenic indices do not adequately measure the genetic propensity.

For the traits that did show evidence of assortative mating, I used differences in variance across generations and discrepancy between the expected and observed parents-offspring correlation to infer whether assortment has been occurring over many generations or not (that is, whether it was in equilibrium). I found evidence suggesting that, while assortment on educational attainment appear to have been occurring for several generations, it was not consistent with equilibrium. This suggests that the genetic variance and similarity in families are still increasing, thus leading to *increasing* differences across generations (not just maintained differences).

Chapter 7: General discussion

In this thesis, I have provided evidence that furthers our understanding of the intergenerational transmission of social differences and mental health. First and foremost, my findings reiterate that there are strong associations between social differences and mental health both across and within generations. While there was evidence of some causal influences from parents to offspring, the intergenerational association appears most consistent with social selection. This implies that the causal processes that are leading to within-individual correlations between socioeconomic position and mental health are likely repeating anew in each new generation, for example via poorer school performance among those with mental disorders. The direct causal effects of parents are coming atop of this, and differences in starting points are further increased by assortative mating, suggesting Matthew effects. In this chapter, I will briefly discuss the implications of the results before a lengthy discussion about the complications and caveats that underlie these conclusions. I will do that by first explaining what quantitative genetic models do and do not tell us, before discussing methodological considerations that were not thoroughly addressed in chapter 5.

7.1 Intergenerational versus within-individual processes

In the introduction, I differentiated between intergenerational correlations and within-individual correlations. Both Paper 1 and Paper 2 suggest a limited role of social causation for intergenerational correlations. In Paper 1, I observed that the strong association between ADHD and school performance persisted in sibling models, which controls for familial confounders under the assumption that siblings are equally influenced. This suggests that this association is not primarily caused by shared family environment or parental socioeconomic position. Paper 2 further supports this interpretation, attributing the majority (but not the entirety) of the association between parental income rank and offspring liability to mental disorders to genetic similarity. These findings imply that individual-level causal processes or exposure to third variables independent of the family are the primary contributors to the health gradient in Norway. In other words, the associations between socioeconomic position and mental health within individuals appear *not* to be confounded by parental socioeconomic position or other familial factors.

Despite these insights, the results are largely agnostic as to why these traits co-occur in the same individuals. Paper 1 suggests a role of mental health on school performance, but the limitations of the design make it difficult to infer causality without making questionable assumptions. Indeed, causal inference for within-individual associations is generally more challenging in quantitative genetic models due to limitations in the conclusions that can be drawn from comparing twins and other relatives (Duffy & Martin, 1994; Rasmussen et al., 2019). When these results are interpreted in light of the prior literature discussed in section 2.8, I find it plausible that there are bidirectional causal influences between mental health and socioeconomic position that occurs independent of parental socioeconomic position, but the jury is still out. Given these findings, future research should focus on exploring causal processes independent of the family, such as individual experiences and the societal structuring of opportunities and constraints for people with certain traits (Goldberg, 2001). It should then be possible to tell what kind of intervention would reduce the health gradient: decoupling socioeconomic position from health versus decreasing socioeconomic inequalities.

Note that these results may not generalize globally, and may hide effects that are specific to a subgroup of the population. It could also be the case that results would differ for other indicators of mental health and socioeconomic position (see section 7.4 and 7.6).

7.2 Co-occurring causal pathways increases differences further

Both Paper 2 and Paper 3 presents evidence suggesting that differences arising from intergenerational transmission is not merely the sum of the individual causal pathways. Assortative mating on socioeconomic traits, for example, appears to have resulted in correlations between the genetic variants inherited from either parent. This process have increased genetic variance across generations and appears to still be increasing for socioeconomic traits. The larger variance in genetic starting points may amplify consequences for later differences in socioeconomic position and mental health. Assortative mating may also amplify environmental pathways, as any causal effect of the parental phenotype is likely to co-occur with similar effects from the other parent.

Paper 2 also highlights another source of correlated pathways: Here, I found that the correlation between genetic and environmental pathways contributed more to differences in liability to mental disorders than the environmental pathway alone. Furthermore, I found evidence of both assortative mating and gene-environment correlations, which further exacerbate this phenomenon. For example, the genetic variants inherited from one parent will be correlated with the environmental effect of the other parent. A small but non-negligible portion of the parent-offspring correlation in Paper 2 could be ascribed to such cross-parent correlations. These findings imply that multiple processes act together when socioeconomic differences and mental health are reproduced across generations, and that the resulting differences are not just the sum of the individual causes (see section 2.7). This raises questions about whether individual processes can be fully understood in isolation.

7.3 How to interpret findings from quantitative genetics

Paper 2 suggests that genetic confounding plays a large role in the association between parental income and offspring mental disorders, and Paper 3 rests on the premise that genetic differences are important for differences in educational attainment and mental health. This adds to a long list of papers that provide evidence that genetic differences are important for differences in mental health and socioeconomic position (Polderman et al., 2015). Claims that social differences, whether in health or income, are related to genes are prone to be misinterpreted and misused (Harden, 2021; Meyer et al., 2023). Because a correct interpretation of what these findings imply is paramount, I want to provide a comprehensive explanation of what quantitative genetic models can and cannot tells us.

7.3.1 The genetics of a single trait: What does heritability mean?

The children-of-twins-model in Paper 2 indicated that income rank was about 40% heritable, with the rest being attributable to unique environmental factors. Money does not grow on trees, nor is it made of proteins. How is it then possible to claim that genetics play a role? The first thing to remember is that heritability is just a statistical concept that tells us how much phenotypic differences can be explained by genotypic differences, similar to what R^2 tells you in a regression model. While it does have causal implications, a heritability estimate is completely agnostic to what mediates these effects. It is drawn as A → P in the models, but the true causal picture probably looks more like A → ? → ? → ? → P. Remember, mediation is causation (section 2.5).

What it does say something about, though, is why family members resemble each other (Turkheimer, 2000). It means that familial associations (i.e., parent-offspring correlations or sibling correlations) cannot be fully ascribed to family members having causal effects on other family members. Instead, family members tend to be similarly disposed and therefore undergo similar *within-individual* causal processes. Hypothetically, if employers consistently favoured taller individuals for higher-paying positions, then siblings would tend to have similar incomes because they were genetically similar, not because of some causal process within the family. Height is not likely to be the most important mediator, but we simply do not know what lies along the long causal path between genetic differences and income differences. Odds are high that many would call them environmental.

A useful analogy could be the causal effect of sex at birth (which, incidentally, is 100% heritable). Because sex at birth is practically random, any association with sex cannot be attributed to confounders or reverse causation. Assuming there are no issues with collider bias or sampling bias, all true associations between sex and another variable must therefore be causal (in the sense described in chapter 2). For example, girls do better than boys in school: sex at birth explains roughly 7% of the variance (see paper 1). It would be foolish to say that school performance causes sex at birth or that, say, socioeconomic position causes both school performance and sex at birth. The only other explanation is that sex has a causal effect on school performance. This is so obvious that scientists rarely stop to think about it. Instead, they are busy asking the follow-up question, namely what mediates this association? Are teachers favouring girls (Terrier, 2020)? Are boys less self-disciplined (Duckworth & Seligman, 2006)? Do girls mature earlier, which in turn make them better at school (Torvik et al., 2021)? Few people are claiming that, because we know sex explains 7% of the variance in school performance, then 7% of school performance must be determined at birth and therefore immune to social policy. Heritability should be interpreted in the same vein. This is the next task for scientists: why do individuals with different genetic propensities exhibit corresponding phenotypes?

Relatedly, population heritability depends on the relative importance of genetic and environmental variance to phenotypic differences in the population, all of which are likely to change across time and place. For example, the heritability of educational attainment in Norway increased among men born after the second world war, a change that was attributed to the introduction of favourable student loans (Heath et al., 1985). That is, the environmental variance contributed less to differences in education, increasing the heritability. Similar findings exist for Estonia after the fall of the Soviet Union (Rimfeld et al., 2018), but results are mixed for the western world in general (Silventoinen et al., 2020). Paper 2 adds to this literature as the heritability of parental income was slightly higher in the younger age groups (whose parents are presumably from later cohorts). It is also important to distinguish the true, population heritability at any given time – the estimand – from specific heritability estimates. It could be that estimates are inaccurate if the assumptions are violated or simply because of sampling variation.

7.3.2 Are mental disorders genetic disorders?

In my second paper, I corroborated existing findings demonstrating the high heritability of mental disorders, which I estimated to be between 47% and 70%. Does this suggest that mental disorders are genetic disorders? The first law of behavioural genetics posits that all traits are heritable, but this should not be misconstrued as implying that all traits are inherently "genetic" (Turkheimer, 2000). The first law is intended to convey a sense of irony, as even behaviours with no apparent genetic basis – like the number of hours spent watching

television – are also heritable. Consequently, heritability alone does not suffice to classify a trait as genetic. The causal mechanisms linking genetic variance to differences in mental health outcomes remain as obscure as those contributing to income differences (Giangrande et al., 2022). It is plausible that some mental disorders could be genetically rooted – perhaps due to malfunctions in proteins that upset neural development – but heritability does not inherently imply this claim. What it does imply is that environmental causal processes shared by family members is not the primary reason for why mental disorders tend to run in families (although it may play a minor role).

7.3.3 The genetics of multiple traits: What does genetic confounding mean?

In addition to explaining why the same traits co-occur among related individuals, genetic factors may also explain why different traits co-occur among related individuals (or within the same individual). This occurs when there is a genetic correlation between traits, meaning genetic variants influencing one trait co-occur with those affecting another. Like heritability, genetic correlations are blind to the specific causal processes linking two traits. There are three primary processes that result in genetic correlations: The first two involve pleiotropy, where specific genetic variants influence both traits. In horizontal pleiotropy, these genetic variants independently affect each trait, leading to confounding, while in vertical pleiotropy, the variants influence one trait, which in turn affects the other, resulting in mediation. The third process, cross-trait assortative mating, leads to co-occurring genetic variants despite no causal relationship, mimicking the confounding effects of horizontal pleiotropy (Border et al., 2022).

In Paper 2, a genetic correlation between income rank and mental disorders was the primary reason behind the association between parental income rank and offspring mental disorders. Insofar as this is correct, the genetic variants influencing income rank tend to co-occur with those associated with mental disorders, leading to correlations between related individuals such as parents and offspring. In other words, it rules out familial between-individual causal processes as the ultimate cause. However, it doesn't explain why income rank and mental disorders are correlated within the same individual. As mentioned, several scenarios could account for this, such as mental disorders leading to income differences, income differences affecting susceptibility to mental disorders, or a third factor causing both. All these scenarios would be consistent with a genetic correlation. A genetic correlation by itself does therefore not imply that a within-individual association is confounded.

This agnosticism is the price we pay for an otherwise very powerful method. However, we could speculate on why there is a genetic correlation between income and mental health, or the very least provide examples that would be consistent with this finding. To link the findings from Paper 2 with the findings of Paper 1, if (1) propensity for mental disorders ran in families for genetic reasons (Polderman et al., 2015), and (2) the current school system disadvantaged individuals with a propensity for mental disorders (Nordmo et al., 2022; Shen et al., 2016; Sunde et al., 2022), and (3) lower school performance lowered their later salaries and chances on the job market (Nordmo et al., 2022; Sunde et al., 2022), then this would result in an intergenerational correlation between parental income rank and offspring mental disorders explained by genetic similarity. This is consistent with evidence that appears to support within-individual causal associations of income on mental health (Thomson et al., 2022).

The factors that link income and mental health will likely not be as ontologically neat and tidy as school performance (see also section 7.6). Furthermore, what these traits are will likely vary across time or place. A recent study indicated that the set of genes associated with educational attainment has shifted across generations, indicating that the traits associated with educational attainment have shifted as well (Baier et al., 2022). A similar scenario is plausible for income and mental disorders, as well as the overlap between the two. Another study found that genetic correlations between different mental disorders are influenced by genes associated with socioeconomic position (Marees et al., 2021). Future research should attempt to map the relative importance of horizontal pleiotropy, vertical pleiotropy, and assortative mating, and identify what traits, if any, mediate the genetic correlation between income and mental disorders. In addition to improving our understanding of why socioeconomic position and mental disorders are associated, such a map can improve our understanding of mental disorders in general and why they tend to co-occur.

7.4 Population-average effects hides interactions and dynamic associations

In the first paper, I found that the association between ADHD and school performance varied across parental education. A dynamic association like this suggests that the causal structure linking mental health and socioeconomic position is likely very complex. However, accurately modelling a dynamic causal structure in a way that identifies parameters without overfitting the data is practically impossible in social science. As a result, we must instead resort to linear models which at best can include rudimentary forms of non-linearity (e.g., linear interactions and quadratic effects). Importantly, though, linear models still hold value despite masking underlying complexity. We must simply keep in mind that they estimate effects averaged across the range of observations, and true marginal effects may vary.

This is an important limitation in Paper 2. Parental income rank was associated with the prevalence of offspring mental disorders across the entire income spectrum. That is, offspring of parents in the second highest income quartile were more likely to have mental disorders than offspring of parents in the highest income quartile. However, the differences between the two lowest income quartiles were larger than between the other quartiles. This suggests that having parents at the lower end of the income distribution represents more than just general variation in income. When estimating the correlation between parental income rank and liability to mental disorders, though, this nuance is missed. As a result, the nuance is also missed in the children-of-twins model.

This is a general limitation for most quantitative genetic models: They only estimate population-level effects. In other words, when Paper 2 attributes the parent-offspring correlation between parental income rank and offspring mental disorders to genetic confounding, it is doing so for the general variation across the entire income spectrum. As mentioned in section 5.5.1, there could be large effects for a small subgroup that, in practice, do not make a difference to the overall population average. The effects of poverty could be such an example. There is no straightforward way to account for this in twin models other than running the model separately for those with high and low parental income (cf. Azzolini et al., 2022). Unfortunately, I did not have enough statistical power to do this. Personally, I find it highly plausible that the population-average effect of parental income obscures a larger direct effect among those with parents in the lower quartiles. Future research should investigate the lowest income brackets, which may have a different causal structure than general variation in income rank. There are already several lines of evidence that suggests the effect of

socioeconomic position is particularly strong among those in the lower echelons of society (Costello et al., 2003; Thomson et al., 2022).

The same limitation also applies to all heritability estimates and estimates of genetic correlations. The heritability estimates in Paper 2 and the correlations between partners in Paper 3 could vary across social strata. There are several studies indicating that the heritability of intelligence, for example, is lower among those from lower socioeconomic positions, a phenomenon known as a Scarr-Rowe interaction (Paige Harden et al., 2007; Tucker-Drob & Bates, 2016). Other studies show that there is a stronger within-individual association between socioeconomic position and health among those whose parents had less education and less income (Luo & Waite, 2005). It is plausible that similar gene-environment interactions exist for mental health and socioeconomic position. For example, a recent Norwegian study found that the correlation between individuals' polygenic score for ADHD and their school performance differed significantly between schools (Cheesman et al., 2022). On the other hand, the Scarr-Rowe interaction does not appear to be replicable in Europe (Tucker-Drob & Bates, 2016).

There are two things here I want to call attention to. First, note how this relates to section 2.3, where I discuss how causation depend on variation. By looking at a subgroup of the population, one is limiting the variation, thus potentially changing the relative importance of different causes. The second thing to note is that this problem is mirroring the problem of generalizability. The findings discussed herein might not generalize to other contexts, such as the United States or Liberia, where the mean and variance of various causes could be different. The current population under study is among the countries with the least inequality worldwide (The World Bank, 2022), which is another way of saying that the variance in the putative cause is relatively small. Larger differences could mean that direct causal effects become more important. There is also some evidence suggesting that more inequality is itself associated with worse mental health, including among those who are well off (Patel et al., 2018; Weich et al., 2001).

7.5 Selection bias

A related but slightly different obstacle to human scientific research is that participants in studies may not be representative of the population that it tries to describe. There are two problems that result from this: First, the conclusions may not generalize to the population at large. Second, and more importantly, if participation is conditional on variables of interest, then this could result in spurious correlations in the sample resulting from collider stratification bias (Munafò et al., 2018). For example, it is common for participants in sample-based studies, including large cohort studies like MoBa, to be healthier and more educated than the general population (Nilsen et al., 2009; Vejrup et al., 2022). Because all analyses will automatically condition on participation, the association between health and education will be biased. To get a sense of what would happen, we can for simplicity's sake imagine that participation was a continuous variable. If a is the true correlation between health and education, b is the correlation between health and participation, and c is the correlation between education and participation, then the observed correlation between health and education in the sample would be the partial correlation conditional on participation: $\frac{a-bc}{\sqrt{(1-b^2)(1-c^2)}}$. If bc is positive, which is likely the case here, then the observed correlation will be biased downward. The health-education correlation is therefore likely underestimated in sample-based studies.

The first two studies in this thesis use register data on the entire population and are therefore practically immune to this bias. This is a major strength! The bias is not eliminated completely – there is always implicit conditioning on survival and data availability – but it is far less of an issue than in sample-based studies. We can therefore afford high confidence in the accuracy of the descriptive statistics that make up a large part of both Paper 1 and Paper 2. For the more complicated analyses, selection bias starts to creep back in. For example, in the sibling analyses in Paper 1, I am inadvertently conditioning on families with discordant siblings (i.e., one has ADHD and the other has not). In Paper 2, I am inadvertently conditioning on families where at least on parent has a twin or full sibling with children. Furthermore, I am conditioning on the offspring having cousins of roughly the same age (i.e., both have available data for a given age range). This may bias the results in unintuitive ways. I personally do not think this is a major problem, but it is worth having in the back of your mind. Paper 3 is perhaps the most susceptible to this bias, because the analyses are conditional on genetic data being available for both partners. The sign of the correlation with participation should be the same for either partner, meaning the observed correlations could be biased downward. In the context of this paper, where all observed correlations are positive, selection bias could have increased the likelihood of false negatives.

7.6 Measurement validity

It is important to not confuse a measure of something with the thing itself. Just as the pipe in René Magritte's *The Treachery of Images* is not truly a pipe, the numbers representing an individual's height, educational attainment, or mental health is not the same thing as their height, educational attainment, or mental health. A measure may or may not have construct validity, which is whether it measures what it is supposed to measure (Cronbach & Meehl, 1955). A measure may also be unreliable – inconsistent or noisy – despite being valid (Fried et al., 2022). More importantly, even if measures are reliable and valid, they are also unintended measures of something else. Someone's height, for example, contains information on their weight, arm length, and sex. If you only know someone's height as adults, you will correctly infer their sex 75% of the time (assuming $d = 1.70$). In this sense, height is just an unreliable measure of sex. It is probably not uncommon to find psychological measures with comparable or worse overlap with the thing it is trying to measure (Flake & Fried, 2020), but even if the measure is perfectly valid, it will still unintentionally measure other things. Anything correlated with sex will correlate with height, all else equal.

This problem is important, especially for causal inference, because you cannot always be sure what is doing the causing (or what is being caused). For sex and height, the problem is obvious, and you would simply adjust for the other variable. This is not possible for (1) ontologically diffuse concepts like mental health (Brick et al., 2022), (2) variables with measurement error (see section 5.4.3), or (3) cases where you don't have access to all relevant variables. Take income rank as an example. Paper 2 found that income rank was associated with mental disorders among adolescents even after accounting for genetic similarity. This suggests a causal effect, but what is doing the causing? Maybe it truly is the financial situation of the parents that are somehow influencing offspring mental health. On the other hand, maybe income rank is just an indirect measure of conscientiousness (similar to how height measures sex), and having conscientious parents directly decreases the risk of mental disorders. Numerous indicators of socioeconomic position are lumped together for precisely this reason: It is not straightforward to distinguish an effect of income from an effect of educational attainment, even if you have measured both. Complicating the matter further is that what income and

educational attainment is a measure of has likely changed across cohorts (Baier et al., 2022). This is likely especially true among mothers.

All of this is to say that the problem of confounding factors is not really solved. Even if you have evidence of a causal effect, that does not mean that you truly know where to intervene. However, don't be fooled, because we have made progress. The new confounding problem is less severe than the initial problem. For example, most of the association between parental income and offspring mental disorders could be ascribed to genetic similarity, and this conclusion does not depend on what is being measured by income rank.

Another example is the measures of mental disorders used in Paper 1 and Paper 2. Although registered diagnoses in the health care system is a decent measure of mental disorders, it is also measuring health care use and treatment seeking. This must be considered when interpreting the results. For example, in Paper 1, I found that ADHD was more common among boys but the difference in school performance was larger for girls. If we replace "ADHD" with "being diagnosed with ADHD", then the result is no longer as surprising. Maybe it is not differences in ADHD itself, but rather differences in diagnostic practices related to ADHD that are underlying this result.

One of the weird results in Paper 2 is that adult offspring of parents with higher income appear to have a slightly *increased* risk of mental disorders after taking genetic similarity into account. This sounds implausible at first, but when phrased in terms of health care use, it may not be so unrealistic. If high-income parents cause their offspring to be more active users of the health care system, then this would look like an increased risk of mental disorders. This would normally be "hidden" by fewer health problems but might reappear once that is controlled for. I don't know whether the weird result stems from this or a violated assumption. Even though the latter may be more plausible, it should not be dismissed just because it initially sounds implausible.

Finally, mental disorders may represent different things at different ages and for boys and girls. This is a crucial caveat for interpreting the different results for the different age groups in Paper 2. ADHD is more common among young adolescents, while depression and anxiety is more common among adults, and it could be that the different results for adolescents and adults in Paper 2 is really because the measures represent different disorders. Unfortunately, because specific disorders necessarily have lower prevalence than the prevalence of *any* disorder, and because lower prevalence lowers the statistical power considerably, I was not able to run the models separately for the different disorders. However, even if I were able to do that, the problem would still not be entirely solved, as ADHD among adolescents and ADHD among adults may still be different things.

7.7 Future directions

Reproduction of social differences and mental health across generations is a complex topic, and there are many future avenues to pursue to further understand this topic.

One important avenue would be to clarify the various processes that could lead to partner similarity and assessing their consequences for intergenerational transmission. There is a growing body of evidence suggesting that partner correlations in educational attainment are partly attributable to secondary phenotypic assortative mating, evidenced by higher-than-expected environmental and genetic correlations between partners (Gonggrijp et al., 2023; Okbay et al., 2022; Torvik et al., 2022). Modelling these correctly could have important consequences for intergenerational transmission.

Another important avenue, highlighted in section 7.4, is potential differences in effects between overall variation in socioeconomic position and being especially disadvantaged. Future research should focus on the lower income brackets and poverty in particular. Because this group is usually underrepresented in sample-based studies, register-based studies may be especially valuable in this regard.

Finally, the overall results suggest that intergenerational correlations are largely (but not entirely) confounded by genetic similarity. Future research should attempt to identify non-familial factors that are causally related to both socioeconomic position and mental health, and to figure out what mediates the genetic effects on both.

Chapter 8: Concluding Remarks

In this thesis, I have attempted to advance our understanding of why socioeconomic position and mental health are correlated within and across generations. It is worth reiterating that these associations are robust and relatively large: It is no surprise that I found similar associations in my studies. When it comes to the "*why*", it is a bit more complicated. I have devoted large parts of this thesis to discussing assumptions and methodological considerations, as any interpretation of the findings could be misleading without understanding the crutches they stand on. It is these very assumptions that enable us to draw conclusions, so they must be taken seriously. By discussing these matters thoroughly, I hope I have made it possible for you – the reader – to evaluate the findings and the implications I describe without taking my word for it, and perhaps make up your own mind should some of the assumptions be a step to far.

Given the assumptions and considerations laid out in Chapter 5 and 7, a key takeaway from this thesis is that the association between socioeconomic differences and mental health seems to be *reproduced* in each generation, not merely continued. Future research should therefore shift focus from the family environment to understanding why individuals with different characteristics and dispositions end up with different socioeconomic positions and mental health. As for policy implications, these depend on our objectives (the "*ought*"). If the aim is to reduce social differences and its correlation with mental health, then we must consider strategies that aim to minimize the influence of different starting points in life on later outcomes.

References

Abdellaoui, A., & Verweij, K. J. H. (2021). Dissecting polygenic signals from genome-wide association studies on human behaviour. *Nature Human Behaviour*, *5*(6), 686-694. https://doi.org/10.1038/s41562-021-01110-y

Abdellaoui, A., Yengo, L., Verweij, K. J. H., & Visscher, P. M. (2023). 15 years of GWAS discovery: Realizing the promise. *The American Journal of Human Genetics*, *110*(2), 179-194. https://doi.org/https://doi.org/10.1016/j.ajhg.2022.12.011

Akee, R., Copeland, W., Costello, E. J., & Simeonova, E. (2018). How Does Household Income Affect Child Personality Traits and Behaviors? *American Economic Review*, *108*(3), 775-827. https://doi.org/10.1257/aer.20160133

APA. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5*. American Psychiatric Association.

Aristodemou, M. E., Kievit, R. A., Murray, A. L., Eisner, M., Ribeaud, D., & Fried, E. I. (2023). Common Cause Versus Dynamic Mutualism: An Empirical Comparison of Two Theories of Psychopathology in Two Large Longitudinal Cohorts. *Clinical Psychological Science*, 216770262311628. https://doi.org/10.1177/21677026231162814

Azzolini, F., Berentsen, G. D., Skaug, H. J., Hjelmborg, J. V. B., & Kaprio, J. A. (2022). The heritability of BMI varies across the range of BMI—a heritability curve analysis in a twin cohort. *International Journal of Obesity*, *46*(10), 1786-1791. https://doi.org/10.1038/s41366-022-01172-6

Bachman, J. G., & O'Malley, P. M. (1977). Self-esteem in young men: a longitudinal analysis of the impact of educational and occupational attainment. *Journal of Personality and Social Psychology*, *35*(6), 365-380. https://doi.org/10.1037//0022-3514.35.6.365

Baier, T., Eilertsen, E. M., Ystrøm, E., Zambrana, I. M., & Lyngstad, T. H. (2022). An anatomy of the intergenerational correlation of educational attainment – Learning from the educational attainments of Norwegian twins and their children. *Research in Social Stratification and Mobility*, *79*, 100691. https://doi.org/10.1016/j.rssm.2022.100691

Balbona, J. V., Kim, Y., & Keller, M. C. (2021). Estimation of Parental Effects Using Polygenic Scores. *Behavior Genetics*, *51*(3), 264-278. https://doi.org/10.1007/s10519-020-10032-w

Biele, G., de Aguas, J., & Varnet Pérez, T. (2022). What can we conclude about the effect of parental income on offspring mental health? *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyac144

Bor, J., Cohen, G. H., & Galea, S. (2017). Population health in an era of rising income inequality: USA, 1980-2015. *The Lancet*, *389*(10077), 1475-1490. https://doi.org/10.1016/S0140-6736(17)30571-8

Border, R., Athanasiadis, G., Buil, A., Schork, A. J., Cai, N., Young, A. I., Werge, T., Flint, J., Kendler, K. S., Sankararaman, S., Dahl, A. W., & Zaitlen, N. A. (2022). Cross-trait assortative mating is widespread and inflates genetic correlation estimates. *Science*, *378*(6621), 754-761. https://doi.org/10.1126/science.abo2059

Borghans, L., Golsteyn, B. H. H., Heckman, J. J., & Humphries, J. E. (2016). What grades and achievement tests measure. *Proceedings of the National Academy of Sciences*, *113*(47), 13354-13359. https://doi.org/10.1073/pnas.1601135113

Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry*, *16*(1), 5-13. https://doi.org/10.1002/wps.20375

Bortolus, R., Parazzini, F., Chatenoud, L., Benzi, G., Bianchi, M., & Marini, A. (1999). The epidemiology of multiple births. *Human Reproduction Update*, *5*(2), 179-187. https://doi.org/10.1093/humupd/5.2.179

Braveman, P. A., Cubbin, C., Egerter, S., Chideya, S., Marchi, K. S., Metzler, M., & Posner, S. (2005). Socioeconomic Status in Health ResearchOne Size Does Not Fit All. *JAMA*, *294*(22), 2879-2888. https://doi.org/10.1001/jama.294.22.2879

Brick, C., Hood, B., Ekroll, V., & De-Wit, L. (2022). Illusory Essences: A Bias Holding Back Theorizing in Psychological Science. *Perspectives on Psychological Science*, *17*(2), 491-506. https://doi.org/10.1177/1745691621991838

Bulmer, M. G. (1980). *The Mathematical Theory of Quantitative Genetics*. Oxford University Press.

Caspi, A., & Moffitt, T. E. (2018). All for One and One for All: Mental Disorders in One Dimension. *American Journal of Psychiatry*, *175*(9), 831-844. https://doi.org/10.1176/appi.ajp.2018.17121383

Cheesman, R., Eilertsen, E. M., Ayorech, Z., Borgen, N. T., Andreassen, O. A., Larsson, H., Zachrisson, H., Torvik, F. A., & Ystrom, E. (2022). How interactions between ADHD and schools affect educational achievement: a family-based genetically sensitive study. *Journal of Child Psychology and Psychiatry*, *63*(10), 1174-1185. https://doi.org/10.1111/jcpp.13656

Chou, I.-J., Kuo, C.-F., Huang, Y.-S., Grainge, M. J., Valdes, A. M., See, L.-C., Yu, K.-H., Luo, S.-F., Huang, L.-S., Tseng, W.-Y., Zhang, W., & Doherty, M. (2016). Familial Aggregation and Heritability of Schizophrenia and Co-aggregation of Psychiatric Illnesses in Affected Families. *Schizophrenia Bulletin*, *43*(5), 1070-1078. https://doi.org/10.1093/schbul/sbw159

Cloninger, C. R. (1980). Interpretation of intrinsic and extrinsic structural relations by path analysis: theory and applications to assortative mating. *Genetical Research*, *36*(2), 133-145. https://doi.org/10.1017/s0016672300019765

Corfield, E. C., Frei, O., Shadrin, A. A., Rahman, Z., Lin, A., Athanasiu, L., Akdeniz, B. C., Hannigan, L., Wootton, R. E., Austerberry, C., Hughes, A., Tesli, M., Westlye, L. T., Stefánsson, H., Stefánsson, K., Njølstad, P. R., Magnus, P., Davies, N. M., Appadurai, V., . . . Havdahl, A. (2022). *The Norwegian Mother, Father, and Child cohort study (MoBa) genotyping data resource: MoBaPsychGen pipeline v.1*. BioRxiv. https://doi.org/10.1101/2022.06.23.496289

Costello, E. J., Compton, S. N., Keeler, G., & Angold, A. (2003). Relationships Between Poverty and Psychopathology. *JAMA*, *290*(15), 2023. https://doi.org/10.1001/jama.290.15.2023

Cronbach, L. J., & Meehl, P. E. (1955). Construct validity in psychological tests. *Psychological Bulletin*, *52*(4), 281-302. https://doi.org/10.1037/h0040957

Cuthbert, B. N. (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry*, *13*(1), 28-35. https://doi.org/10.1002/wps.20087

Dalsgaard, S., John Mcgrath, Dinesen Østergaard, S., R. Wray, N., Bøcker Pedersen, C., Bo Mortensen, P., & Liselotte Petersen. (2020). Association of Mental Disorder in Childhood and Adolescence With Subsequent Educational Achievement. *JAMA Psychiatry*, *77*(8), 797. https://doi.org/10.1001/jamapsychiatry.2020.0217

Davies, N. M., Dickson, M., Davey Smith, G., Van Den Berg, G. J., & Windmeijer, F. (2018). The causal effects of education on health outcomes in the UK Biobank. *Nature Human Behaviour*, *2*(2), 117-125. https://doi.org/10.1038/s41562-017-0279-y

Demange, P. A., Boomsma, D. I., Van Bergen, E., & Nivard, M. G. (2023). *Evaluating the causal relationship between educational attainment and mental health*. BioRxiv. https://doi.org/10.1101/2023.01.26.23285029

Diemer, M. A., Mistry, R. S., Wadsworth, M. E., López, I., & Reimers, F. (2013). Best Practices in Conceptualizing and Measuring Social Class in Psychological Research. *Analyses of Social Issues and Public Policy*, *13*(1), 77-113. https://doi.org/https://doi.org/10.1111/asap.12001

Dohrenwend, B. P., Levav, I., Shrout, P. E., Schwartz, S., Naveh, G., Link, B. G., Skodol, A. E., & Stueve, A. (1992). Socioeconomic Status and Psychiatric Disorders: The Causation-Selection Issue. *Science*, *255*(5047), 946-952. https://doi.org/doi:10.1126/science.1546291

Duckworth, A. L., & Seligman, M. E. P. (2006). Self-discipline gives girls the edge: Gender in self-discipline, grades, and achievement test scores. *Journal of Educational Psychology*, *98*, 198-208. https://doi.org/10.1037/0022-0663.98.1.198

Duffy, D. L., & Martin, N. G. (1994). Inferring the direction of causation in cross-sectional twin data: Theoretical and empirical considerations. *Genetic Epidemiology*, *11*(6), 483-502. https://doi.org/https://doi.org/10.1002/gepi.1370110606

Eilertsen, E. M., Cheesman, R., Ayorech, Z., Røysamb, E., Pingault, J. B., Njølstad, P. R., Andreassen, O. A., Havdahl, A., Mcadams, T. A., Torvik, F. A., & Ystrøm, E. (2022). On the importance of parenting in externalizing disorders: an evaluation of indirect genetic effects in families. *Journal of Child Psychology and Psychiatry*, *63*(10), 1186-1195. https://doi.org/10.1111/jcpp.13654

Eronen, M. I., & Bringmann, L. F. (2021). The Theory Crisis in Psychology: How to Move Forward. *Perspectives on Psychological Science*, 174569162097058. https://doi.org/10.1177/1745691620970586

Evensen, M., Klitkou, S. T., Tollånes, M. C., Øverland, S., Lyngstad, T. H., Vollset, S. E., & Kinge, J. M. (2021). Parental income gradients in adult health: a national cohort study. *BMC Medicine*, *19*(1). https://doi.org/10.1186/s12916-021-02022-4

Fisher, R. A. (1918). The Correlation between Relatives on the Supposition of Mendelian Inheritance. *Transactions of the Royal Society of Edinburgh*, *52*(2), 399-433. https://doi.org/10.1017/s0080456800012163

Flake, J. K., & Fried, E. I. (2020). Measurement Schmeasurement: Questionable Measurement Practices and How to Avoid Them. *Advances in Methods and Practices in Psychological Science*, *3*(4), 456-465. https://doi.org/10.1177/2515245920952393

Fried, E. I., Flake, J. K., & Robinaugh, D. J. (2022). Revisiting the theoretical and methodological foundations of depression measurement. *Nature Reviews Psychology*, 358–368. https://doi.org/10.1038/s44159-022-00050-2

Fristad, M. A., & Clayton, T. L. (1991). Family dysfunction and family psychopathology in child psychiatry outpatients. *Journal of Family Psychology*, *5*(1), 46-59. https://doi.org/10.1037/0893-3200.5.1.46

Fryers, T., Melzer, D., & Jenkins, R. (2003). Social inequalities and the common mental disorders. *Social Psychiatry and Psychiatric Epidemiology*, *38*(5), 229-237. https://doi.org/10.1007/s00127-003-0627-2

Fujiwara, T., & Kawachi, I. (2009). Is education causally related to better health? A twin fixed-effect study in the USA. *International Journal of Epidemiology*, *38*(5), 1310-1322. https://doi.org/10.1093/ije/dyp226

Giangrande, E. J., Weber, R. S., & Turkheimer, E. (2022). What Do We Know About the Genetic Architecture of Psychopathology? *Annual Review of Clinical Psychology*, *18*(1), 19-42. https://doi.org/10.1146/annurev-clinpsy-081219-091234

Gleick, J. (1987). *Chaos: Making a New Science*. Penguin.

Goldberg, D. (2001). Vulnerability factors for common mental illnesses. *British Journal of Psychiatry*, *178*(S40), s69-s71. https://doi.org/10.1192/bjp.178.40.s69

Goldman, N. (1994). Social factors and health: the causation-selection issue revisited. *Proceedings of the National Academy of Sciences*, *91*(4), 1251-1255. https://doi.org/10.1073/pnas.91.4.1251

Gonggrijp, B., Silventoinen, K., Dolan, C. V., Boomsma, D., Kaprio, J., & Willemsen, G. (2023). The mechanisms of assortative mating for educational attainment: insights from two European twin-spouse cohorts. *Frontiers in Genetics*, *14*, 910. https://doi.org/10.3389/fgene.2023.1150697

Grosz, M. P., Rohrer, J. M., & Thoemmes, F. (2020). The Taboo Against Explicit Causal Inference in Nonexperimental Psychology. *Perspectives on Psychological Science*, *15*(5), 1243-1255. https://doi.org/10.1177/1745691620921521

Hackman, D. A., Farah, M. J., & Meaney, M. J. (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews Neuroscience*, *11*(9), 651-659. https://doi.org/10.1038/nrn2897

Halpern-Manners, A., Schnabel, L., Hernandez, E. M., Silberg, J. L., & Eaves, L. J. (2016). The Relationship between Education and Mental Health: New Evidence from a Discordant Twin Study. *Social Forces*, *95*(1), 107-131. https://doi.org/10.1093/sf/sow035

Harden, K. P. (2021). *The Genetic Lottery: Why DNA Matters for Social Equality*. Princeton University Press. https://books.google.no/books?id=R9oiEAAAQBAJ

Haslam, N., Holland, E., & Kuppens, P. (2012). Categories versus dimensions in personality and psychopathology: a quantitative review of taxometric research. *Psychological Medicine*, *42*(5), 903-920. https://doi.org/10.1017/S0033291711001966

Heath, A. C., Berg, K., Eaves, L. J., Solaas, M. H., Corey, L. A., Sundet, J., Magnus, P., & Nance, W. E. (1985). Education policy and the heritability of educational attainment. *Nature*, *314*(6013), 734-736. https://doi.org/10.1038/314734a0

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders. *American Journal of Psychiatry*, *158*(10), 1568-1578. https://doi.org/10.1176/appi.ajp.158.10.1568

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2018). Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. *Biological Psychiatry*, *83*(6), 492-498. https://doi.org/10.1016/j.biopsych.2017.08.017

Horwitz, A. V. (2021). *DSM: A History of Psychiatry's Bible*. Johns Hopkins University Press. https://books.google.no/books?id=qY0vEAAAQBAJ

Horwitz, T. B., Balbona, J. V., Paulich, K. N., & Keller, M. C. (2023). *Correlations between human mating partners: a comprehensive meta-analysis of 22 traits and raw data analysis of 133 traits in the UK Biobank*. BioRxiv. www.doi.org/10.1101/2022.03.19.484997

Hyman, S. E. (2010). The Diagnosis of Mental Disorders: The Problem of Reification. *Annual Review of Clinical Psychology*, *6*(1), 155-179. https://doi.org/10.1146/annurev.clinpsy.3.022806.091532

Jangmo, A., Kuja-Halkola, R., Pérez-Vigil, A., Almqvist, C., Bulik, C. M., D'Onofrio, B., Lichtenstein, P., Ahnemark, E., Werner-Kiechle, T., & Larsson, H. (2021). Attention-deficit/hyperactivity disorder and occupational outcomes: The role of educational attainment, comorbid developmental disorders, and intellectual disability. *PLOS ONE*, *16*(3), e0247724. https://doi.org/10.1371/journal.pone.0247724

Jenkins, R., Bhugra, D., Bebbington, P., Brugha, T., Farrell, M., Coid, J., Fryers, T., Weich, S., Singleton, N., & Meltzer, H. (2008). Debt, income and mental disorder in the general population. *Psychological Medicine*, *38*(10), 1485-1493. https://doi.org/10.1017/s0033291707002516

Kaplan, J. M., & Turkheimer, E. (2021). Galton's Quincunx: Probabilistic causation in developmental behavior genetics. *Studies in History and Philosophy of Science Part A*, *88*, 60-69. https://doi.org/https://doi.org/10.1016/j.shpsa.2021.04.001

Kessler, R. C., Tat Chiu, W., Olga Demler, & E. Walters, E. (2005). Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617. https://doi.org/10.1001/archpsyc.62.6.617

Keyes, K. M., & Susser, E. (2022). Uses and misuses of sibling designs. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyac187

Kinge, J. M., Heibø Modalsli, J., Simon Øverland, Kristian Gjessing, H., Christophersen Tollånes, M., Kristin Knudsen, A., Vegard Skirbekk, Heine Strand, B., Eldevik Håberg, S., & Emil Vollset, S. (2019). Association of Household Income With Life Expectancy and Cause-Specific Mortality in Norway, 2005-2015. *JAMA*, *321*(19), 1916. https://doi.org/10.1001/jama.2019.4329

Kinge, J. M., Øverland, S., Flatø, M., Dieleman, J., Røgeberg, O., Magnus, M. C., Evensen, M., Tesli, M., Skrondal, A., Stoltenberg, C., Vollset, S. E., Håberg, S., & Torvik, F. A. (2021). Parental income and mental disorders in children and adolescents: prospective register-based study. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyab066

Knopik, V. S., Neiderhiser, J. M., DeFries, J. C., & Plomin, R. (2017). *Behavioral Genetics* (7th ed.). Worth Publishers.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., Brown, T. A., Carpenter, W. T., Caspi, A., Clark, L. A., Eaton, N. R., Forbes, M. K., Forbush, K. T., Goldberg, D., Hasin, D., Hyman, S. E., Ivanova, M. Y., Lynam, D. R., Markon, K., . . . Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, *126*(4), 454-477. https://doi.org/10.1037/abn0000258

Kröger, H., Pakpahan, E., & Hoffmann, R. (2015). What causes health inequality? A systematic review on the relative importance of social causation and health selection. *European Journal of Public Health*, *25*(6), 951-960. https://doi.org/10.1093/eurpub/ckv111

Krueger, R. F., & Eaton, N. R. (2015). Transdiagnostic factors of mental disorders. *World Psychiatry*, *14*(1), 27-29. https://doi.org/10.1002/wps.20175

Lahey, B. B., Moore, T. M., Kaczkurkin, A. N., & Zald, D. H. (2021). Hierarchical models of psychopathology: empirical support, implications, and remaining issues. *World Psychiatry*, *20*(1), 57-63. https://doi.org/10.1002/wps.20824

Larsson, H., Sariaslan, A., Långström, N., D'Onofrio, B., & Lichtenstein, P. (2014). Family income in early childhood and subsequent attention deficit/hyperactivity disorder: a quasi-experimental study. *Journal of Child Psychology and Psychiatry*, *55*(5), 428-435. https://doi.org/10.1111/jcpp.12140

Ledberg, A., Rajaleid, K., & Modin, B. (2022). Are there really no causal associations between childhood family income and subsequent outcomes? *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyac016

Liao, T. F., & De Maio, F. (2021). Association of Social and Economic Inequality With Coronavirus Disease 2019 Incidence and Mortality Across US Counties. *JAMA Network Open*, *4*(1), e2034578. https://doi.org/10.1001/jamanetworkopen.2020.34578

Lorant, V., Croux, C., Weich, S., Deliège, D., Mackenbach, J., & Ansseau, M. (2007). Depression and socio-economic risk factors: 7-year longitudinal population study. *British Journal of Psychiatry*, *190*(4), 293-298. https://doi.org/10.1192/bjp.bp.105.020040

Lorant, V., Deliège, D., Eaton, W., Robert, A., Philippot, P., & Ansseau, M. (2003). Socioeconomic Inequalities in Depression: A Meta-Analysis. *American Journal of Epidemiology*, *157*(2), 98-112. https://doi.org/10.1093/aje/kwf182

Lundberg, I., Johnson, R., & Stewart, B. M. (2021). What Is Your Estimand? Defining the Target Quantity Connects Statistical Evidence to Theory. *American Sociological Review*, *86*(3), 532-565. https://doi.org/10.1177/00031224211004187

Luo, Y., & Waite, L. J. (2005). The Impact of Childhood and Adult SES on Physical, Mental, and Cognitive Well-Being in Later Life. *The Journals of Gerontology: Series B*, *60*(2), S93-S101. https://doi.org/10.1093/geronb/60.2.S93

Lynch, M., & Walsh, B. (1998). *Genetics and Analysis of Quantitative Traits*. Sinauer Associates, Inc.

Macintyre, A., Ferris, D., Gonçalves, B., & Quinn, N. (2018). What has economics got to do with it? The impact of socioeconomic factors on mental health and the case for collective action. *Palgrave Communications*, *4*(1). https://doi.org/10.1057/s41599-018-0063-2

Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A. K., Handal, M., Haugen, M., Høiseth, G., Knudsen, G. P., Paltiel, L., Schreuder, P., Tambs, K., Vold, L., & Stoltenberg, C. (2016). Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology*, *45*(2), 382-388. https://doi.org/10.1093/ije/dyw029

Marees, A. T., Smit, D. J. A., Abdellaoui, A., Nivard, M. G., Van Den Brink, W., Denys, D., Galama, T. J., Verweij, K. J. H., & Derks, E. M. (2021). Genetic correlates of socio-economic status influence the pattern of shared heritability across mental health traits. *Nature Human Behaviour*. https://doi.org/10.1038/s41562-021-01053-4

Markussen, E., Daus, S., & Hovdhaugen, E. (2020). *Fra 16 til 30: Om utdanning, jobb og inntekt for 9341 unge fra Østlandet, 14 år etter at de gikk ut av tiende klasse i 2002* (2020-2). NIFU. https://hdl.handle.net/11250/2675748

Mcadams, T. A., Hannigan, L. J., Eilertsen, E. M., Gjerde, L. C., Ystrom, E., & Rijsdijk, F. V. (2018). Revisiting the Children-of-Twins Design: Improving Existing Models for the Exploration of Intergenerational Associations. *Behavior Genetics*, *48*(5), 397-412. https://doi.org/10.1007/s10519-018-9912-4

Mcgrath, J. J., Lim, C. C. W., Plana-Ripoll, O., Holtz, Y., Agerbo, E., Momen, N. C., Mortensen, P. B., Pedersen, C. B., Abdulmalik, J., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., Bunting, B., De Almeida, J. M. C., De Girolamo, G., De Vries, Y. A., Florescu, S., . . . De Jonge, P. (2020). Comorbidity within mental disorders: a comprehensive analysis based on 145 990 survey respondents from 27 countries. *Epidemiology and Psychiatric Sciences*, *29*. https://doi.org/10.1017/s2045796020000633

Meng, X., Liu, A., D'Arcy, C., & Caron, J. (2020). Baseline income, follow-up income, income mobility and their roles in mental disorders: a longitudinal intra-generational community-based study. *BMC Psychiatry*, *20*(1). https://doi.org/10.1186/s12888-020-02578-0

Merton, R. K. (1968). The Matthew Effect in Science. *Science*, *159*(3810), 56-63. https://doi.org/doi:10.1126/science.159.3810.56

Meyer, M. N., Appelbaum, P. S., Benjamin, D. J., Callier, S. L., Comfort, N., Conley, D., Freese, J., Garrison, N. A., Hammonds, E. M., Harden, K. P., Lee, S. S. J., Martin, A. R., Martschenko, D. O., Neale, B. M., Palmer, R. H. C., Tabery, J., Turkheimer, E., Turley, P., & Parens, E. (2023). Wrestling with Social and Behavioral Genomics: Risks, Potential Benefits, and Ethical Responsibility. *Hastings Center Report*, *53*(S1). https://doi.org/10.1002/hast.1477

Moffitt, T. E., L. Arseneault, D. Belsky, N. Dickson, J. Hancox, R., H. Harrington, R. Houts, R. Poulton, W. Roberts, B., S. Ross, R. Sears, M., M. Thomson, W., & A. Caspi. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, *108*(7), 2693-2698. https://doi.org/10.1073/pnas.1010076108

Munafò, M. R., Tilling, K., Taylor, A. E., Evans, D. M., & Davey Smith, G. (2018). Collider scope: when selection bias can substantially influence observed associations. *International Journal of Epidemiology*, *47*(1), 226-235. https://doi.org/10.1093/ije/dyx206

Muntaner, C., Eaton, W. W., Miech, R., & O'Campo, P. (2004). Socioeconomic Position and Major Mental Disorders. *Epidemiologic Reviews*, *26*(1), 53-62. https://doi.org/10.1093/epirev/mxh001

Musser, E. D., Hawkey, E., Kachan-Liu, S. S., Lees, P., Roullet, J.-B., Goddard, K., Steiner, R. D., & Nigg, J. T. (2014). Shared familial transmission of autism spectrum and attention-deficit/hyperactivity disorders. *Journal of Child Psychology and Psychiatry*, *55*(7), 819-827. https://doi.org/10.1111/jcpp.12201

Neale, M. C., Hunter, M. D., Pritikin, J. N., Zahery, M., Brick, T. R., Kirkpatrick, R. M., Estabrook, R., Bates, T. C., Maes, H. H., & Boker, S. M. (2016). OpenMx 2.0: Extended Structural Equation and Statistical Modeling. *Psychometrika*, *81*(2), 535-549. https://doi.org/10.1007/s11336-014-9435-8

Newson, J. J., Hunter, D., & Thiagarajan, T. C. (2020). The Heterogeneity of Mental Health Assessment. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00076

Nilsen, R. M., Vollset, S. E., Gjessing, H. K., Skjærven, R., Melve, K. K., Schreuder, P., Alsaker, E. R., Haug, K., Daltveit, A. K., & Magnus, P. (2009). Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatric and Perinatal Epidemiology*, *23*(6), 597-608. https://doi.org/https://doi.org/10.1111/j.1365-3016.2009.01062.x

Nilsen, T. S., Brandt, I., Magnus, P., & Harris, J. R. (2012). The Norwegian Twin Registry. *Twin Research and Human Genetics*, *15*(6), 775-780. https://doi.org/10.1017/thg.2012.57

Nordmo, M., Kinge, J. M., Reme, B.-A., Flatø, M., Surén, P., Wörn, J., Magnus, P., Stoltenberg, C., & Torvik, F. A. (2022). The educational burden of disease: a cohort study. *The Lancet Public Health*, *7*(6), e549-e556. https://doi.org/10.1016/s2468-2667(22)00059-7

Nordsletten, A. E., Henrik Larsson, J. Crowley, J., Catarina Almqvist, Paul Lichtenstein, & David Mataix-Cols. (2016). Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders. *JAMA Psychiatry*, *73*(4), 354. https://doi.org/10.1001/jamapsychiatry.2015.3192

OECD. (2016). *PISA 2015 Results (Volume I)*. OECD Publishing. https://doi.org/10.1787/9789264266490-en

OECD. (2022). *Income inequality (indicator)*. Retrieved November 2022 from www.doi.org/10.1787/459aa7f1-en

Okbay, A., Wu, Y., Wang, N., Jayashankar, H., Bennett, M., Nehzati, S. M., Sidorenko, J., Kweon, H., Goldman, G., Gjorgjieva, T., Jiang, Y., Hicks, B., Tian, C., Hinds, D. A., Ahlskog, R., Magnusson, P. K. E., Oskarsson, S., Hayward, C., Campbell, A., . . . Young, A. I. (2022). Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nature Genetics*, *54*(4), 437-449. https://doi.org/10.1038/s41588-022-01016-z

Paige Harden, K., Eric Turkheimer, & C. Loehlin, J. (2007). Genotype by Environment Interaction in Adolescents' Cognitive Aptitude. *Behavior Genetics*, *37*(2), 273-283. https://doi.org/10.1007/s10519-006-9113-4

Palmer, T. (2022). *The Primacy of Doubt: From climate change to quantum physics, how the science of uncertainty can help predict and understand our chaotic world*. OUP Oxford. https://books.google.no/books?id=viyWEAAAQBAJ

Patel, V., Burns, J. K., Dhingra, M., Tarver, L., Kohrt, B. A., & Lund, C. (2018). Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. *World Psychiatry*, *17*(1), 76-89. https://doi.org/10.1002/wps.20492

Paul, K. I., & Moser, K. (2009). Unemployment impairs mental health: Meta-analyses. *Journal of Vocational Behavior*, *74*(3), 264-282. https://doi.org/https://doi.org/10.1016/j.jvb.2009.01.001

Pazokitoroudi, A., Chiu, A. M., Burch, K. S., Pasaniuc, B., & Sankararaman, S. (2021). Quantifying the contribution of dominance deviation effects to complex trait variation in biobank-scale data. *The American Journal of Human Genetics*, *108*(5), 799-808. https://doi.org/10.1016/j.ajhg.2021.03.018

Pearl, J., & Mackenzie, D. (2018). *The Book of Why: The New Science of Cause and Effect*. Basic Books. https://books.google.no/books?id=BzM0DwAAQBAJ

Peverill, M., Dirks, M. A., Narvaja, T., Herts, K. L., Comer, J. S., & Mclaughlin, K. A. (2021). Socioeconomic status and child psychopathology in the United States: A meta-analysis of population-based studies. *Clinical Psychology Review*, *83*, 101933. https://doi.org/10.1016/j.cpr.2020.101933

Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., De Jonge, P., Fan, C. C., Degenhardt, L., Ganna, A., Greve, A. N., Gunn, J., Iburg, K. M., Kessing, L. V., Lee, B. K., Lim, C. C. W., Mors, O., Nordentoft, M., Prior, A., Roest, A. M., . . . Mcgrath, J. J. (2019). Exploring Comorbidity Within Mental Disorders Among a Danish National Population. *JAMA Psychiatry*, *76*(3), 259. https://doi.org/10.1001/jamapsychiatry.2018.3658

Plomin, R., Haworth, C. M. A., & Davis, O. S. P. (2009). Common disorders are quantitative traits. *Nature Reviews Genetics*, *10*(12), 872-878. https://doi.org/10.1038/nrg2670

Polderman, T. J. C., Benyamin, B., De Leeuw, C. A., Sullivan, P. F., Bochoven, A. V., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics*, *47*(7), 702-709. https://doi.org/10.1038/ng.3285

R Core Team. (2022). *R: A language and environment for statistical computing*. In R Foundation for Statistical Computing. https://www.R-project.org/

Rasmussen, S. H. R., Ludeke, S., & Hjelmborg, J. V. B. (2019). A Major Limitation of the Direction of Causation Model: Non-Shared Environmental Confounding. *Twin Research and Human Genetics*, *22*(1), 14-26. https://doi.org/10.1017/thg.2018.67

Rimfeld, K., Krapohl, E., Trzaskowski, M., Coleman, J. R. I., Selzam, S., Dale, P. S., Esko, T., Metspalu, A., & Plomin, R. (2018). Genetic influence on social outcomes during and after the Soviet era in Estonia. *Nature Human Behaviour*, *2*(4), 269-275. https://doi.org/10.1038/s41562-018-0332-5

Ritsher, J. E. B., Warner, V., Johnson, J. G., & Dohrenwend, B. P. (2001). Inter-generational longitudinal study of social class and depression: A test of social causation and social selection models. *British Journal of Psychiatry*, *178*(S40), s84-s90. https://doi.org/10.1192/bjp.178.40.s84

Rod, N. H., Lange, T., & Petersen, A. H. (2021). Do sibling comparisons answer the causal question? In response to 'No causal associations between childhood family income and subsequent psychiatric disorders, substance misuse and violent crime arrests'. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyab235

Rohrer, J. M. (2018). Thinking Clearly About Correlations and Causation: Graphical Causal Models for Observational Data. *Advances in Methods and Practices in Psychological Science*, *1*(1), 27-42. https://doi.org/10.1177/2515245917745629

Sariaslan, A., Mikkonen, J., Aaltonen, M., Hiilamo, H., Martikainen, P., & Fazel, S. (2021). No causal associations between childhood family income and subsequent psychiatric disorders, substance misuse and violent crime arrests: a nationwide Finnish study of >650 000 individuals and their siblings. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyab099

Sariaslan, A., Mikkonen, J., Aaltonen, M., Hiilamo, H., Martikainen, P., & Fazel, S. (2022). What can siblings and cousins tell us about the role of early life family income in the aetiologies of violent crime, substance misuse and psychiatric morbidity? *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyac035

Shen, H., Magnusson, C., Rai, D., Lundberg, M., Lê-Scherban, F., Dalman, C., & Lee, B. K. (2016). Associations of Parental Depression With Child School Performance at Age 16 Years in Sweden. *JAMA Psychiatry*, *73*(3), 239. https://doi.org/10.1001/jamapsychiatry.2015.2917

Silventoinen, K., Jelenkovic, A., Sund, R., Latvala, A., Honda, C., Inui, F., Tomizawa, R., Watanabe, M., Sakai, N., Rebato, E., Busjahn, A., Tyler, J., Hopper, J. L., Ordoñana, J. R., Sánchez-Romera, J. F., Colodro-Conde, L., Calais-Ferreira, L., Oliveira, V. C., Ferreira, P. H., . . . Kaprio, J. (2020). Genetic and environmental variation in educational attainment: an individual-based analysis of 28 twin cohorts. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-69526-6

Sirin, S. R. (2005). Socioeconomic Status and Academic Achievement: A Meta-Analytic Review of Research. *Review of Educational Research*, *75*(3), 417-453. https://doi.org/10.3102/00346543075003417

Sjaarda, J., & Kutalik, Z. (2023). Partner choice, confounding and trait convergence all contribute to phenotypic partner similarity. *Nature Human Behaviour*, 776–789. https://doi.org/10.1038/s41562-022-01500-w

Statistics Norway. (2020). *11689: Elever, etter kjønn, grunnskolepoeng og foreldrenes utdanningsnivå 2015 - 2019*. Retrieved August 24, 2020 from https://www.ssb.no/statbank/table/11689

Statistics Norway. (2022). *12935: Utdanningsnivå, etter foreldrenes utdanningsnivå og kjønn 2018 - 2022*. Retrieved May 24, 2023 from https://www.ssb.no/statbank/table/12935/

Steinhausen, H.-C., Foldager, L., Perto, G., & Munk-Jørgensen, P. (2009). Family aggregation of mental disorders in the nationwide Danish three generation study. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(5), 270-277. https://doi.org/10.1007/s00406-008-0865-0

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *American Journal of Psychiatry*, *157*(10), 1552-1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Sunde, H. F., Kleppestø, T. H., Gustavson, K., Nordmo, M., Reme, B. A., & Torvik, F. A. (2022). The ADHD deficit in school performance across sex and parental education: A prospective sibling-comparison register study of 344,152 Norwegian adolescents. *JCPP Advances*. https://doi.org/10.1002/jcv2.12064

Tambs, K., Kendler, K. S., Reichborn-Kjennerud, T., Aggen, S. H., Harris, J. R., Neale, M. C., Hettema, J. M., Sundet, J. M., Battaglia, M., & Røysamb, E. (2012). Genetic and environmental contributions to the relationship between education and anxiety disorders - a twin study. *Acta Psychiatrica Scandinavica*, *125*(3), 203-212. https://doi.org/10.1111/j.1600-0447.2011.01799.x

Terrier, C. (2020). Boys lag behind: How teachers' gender biases affect student achievement. *Economics of Education Review*, *77*, 101981. https://doi.org/10.1016/j.econedurev.2020.101981

The World Bank. (2022). *Gini Index*. Retrieved November 2022 from https://data.worldbank.org/indicator/SI.POV.GINI

Thomson, R. M., Igelström, E., Purba, A. K., Shimonovich, M., Thomson, H., McCartney, G., Reeves, A., Leyland, A., Pearce, A., & Katikireddi, S. V. (2022). How do income changes impact on mental health and wellbeing for working-age adults? A systematic review and meta-analysis. *The Lancet Public Health*, *7*(6), e515-e528. https://doi.org/10.1016/S2468-2667(22)00058-5

Torvik, F. A., Eilertsen, E. M., Hannigan, L. J., Cheesman, R., Howe, L. J., Magnus, P., Reichborn-Kjennerud, T., Andreassen, O. A., Njølstad, P. R., Havdahl, A., & Ystrom, E. (2022). Modeling assortative mating and genetic similarities between partners, siblings, and in-laws. *Nature Communications*, *13*(1), 1108. https://doi.org/10.1038/s41467-022-28774-y

Torvik, F. A., Eilertsen, E. M., McAdams, T. A., Gustavson, K., Zachrisson, H. D., Brandlistuen, R., Gjerde, L. C., Havdahl, A., Stoltenberg, C., Ask, H., & Ystrom, E. (2020). Mechanisms linking parental educational attainment with child ADHD, depression, and academic problems: a study of extended families in The Norwegian Mother, Father and Child Cohort Study. *Journal of Child Psychology and Psychiatry*, *61*(9). https://doi.org/10.1111/jcpp.13197

Torvik, F. A., Flatø, M., Mcadams, T. A., Colman, I., Silventoinen, K., & Stoltenberg, C. (2021). Early Puberty Is Associated With Higher Academic Achievement in Boys and Girls and Partially Explains Academic Sex Differences. *Journal of Adolescent Health*, *69*(3), 503-510. https://doi.org/10.1016/j.jadohealth.2021.02.001

Tucker-Drob, E. M., & Bates, T. C. (2016). Large Cross-National Differences in Gene × Socioeconomic Status Interaction on Intelligence. *Psychological Science*, *27*(2), 138-149. https://doi.org/10.1177/0956797615612727

Turkheimer, E. (2000). Three Laws of Behavior Genetics and What They Mean. *Current Directions in Psychological Science*, *9*(5), 160-164. https://doi.org/10.1111/1467-8721.00084

Uffelmann, E., Huang, Q. Q., Munung, N. S., de Vries, J., Okada, Y., Martin, A. R., Martin, H. C., Lappalainen, T., & Posthuma, D. (2021). Genome-wide association studies. *Nature Reviews Methods Primers*, *1*(1), 59. https://doi.org/10.1038/s43586-021-00056-9

Vejrup, K., Magnus, P., & Magnus, M. (2022). Lost to follow-up in the Norwegian mother, father and child cohort study. *Paediatric and Perinatal Epidemiology*, *36*(2), 300-309. https://doi.org/10.1111/ppe.12821

Verhoef, E., Demontis, D., Burgess, S., Shapland, C. Y., Dale, P. S., Okbay, A., Neale, B. M., Faraone, S. V., Stergiakouli, E., Davey Smith, G., Fisher, S. E., Børglum, A. D., & St Pourcain, B. (2019). Disentangling polygenic associations between attention-deficit/hyperactivity disorder, educational attainment, literacy and language. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-018-0324-2

Waters, C. K. (2007). Causes That Make a Difference. *Journal of Philosophy*, *104*(11), 551-579. https://doi.org/10.5840/jphil2007104111

Weich, S., Lewis, G., & Jenkins, S. P. (2001). Income inequality and the prevalence of common mental disorders in Britain. *British Journal of Psychiatry*, *178*(3), 222-227. https://doi.org/10.1192/bjp.178.3.222

Westfall, J., & Yarkoni, T. (2016). Statistically Controlling for Confounding Constructs Is Harder than You Think. *PLOS ONE*, *11*(3), e0152719. https://doi.org/10.1371/journal.pone.0152719

WHO. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization.

WHO. (2022). *World mental health report: transforming mental health for all*. https://www.who.int/publications/i/item/9789240049338

WONCA. (2005). *ICPC-2-R: International Classification of Primary Care*. Oxford University Press.

Wright, S. (1921). Correlation and Causation. *Journal of Agricultural Research*, *20*, 557-585.

Wright, S. (1934). The Method of Path Coefficients. *The Annals of Mathematical Statistics*, *5*(3), 161-215. http://www.jstor.org/stable/2957502

Young, A. I. (2019). Solving the missing heritability problem. *PLOS Genetics*, *15*(6), e1008222. https://doi.org/10.1371/journal.pgen.1008222

Paper 1

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Sunde, H. F., Kleppestø, T. H., Gustavson, K., Nordmo, M., Reme, B. A., & Torvik, F. A. (2022). The ADHD deficit in school performance across sex and parental education: A prospective sibling-comparison register study of 344,152 Norwegian adolescents. *JCPP Advances*. https://doi.org/10.1002/jcv2.12064

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ORIGINAL ARTICLE

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The ADHD deficit in school performance across sex and parental education: A prospective sibling-comparison register study of 344,152 Norwegian adolescents

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Abstract

Background: Attention-Deficit Hyperactivity Disorder (ADHD) is associated with impaired school performance, but the impact of ADHD may vary across sex, family background, and school subjects. By using prospective population-wide register data, we describe impairment in academic performance related to ADHD across different school subjects and investigate how this impairment differ across sex and parental education.

Methods: We examined grades and Grade Point Averages (GPA) at age ~16 among 344,152 Norwegian children born between 1997 and 2002. We linked grades with diagnoses from publicly funded general practitioners and with demographic information. Associations between ADHD diagnosed between age 10 and 16 and school performance were estimated with linear models, including sibling-models which control for unobserved variables shared within families.

Results: Children with ADHD (4.0%) had −1.11 standard deviations lower GPAs compared to children without ADHD. This difference remained substantial after adjusting for demographic factors (−0.87), comorbid mental disorders (−0.82), early school performance (−0.54), and when comparing full siblings (−0.60). The relative ADHD deficit was 22% larger for girls than for boys and 39% larger for children with highly educated parents than for children of parents without completed high school, but the absolute deficit was smaller.

Conclusion: The ADHD deficit in school performance was large and not easily attributable to other factors. Because the ADHD deficit was large in all school subjects, interventions should ideally address factors that affect school performance broadly, although targeting theoretical subjects specifically may be most effective given limited resources.

KEYWORDS

ADHD, register data, school performance, sex differences, socioeconomic status

INTRODUCTION

Attention Deficit-Hyperactivity Disorder (ADHD) is a heritable neurodevelopmental disorder characterized by dysfunctional inattention, impulsivity, and hyperactivity (APA, 2013). ADHD has substantial socioeconomic costs, both for individuals and society (Faraone et al., 2021). Reduced school performance may be partially responsible for this: ADHD is associated with impaired school performance (Arnold et al., 2020; Daley & Birchwood, 2010; Kent et al., 2011; Polderman et al., 2010; Sayal et al., 2015), which again is an important determinant for adult education, employment, and income (Jangmo et al., 2021; Markussen et al., 2020).

Attention-Deficit Hyperactivity Disorder is substantially more prevalent among boys than girls and among children of parents with less education or less income (Kinge et al., 2021; Larsson et al., 2014; Russell et al., 2016; Torvik et al., 2020). School performance also varies with sex and social background, like ADHD does. Girls generally outperform boys (OECD, 2015; Voyer & Voyer, 2014), and children with highly educated parents or from high income households generally outperform less advantaged children (OECD, 2016; Sirin, 2005; Statistics Norway, 2020). Different school performance in groups with different prevalence of ADHD raises the question of how the impact of ADHD may differ across groups. To the best of our knowledge, no study has investigated how the impact of ADHD varies by social background, and the studies on sex differences have been small and underpowered (e.g., DuPaul et al., 2006; Gershon, 2002). Furthermore, although ADHD has been linked with both reading disabilities and arithmetic difficulties (Taanila et al., 2012), little is known about to what extent ADHD leads to general deficits in school performance versus deficits specific to some school subjects. By investigating relative performance in different school subjects, we can point out where children are most affected by ADHD and hence where to target potential interventions.

The association between ADHD and school performance could be confounded by several factors that influence both (Polderman et al., 2010). First, family characteristics such as parental education are robustly associated with both school performance and ADHD (Kinge et al., 2021; Sirin, 2005). We account for this by comparing full siblings, which controls for unobserved variables shared within families, such as social, geographic, and parental characteristics, as well as half of the genetic risk (Taylor, 2021). Second, children with ADHD often have comorbid mental disorders, which are also associated with lower academic performance (Fröjd et al., 2008; Lawrence et al., 2019). By adjusting for comorbid mental disorders, we test whether reduced school performance is specific to ADHD. Third, children may be diagnosed with ADHD because they perform poorly in school, rather than the other way around. We therefore control for early school performance to see how ADHD is associated with progress.

To summarize, the aims of this study are to (1) accurately describe the ADHD deficit in school performance, (2) describe how the ADHD deficit in school performance varies across sex and parental education, and (3) compare the ADHD deficit in different school subjects. We do this using register data on all Norwegian children with appropriate statistical controls, including sibling-comparisons, which should result in precise and representative analyses.

Key points

- Children with ADHD have substantially poorer school performance than unaffected children. The ADHD deficit is not easily attributable to other factors, which suggest that interventions must target ADHD symptoms directly independent of sex, parental education, early school performance, and other psychiatric disorders
- The relative ADHD deficit is larger for girls and for children of highly educated parents, but the absolute deficit is smaller (i.e., girls with ADHD still outperform boys with ADHD, and children with ADHD and highly educated parents still outperform children with ADHD and less educated parents with ADHD)
- The ADHD deficit is large in all school subjects, meaning interventions should target factors that is shared across different school subject, although the potential for improvement appears to be largest in theoretical subjects where the ADHD deficit is largest.

METHODS

Sample

This study comprises all Norwegian inhabitants born between 1997 and 2002 that were alive and living in Norway between age 10 and 16 (N = 359,492). The Norwegian national population register includes personal identification numbers of all inhabitants, which allowed us to link data from separate sources. We linked data from publicly funded health services with data on school performance, parental education, and parentage from Statistics Norway. Norwegian school is compulsory up to 10th grade (age 16), meaning the resulting grades and GPAs are largely representative of the population. We identified 344,523 (95.7%) individuals who had GPA registered within 1 year of normed time (age 16) which we included in the main analyses (see Figure S1). Only an additional 14,969 (4.3%) individuals did not have a GPA registered within normed time, which we included in sensitivity analyses. Relatedness data were used to identify 145,051 full siblings nested in 69,765 sibships. The dataset was constructed to maximize the number of children with health data (born 1997 and later) and school performance data (born 2002 and before).

Measures

Exposure: ADHD

Due to the subsidized nature of the Norwegian healthcare system, general practitioners send reimbursement claims to the government each time a patient uses primary care facilities. These data are then indexed in the Norwegian Control and Payment of Health Refunds Database. These claims include the reason for encounter, which is documented with diagnostic codes or symptom codes according to the International Classification of Primary Care

version 2 (ICPC-2, WONCA, 2005). Just like ICD-10 (WHO, 1992), ICPC-2 does not differentiate between different kinds of attention disorders such as ADD and ADHD, but instead uses the term *Hyperkinetic Disorder* (code P81). Henceforth, we treat ADHD and hyperkinetic disorder as synonymous. We defined individuals as diagnosed with ADHD if they, between the age of 10 and 16, had at least one contact with the primary care system registered with code P81.

Outcome: School performance

At the end of 10th grade, children – normally 16 years old – are graded based on their whole-year performance and take exams. Grades are integers on a scale from one to six and the grade point average (GPA) are the mean of all grades, including final exams (M = 4.12, SD = 0.83). The higher the grade, the better the performance. GPA was standardized to z-scores (M = 0, SD = 1) before analyses, meaning all coefficients can be interpreted as standard deviations. For individual school subjects, we limited our analyses to grades that most pupils share (e.g., excluding electives, see Table S1). For these grades, we standardized using the combined mean and standard deviation of all grades irrespective of school subject (M = 4.17, SD = 1.08).

We also used scores from standardized national tests in mathematics and reading, which pupils take in fifth, eight, and ninth grade (approx. 10, 13, and 14 years old, respectively). These were also standardized to z-scores.

Parental education and other demographic information

Statistics Norway provided information on parental education at the time of the child's graduation (i.e., age 16), which we coded into four categories reflecting the highest achieved education of either parent: Master's degree or equivalent (n = 53,648), Bachelor's degree or equivalent (n = 130,155), high school (n = 116,920), or not completed high school (n = 30,860), and a fifth category for children with missing information (n = 12,569). Statistics Norway also provided information on sex, parentage (for within-family analyses, see below), birth month, and parity (i.e., maternal birth order).

Comorbid psychiatric disorders

Comorbid psychiatric disorders were defined in a similar way to ADHD: at least one contact with the primary care system registered with diagnostic codes for psychiatric disorders between the ages of 10 and 16. For each individual, we counted the total number of unique psychological diagnostic codes (P70 and above, excluding P81) from the ICPC-2, and entered the count as a categorical variable (truncated at three). In an alternative model, we used separate indicator variables for all individual disorders with a prevalence above 0.1% (see Table S2).

Statistical analyses

To estimate the ADHD deficit, we calculated bivariate and adjusted associations between ADHD and GPA with linear regression models. The covariates included in the adjusted models were sex, parental education, birth year, parity (truncated at five), and birth month. All of these were treated as categorical variables. The adjusted model only included covariates where reverse causation (and hence potential collider bias) is impossible or unlikely. Early school performance and comorbid mental disorders were therefore included in separate models. We used standardized test scores from fifth grade as a measure of early school performance. This variable had 28,765 missing observations, which were not included in the analyses using this variable. To investigate how the ADHD deficit varied across sex and parental education, we allowed ADHD to interact with sex and parental education in separate models. For comparison, we also estimated a regression model with covariates only (i.e., without ADHD).

The models were then re-estimated in within-family models (random-intercept multilevel models with parents as grouping variable) where we compared full siblings with and without ADHD. Only children with full siblings in the sample were included in these models (N = 145,051). Of the 69,765 sibships, 3952 (5.7%) included siblings discordant on ADHD. Covariates that vary within families (sex, parity, birth year, birth month) were included. As most full siblings will have equally educated parents, only the interaction between ADHD and sex was estimated with a within-family model.

Finally, the adjusted and within-family models with and without interactions were re-estimated with each individual school subject as the dependent variable.

We performed sensitivity analyses with several alternative outcomes. First, we re-estimated all models with standardized tests from eighth and ninth grade as dependent variables. Second, we included the 14,969 individuals who did not have registered GPA within normed time and used logistic regressions to re-run the adjusted models with missing GPA as the dependent variable.

Analyses were conducted in *R 4.0.3* (R Core Team, 2021), using *tidyverse* (Wickham et al., 2019), *lme4* (Bates et al., 2015) and *emmeans* (Lenth, 2021).

RESULTS

Of the 344,152 included children (51% boys), 13,800 (4.01%) were diagnosed with ADHD (see Figure 1). The prevalence was more than twice as high among boys (5.54%) than among girls (2.42%). The prevalence was more than three times higher among children of parents where neither had completed high school (6.87%) compared with children where at least one parent had a Master's degree or equivalent (1.91%).

The ADHD deficit in GPA

ADHD-affected children's average GPA was 3.24 (SD = 0.75) whereas unaffected children's average GPA was 4.16 (SD = 0.82), meaning

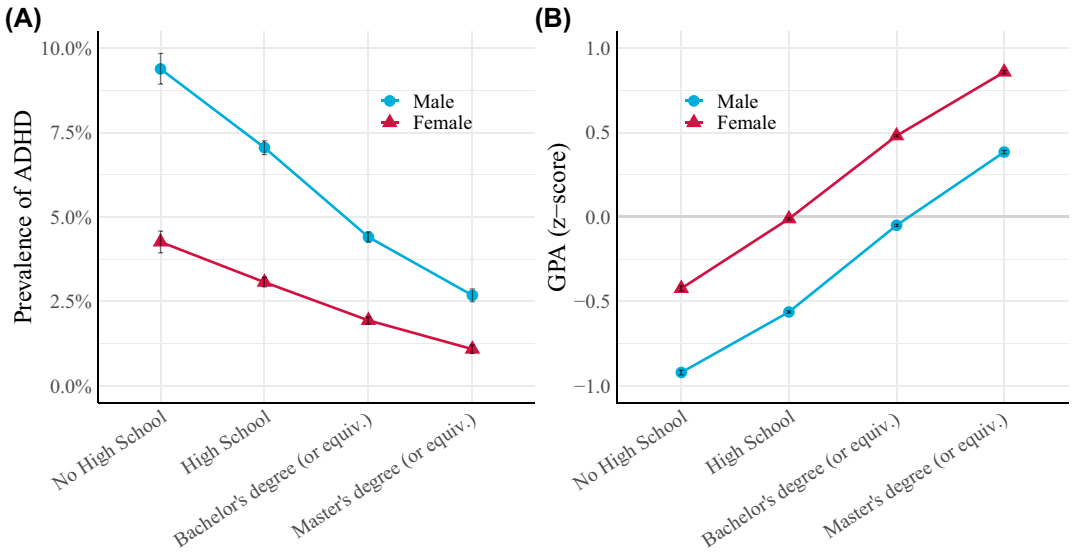

FIGURE 1 (A) Prevalence of Attention-Deficit Hyperactivity Disorder (ADHD) (with 95% CIs) across sex and parental education among 331,583 Norwegian children born between 1997 and 2002. ADHD were defined as at least one contact with the primary care system registered with code P81 (hyperkinetic disorder) between age 10 and 16. (B) Standardized GPAs (with 95% CIs) at the end of 10th grade (~age 16) across sex and parental education for the same sample

children with ADHD had on average −1.11 (95% CI: −1.12, −1.09) standard deviations lower GPA than children without ADHD (see Figure 2). When adjusting for covariates, the difference was reduced to −0.86 (−0.88, −0.85). In the within-family model, children with ADHD had on average −0.60 (−0.63, −0.58) standard deviations lower GPA than their same-sex siblings without ADHD.

The ADHD deficit was reduced but still substantial when accounting for earlier school performance. Among pupils who did equally well in fifth grade, those with ADHD had on average −0.54 (−0.56, −0.53) standard deviations lower GPA at the end of 10th grade compared to those without ADHD. Among siblings who did equally well in fifth grade, those with ADHD had on average −0.33 (−0.36, −0.30) standard deviations lower GPA.

Of the 13,800 individuals with ADHD, 2293 (19.8%) had at least one other psychiatric diagnosis. When statistically controlling for other diagnoses, the ADHD deficit was attenuated down from −0.86 to −0.82 (−0.83, −0.80) standard deviations in the adjusted model and from −0.60 to −0.58 (−0.61, −0.55) in the sibling model. This is still larger than the deficit associated with having three or more other registered diagnoses. Entering each individual diagnosis as separate indicator variables yielded similar coefficients (see Figure 2). The ADHD deficit was substantially larger than deficits associated with any other diagnoses (see Table S3-S4).

The effects of covariates on GPA were only negligibly attenuated compared to a model where ADHD was not included (see Table S3-S4). For example, in a model without ADHD, girls had on average 0.52 (0.52, 0.53) standard deviations higher GPA than boys, whereas in a model with ADHD, the difference was 0.50 (0.49, 0.50).

The ADHD deficit across sex and parental education

The ADHD deficit was −0.17 (−0.20, −0.14) standard deviations larger for girls than for boys. As seen in Figure 2, boys with ADHD had on average −0.81 (−0.83, −0.80) standard deviations lower GPA than boys without ADHD, whereas girls with ADHD had on average −0.99 (−1.01, −0.96) lower GPA than girls without ADHD. That is a 22% bigger deficit. The within-family model had similar results (see Table S4).

Similarly, the ADHD deficit was substantially greater among children of more educated parents, although it did not differ between the two highest education levels as illustrated by the overlapping confidence intervals in Figure 2. Among children of parents who did not complete high school, those with ADHD had on average −0.70 (−0.74, −0.67) standard deviations lower GPA than those without ADHD. Among children with at least one highly educated parent, the deficit was 39% larger, or −0.26 (−0.33, −0.20) standard deviations: Those with ADHD had on average −0.97 (−1.02, −0.92) standard deviations lower GPAs than those without ADHD.

Which school subjects are most strongly affected by ADHD?

We repeated the above analyses for each school subject, with similar results (See Figure 3 and Tables S5–S9). Those with ADHD had lower grades in all school subjects compared to those without ADHD. Nonetheless, we found some variation, with the average ADHD deficit varying from −0.47 (−0.48, −0.45) standard deviations in Arts and Crafts to −0.82 (−0.84, −0.81) in Mathematics. To ease interpretation, we can broadly categorize school subjects into three groups: language subjects (i.e., Norwegian and English), theoretical subjects (i.e., Mathematics and Social Studies), and practical subjects (i.e., Sports and Arts/Crafts). The ADHD deficit was largest and most consistent in the theoretical subjects (−0.82 to −0.80), slightly smaller and more variable for language subjects (−0.70 to −0.62), and smaller still for practical subjects (−0.60 to −0.47).

Similar interactions were also observed across each subject: The ADHD deficit was consistently larger for girls than for boys in all subjects. The deficit difference varied from −0.20 (−0.24, −0.17) in

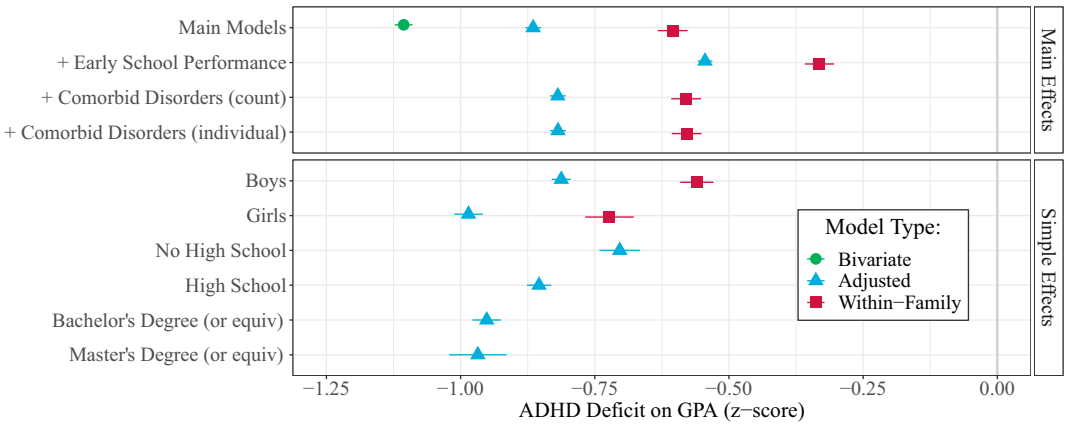

FIGURE 2 Coefficients (with 95% CIs) showing the Attention-Deficit Hyperactivity Disorder (ADHD) deficit on GPA (z-scores) bivariate and adjusted for sex, parental education, birth year, parity, and birth month, and additionally adjusted for early school performance and comorbid disorders. The lower panel shows the ADHD deficit by sex and parental education. As most full siblings will have equally educated parents, we did not include parental education in the within-family models (hence no interaction between parental education and ADHD in the within-family model)

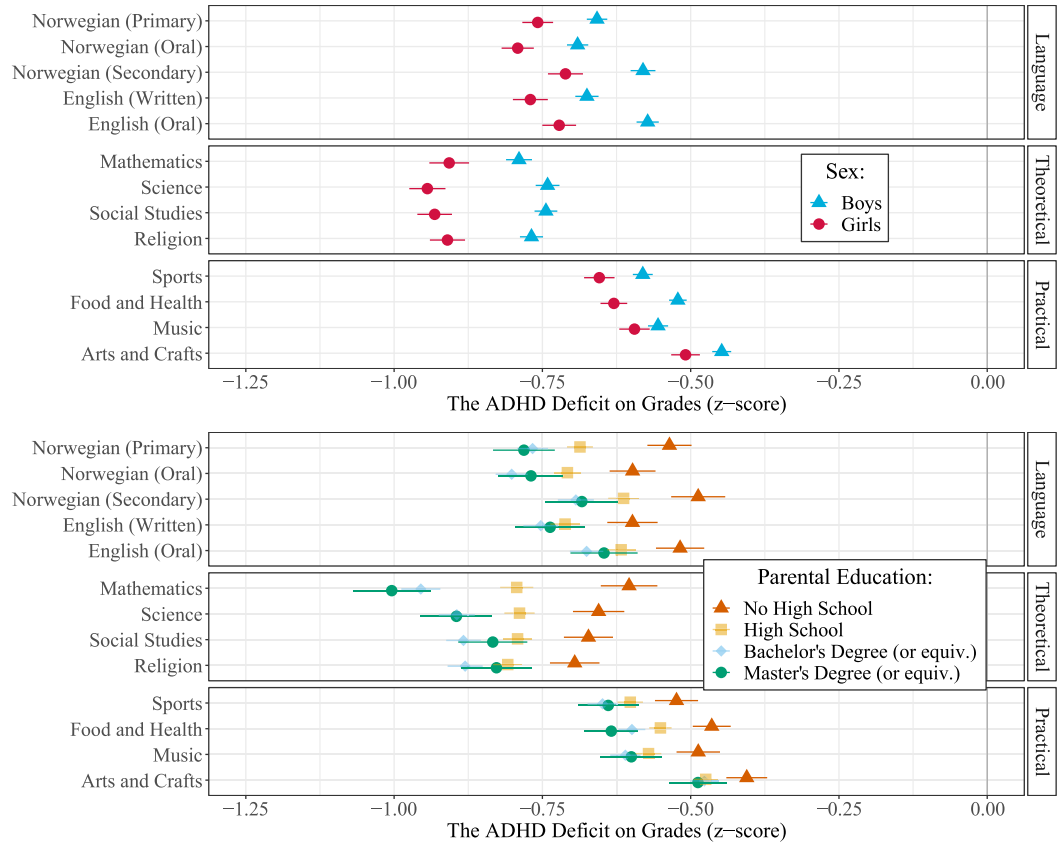

FIGURE 3 Coefficients (with 95% CIs) showing the relative Attention-Deficit Hyperactivity Disorder (ADHD) deficit on grades in specific subjects (z-scores) stratified by sex (top) and parental education (bottom). All coefficients are adjusted for birth year, parity, and birth month, in addition to parental education (top) and sex (bottom)

Science to −0.04 (−0.07, −0.01) in Music. Regarding interaction effects between ADHD and parental education, we found few differences between the top three education levels, but the ADHD deficit was consistently larger than for children of parents who had not completed high school. The difference in ADHD deficit was particularly pronounced in Mathematics, with the ADHD deficit being −0.40 (−0.48, −0.32) standard deviations larger for children of highly educated parents compared to children of parents who had not completed high school.

Neither the ADHD deficit, general sex differences, nor parental educational differences are constant across school subjects, which must be considered when interpreting the relative deficits. Figure 4 presents expected grades (z-scores) for individuals with and without ADHD across sex or parental education (see also Figure S2-S3). In some school subjects, the sex difference is almost as large as the ADHD deficit. Thus, in school subjects with large sex differences such as Norwegian (i.e., language skills), boys *without* ADHD barely outperformed girls *with* ADHD, despite the ADHD deficit being larger

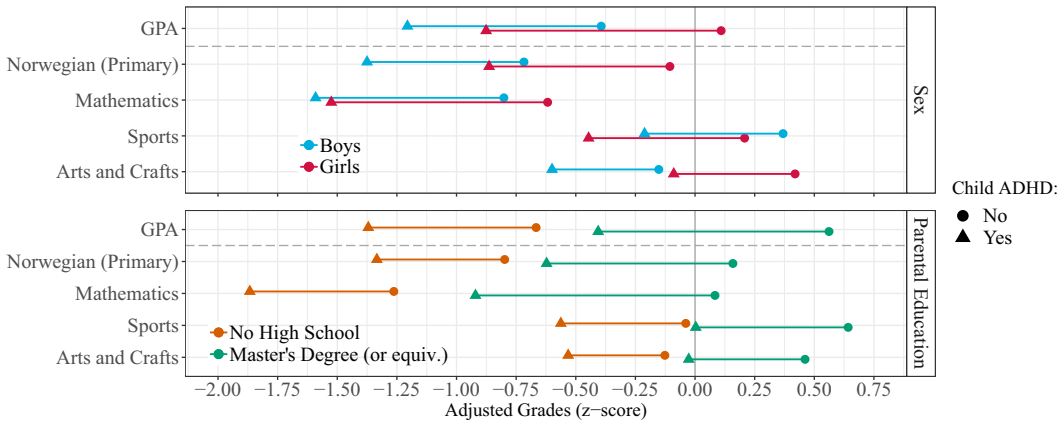

FIGURE 4 Adjusted mean grades (z-scores) for those with and without Attention-Deficit Hyperactivity Disorder (ADHD) in a selection of subjects stratified by sex (top) and parental education (bottom). See Supplementary Figures S2 and S3 for extended versions of these plots with all school subjects

for girls. Because grade differences by parental education are larger than sex differences, this pattern becomes more pronounced for parental education. Children with ADHD and highly educated parents perform better in most school subjects than children without ADHD but with parents who had not completed high school.

Sensitivity analyses

All analyses were repeated with standardized tests from eighth and ninth grade as outcome variables, which yielded similar results (Tables S10–S17 and Figures S4–S7). Missing GPA was also analyzed with logistic regressions, again with similar results. Children with ADHD were 4.28 (4.08, 4.49) times more likely than unaffected children to not have GPA registered, adjusting for covariates (see Table S18 and Figure S8). There were no statistically significant interaction effects in this set of analyses.

DISCUSSION

Using large and representative register data, we have found: (1) that the ADHD deficit in school performance is large and evident even when comparing siblings and when adjusting for comorbid disorders and early school performance, (2) that the relative ADHD deficit is somewhat larger for girls and children of highly educated parents but the absolute deficit is smaller, and (3) the ADHD deficit is largest in theoretical school subjects, but still substantial in all school subjects. In the sensitivity analyses, we also found that ADHD increased the likelihood of not being registered with a GPA, meaning the deficit on GPA is a conservative estimate of the association between ADHD and poor school performance.

Even though children diagnosed with ADHD had substantially lower GPAs than other children, with an overall deficit of −1.11 standard deviations, this was partly due to family confounding. When comparing same-sex siblings and therefore controlling for unobserved family characteristics and genetic similarity, the ADHD deficit was reduced to −0.60 standard deviations. The ADHD deficit remain large after adjusting for potential confounders, but it would nevertheless be premature to conclude that the relationship is causal. For example, siblings share only half of the genetic factors that vary in the population, implying that residual genetic variation may still influence both ADHD and school performance. However, despite both ADHD and school performance being highly heritable (Faraone & Larsson, 2019), the attenuation of the ADHD deficit was relatively small in the within-family model compared to the fully adjusted model, indicating that an association would plausibly exist even with full adjustment for genetic factors.

A second caveat to causal interpretations is reverse causation: ADHD and school performance pose a chicken and egg problem in that children must show age-inappropriate levels of inattention and/or hyperactivity in at least two contexts to be eligible for ADHD diagnosis (APA, 2013; WHO, 1992). For children, school will likely be one of these contexts, meaning that many may have received an ADHD diagnosis because they struggled in school. While our data does not permit us to completely discount reverse causation, controlling for early school performance should give an indication: If poor early school performance was the primary reason children were diagnosed with ADHD, then the association between ADHD and later school performance should disappear or be substantially reduced when adjusting for early school performance. Instead, we found that among children with similar performance in fifth grade, those with ADHD still had on average −0.54 standard deviations lower GPAs at the end of 10th grade compared to those without ADHD. In other words, ADHD is not only associated with poor school performance, but also with worsening school performance relative to peers. This is not consistent with poor early school performance being the primary reason children are diagnosed with ADHD.

Most of the ADHD deficit remained, but it was attenuated by about a third from −0.86 down to −0.54. It can be tempting to interpret this to mean that a third of the ADHD deficit is due to selection bias. We caution against this interpretation, as we cannot disentangle the degree to which the attenuation is caused by selection bias (poor early school performance → ADHD) or mediation (ADHD → poor early school performance), and adjusting for mediators will underestimate the effect.

A third caveat is that ADHD often covaries with other mental disorders, such as depression and anxiety, which might confound the association between ADHD and school performance. We found that

adjusting for other mental disorders had only a negligible impact on the ADHD deficit, meaning the ADHD deficit is generated independently of other mental disorders. This mirrors earlier research finding that ADHD impacts school performance independently of comorbid conduct disorders (Daley & Birchwood, 2010). Overall, we find that the ADHD deficit is not easily attributed to other factors, and that ADHD therefore reflects an independent risk factor of poor school performance.

The effect of covariates on GPA remained similar in models with and without ADHD, suggesting their effect on GPA is not partly mediated by ADHD diagnoses. Differences in school performance across, e.g., sex and parental education must therefore be explained by other factors.

The *relative* ADHD deficit was larger in groups with lower prevalence of ADHD: It was 22% larger for girls than for boys, and 39% larger for children with highly educated parents compared with children of parents who did not complete high school. Similar findings were found for individual school subjects. There are at least two ways of interpreting the larger relative deficit in low-prevalence groups: First, the threshold for receiving an ADHD diagnosis may be higher for girls and for children of highly educated parents, which would result in the average diagnosed case being more severe and consequently would impact school performance more. Whether there are true differences or merely different thresholds for receiving a diagnosis remain debated (e.g., Slobodin & Davidovitch, 2019), but one representative study found sex differences to result from true differences in mean and variance of ADHD symptom severity, not selection bias (Arnett et al., 2015). The second and in our opinion more likely interpretation is that girls and children of highly educated parents appear more impacted by ADHD because their undiagnosed peers have relatively higher grades. In fact, the differences in school performance associated with parental education are often bigger than the relative ADHD deficits, meaning that ADHD-affected children of highly educated parents on average outperform children *without* ADHD with parents who did not complete high school (see Figure 4). Likewise, in some school subjects (e.g., Norwegian), girls with ADHD perform similarly to boys *without* ADHD. In terms of absolute performance, then, girls and children of highly educated parents are less impacted by ADHD.

We found that the ADHD deficit was large in all school subjects. This mirrors Jangmo et al. (2019), who reported similar findings from Swedish registers (see Appendix S1 for a more detailed comparison). We also investigated interactions and found it particularly large between ADHD and parental education in Mathematics. The interaction between sex and ADHD were mostly similar across school subjects, despite varying sex differences. Large ADHD deficits in all school subjects suggest that the effect of ADHD is largely mediated through general factors shared across school subjects. We do not know what these are, but they could relate to classroom size, organisation of homework, or emotion regulation (e.g., Daley & Birchwood, 2010; Rushton et al., 2020). Potential interventions should therefore target general factors that impact school performance in a way that is shared across school subjects. However, if limited resources forces interventions to target specific school subjects, then the potential for improvement appears to be largest in theoretical subjects such as Mathematics or Science, where the ADHD deficit was largest.

Strengths and limitations

Population-wide register studies like this have numerous strengths (Thygesen & Ersbøll, 2014). First, unlike clinic-referred samples and cohort samples, this study does not suffer from non-random attrition and is much less affected by selection bias. In addition to unrepresentative results, selection bias can systematically bias estimates when the investigated variables are associated with likelihood of participation (i.e., collider bias: Munafò et al., 2018). The subsidized and equal-access nature of the Norwegian healthcare system means cases are unlikely to go unregistered, and only a few children (4.3%) did not have GPA registered (which we included in sensitivity analyses), meaning this study captures a representative picture of the association between ADHD and school performance. Second, register studies have very large sample sizes, which results in narrow confidence intervals and consequently high statistical power. Even large cohort studies can have few participants satisfying several criteria, such as being girls with ADHD and highly educated parents, which would result in low power and large confidence intervals even if the original cohort sample was large (Button et al., 2013). The difference in clinical consequences between the ends of large confidence intervals can be considerable, and small but meaningful differences may go undetected (Funder & Ozer, 2019; Götz et al., 2021; Schönbrodt & Perugini, 2013). Large register studies, on the other hand, can accurately estimate small differences in effects between subgroups, even for relatively rare disorders.

Nevertheless, this study has some limitations. First, diagnoses are all-or-none, meaning we are unable to attribute the ADHD deficit to the different facets of ADHD (e.g., inattention vs. impulsivity) or different symptom severities. Second, we only have data on primary health care visits, not medication use. Medication is common among Norwegian children with ADHD (Karlstad et al., 2017) and has been shown to have a positive effect on school performance (Jangmo et al., 2019), meaning our analyses may underestimate the size of the ADHD deficit. Third, physicians often register only one diagnostic code per visit, meaning the data do not adequately capture concurrent comorbidity, only temporal comorbidity. Fourth, we did not observe individuals before age 10. Nonetheless, because parents would often need renewed medical certificates or prescriptions for medications, it is unlikely that individuals who received their first diagnosis before the observation period would not be re-registered in the observation period. Finally, some relevant variables, such as cognitive ability, are not available in administrative register data and could therefore only be accounted for indirectly – and imperfectly – through early school performance (Borghans et al., 2016).

CONCLUSION

We have found that the ADHD deficit in school performance is large, apparent in all school subjects, and not easily attributable to other factors. This strongly suggests that ADHD symptoms is an important risk factor for poor school performance which must be addressed directly independent of sex, parental education, early school performance, and other psychiatric disorders. Because it affects performance in all school subjects, ADHD must ideally be

addressed by intervening on factors that affect school performance broadly, although interventions targeting theoretical subjects like Mathematics may be most effective given limited resources.

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CONFLICT OF INTEREST

The authors have declared that they have no competing or potential conflicts of interest.

ETHICAL CONSIDERATION

The study was approved by the Regional Committee for Medical and Health Research Ethics.

AUTHOR CONTRIBUTIONS

Hans Fredrik Sunde: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing. **Thomas H. Kleppestø:** Conceptualization; Investigation; Methodology; Writing – review & editing. **Kristin Gustavson:** Conceptualization; Investigation; Methodology; Writing – review & editing. **Magnus Nordmo:** Conceptualization; Investigation; Methodology; Writing – review & editing. **Bjørn-Atle Reme:** Conceptualization; Investigation; Methodology; Writing – review & editing. **Fartein A. Torvik:** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

DATA AVAILABILITY STATEMENT

The register data can be accessed by application to the Regional Committee for Medical and Health Research Ethics in Norway, Statistics Norway, and the Norwegian Directorate of Health. Our ethical approval does not open for storage of data on an individual level in repositories or journals.

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REFERENCES

APA. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. American Psychiatric Association.

Arnett, A. B., Pennington, B. F., Willcutt, E. G., Defries, J. C., & Olson, R. K. (2015). Sex differences in ADHD symptom severity. *Journal of Child Psychology and Psychiatry*, *56*(6), 632–639. https://doi.org/10.1111/jcpp.12337

Arnold, L. E., Hodgkins, P., Kahle, J., Madhoo, M., & Kewley, G. (2020). Long-term outcomes of ADHD: Academic achievement and performance. *Journal of Attention Disorders*, *24*(1), 73–85. https://doi.org/10.1177/1087054714566076

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 48. https://doi.org/10.18637/jss.v067.i01

Borghans, L., Golsteyn, B. H. H., Heckman, J. J., & Humphries, J. E. (2016). What grades and achievement tests measure. *Proceedings of the National Academy of Sciences*, *113*(47), 13354–13359. https://doi.org/10.1073/pnas.1601135113

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365–376. https://doi.org/10.1038/nrn3475

Daley, D., & Birchwood, J. (2010). ADHD and academic performance: Why does ADHD impact on academic performance and what can be done to support ADHD children in the classroom? *Child: Care, Health and Development*, *36*(4), 455–464. https://doi.org/10.1111/j.1365-2214.2009.01046.x

DuPaul, G. J., Jitendra, A. K., Tresco, K. E., Junod, R. E. V., Volpe, R. J., & Lutz, J. G. (2006). Children with attention deficit hyperactivity disorder: Are there gender differences in school functioning? *School Psychology Review*, *35*(2), 292–308. https://doi.org/10.1080/02796015.2006.12087993

Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., Wang, Y., Gignac, M., Al Saud, N. M., Manor, I., Rohde, L. A., Yang, L., Cortese, S., Almagor, D., Stein, M. A., Albatti, T. H., Aljoudi, H. F., Alqahtani, M. M. J., Asherson, P., … Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*, *128*, 789–818. https://doi.org/10.1016/j.neubiorev.2021.01.022

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562–575. https://doi.org/10.1038/s41380-018-0070-0

Fröjd, S. A., Nissinen, E. S., Pelkonen, M. U. I., Marttunen, M. J., Koivisto, A.-M., & Kaltiala-Heino, R. (2008). Depression and school performance in middle adolescent boys and girls. *Journal of Adolescence*, *31*(4), 485–498. https://doi.org/10.1016/j.adolescence.2007.08.006

Funder, D. C., & Ozer, D. J. (2019). Evaluating effect size in psychological research: Sense and nonsense. *Advances in Methods and Practices in Psychological Science*, *2*(2), 156–168. https://doi.org/10.1177/2515245919847202

Gershon, J., & Gershon, J. (2002). A meta-analytic review of gender differences in ADHD. *Journal of Attention Disorders*, *5*(3), 143–154. https://doi.org/10.1177/108705470200500302

Götz, F. M., Gosling, S. D., & Rentfrow, P. J. (2021). Small effects: The indispensable foundation for a cumulative psychological science. *Perspectives on Psychological Science*, *17*, 205–215. https://doi.org/10.1177/1745691620984483

Jangmo, A., Kuja-Halkola, R., Pérez-Vigil, A., Almqvist, C., Bulik, C. M., D'Onofrio, B., Larsson, H., Ahnemark, E., Werner-Kiechle, T., & Larsson, H. (2021). Attention-deficit/hyperactivity disorder and occupational outcomes: The role of educational attainment, comorbid developmental disorders, and intellectual disability. *PLoS One*, *16*(3), e0247724. https://doi.org/10.1371/journal.pone.0247724

Jangmo, A., Stålhandske, A., Chang, Z., Chen, Q., Almqvist, C., Feldman, I., Larsson, H., Lichtenstein, P., D'Onofrio, B., Kuja-Halkola, R., & Larsson, H. (2019). Attention-deficit/hyperactivity disorder, school performance, and effect of medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, *58*(4), 423–432. https://doi.org/10.1016/j.jaac.2018.11.014

Karlstad, Ø., Furu, K., Stoltenberg, C., Håberg, S. E., & Bakken, I. J. (2017). ADHD treatment and diagnosis in relation to children's birth month: Nationwide cohort study from Norway. *Scandinavian Journal of Public Health*, *45*(4), 343–349. https://doi.org/10.1177/1403494817708080

Kent, K. M., Pelham, W. E., Molina, B. S. G., Sibley, M. H., Waschbusch, D. A., Yu, J., Karch, K. M., Biswas, A., Babinski, D. E., & Karch, K. M. (2011). The academic experience of male high school students with ADHD. *Journal of Abnormal Child Psychology*, *39*(3), 451–462. https://doi.org/10.1007/s10802-010-9472-4

Kinge, J. M., Øverland, S., Flatø, M., Dieleman, J., Røgeberg, O., Magnus, M. C., Torvik, F. A., Tesli, M., Skrondal, A., Stoltenberg, C., Vollset, S. E., Håberg, S., & Torvik, F. A. (2021). Parental income and mental disorders in children and adolescents: Prospective register-based study. *International Journal of Epidemiology*, *50*, 1615–1627. https://doi.org/10.1093/ije/dyab066

Larsson, H., Sariaslan, A., Långström, N., D'Onofrio, B., & Lichtenstein, P. (2014). Family income in early childhood and subsequent attention deficit/hyperactivity disorder: A quasi-experimental study. *Journal of Child Psychology and Psychiatry*, *55*(5), 428–435. https://doi.org/10.1111/jcpp.12140

Lawrence, D., Dawson, V., Houghton, S., Goodsell, B., & Sawyer, M. G. (2019). Impact of mental disorders on attendance at school. *Australian Journal of Education*, *63*(1), 5–21. https://doi.org/10.1177/0004944118823576

Lenth, R. V. (2021). *emmeans: Estimated marginal means, aka least-squares means* [R Package version 1.6.1]. https://CRAN.R-project.org/package=emmeans

Markussen, E., Daus, S., & Hovdhaugen, E. (2020). *Fra 16 til 30: Om utdanning, jobb og inntekt for 9341 unge fra Østlandet, 14 år etter at de gikk ut av tiende klasse i 2002 (2020-2)*. https://hdl.handle.net/11250/2675748

Munafò, M. R., Tilling, K., Taylor, A. E., Evans, D. M., & Davey Smith, G. (2018). Collider scope: When selection bias can substantially influence observed associations. *International Journal of Epidemiology*, *47*(1), 226–235. https://doi.org/10.1093/ije/dyx206

OECD. (2015). *The ABC of gender equality in education: Aptitude, behaviour, confidence*. OECD Publishing.

OECD. (2016). *PISA 2015 results* (Vol. I). OECD Publishing.

Polderman, T. J. C., Boomsma, D. I., Bartels, M., Verhulst, F. C., & Huizink, A. C. (2010). A systematic review of prospective studies on attention problems and academic achievement. *Acta Psychiatrica Scandinavica*, *122*(4), 271–284. https://doi.org/10.1111/j.1600-0447.2010.01568.x

R Core Team. (2021). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Rushton, S., Giallo, R., & Efron, D. (2020). ADHD and emotional engagement with school in the primary years: Investigating the role of student–teacher relationships. *British Journal of Educational Psychology*, *90*(S1), 193–209. https://doi.org/10.1111/bjep.12316

Russell, A. E., Ford, T., Williams, R., & Russell, G. (2016). The association between socioeconomic disadvantage and attention deficit/hyperactivity disorder (ADHD): A systematic review. *Child Psychiatry and Human Development*, *47*(3), 440–458. https://doi.org/10.1007/s10578-015-0578-3

Sayal, K., Washbrook, E., & Propper, C. (2015). Childhood behavior problems and academic outcomes in adolescence: Longitudinal population-based study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*(5), 360–368. e362. https://doi.org/10.1016/j.jaac.2015.02.007

Schönbrodt, F. D., & Perugini, M. (2013). At what sample size do correlations stabilize? *Journal of Research in Personality*, *47*(5), 609–612. https://doi.org/10.1016/j.jrp.2013.05.009

Sirin, S. R. (2005). Socioeconomic status and academic achievement: A meta-analytic review of research. *Review of Educational Research*, *75*(3), 417–453. https://doi.org/10.3102/00346543075003417

Slobodin, O., & Davidovitch, M. (2019). Gender differences in objective and subjective measures of ADHD among clinic-referred children. *Frontiers in Human Neuroscience*, *13*. https://doi.org/10.3389/fnhum.2019.00441

Statistics Norway. (2020). Elever, etter kjønn, grunnskolepoeng og foreldrenes utdanningsnivå 2015–2019. https://www.ssb.no/statbank/table/11689

Taanila, A., Ebeling, H., Tiihala, M., Kaakinen, M., Moilanen, I., Hurtig, T., & Yliherva, A. (2012). Association between childhood specific learning difficulties and school performance in adolescents with and without ADHD symptoms: A 16-year follow-up. *Journal of Attention Disorders*, *18*(1), 61–72. https://doi.org/10.1177/1087054712446813

Taylor, M. J. (2021). The need for genetically-informative designs in developmental science: Commentary on Gustavson et al. (2021) and Myers et al (2021). *JCPP Advances*, *1*(2). https://doi.org/10.1002/jcv2.12025

Thygesen, L. C., & Ersbøll, A. K. (2014). When the entire population is the sample: Strengths and limitations in register-based epidemiology. *European Journal of Epidemiology*, *29*(8), 551–558. https://doi.org/10.1007/s10654-013-9873-0

Torvik, F. A., Eilertsen, E. M., McAdams, T. A., Gustavson, K., Zachrisson, H. D., Brandlistuen, R., & Ystrom, E. (2020). Mechanisms linking parental educational attainment with child ADHD, depression, and academic problems: A study of extended families in The Norwegian mother, father and child cohort study. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/jcpp.13197

Voyer, D., & Voyer, S. D. (2014). Gender differences in scholastic achievement: A meta-analysis. *Psychological Bulletin*, *140*(4), 1174–1204. https://doi.org/10.1037/a0036620

WHO (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. World Health Organization.

Wickham, H., Averick, M., Bryan, J., Chang, W., Mcgowan, L., François, R., Yutani, H., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T., Miller, E., Bache, S., Müller, K., Ooms, J., Robinson, D., Seidel, D., … Yutani, H. (2019). Welcome to the tidyverse. *Journal of Open Source Software*, *4*(43), 1686. https://doi.org/10.21105/joss.01686

WONCA (2005). *ICPC-2-R: International classification of primary care*. Oxford University Press.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Paper 1
Supplementary Information

Sunde, H. F., Kleppestø, T. H., Gustavson, K., Nordmo, M., Reme, B. A., & Torvik, F. A. (2022).
The ADHD deficit in school performance across sex and parental education: A prospective sibling-comparison register study of 344,152 Norwegian adolescents. *JCPP Advances*. https://doi.org/10.1002/jcv2.12064

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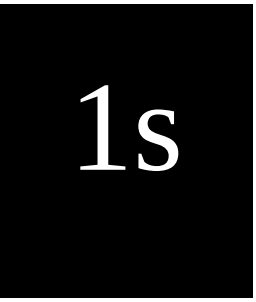
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SUPPLEMENTARY INFORMATION

The ADHD deficit in school performance across sex and parental education: a prospective sibling-comparison register study of 344,152 Norwegian adolescents

Hans Fredrik Sunde (*), Thomas Kleppestø, Kristin Gustavson,
Magnus Nordmo, Bjørn-Atle Reme, Fartein Ask Torvik,

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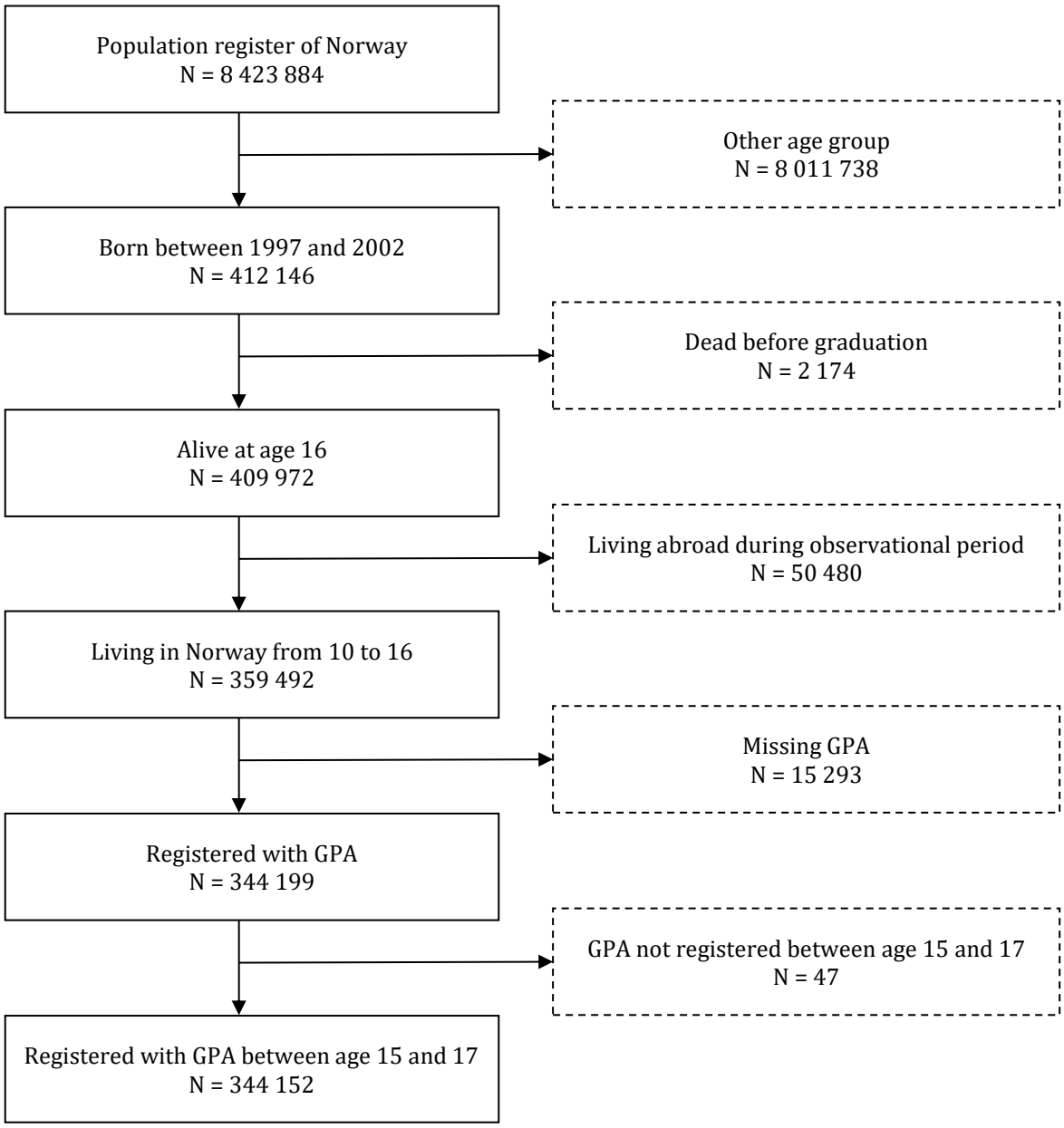


Figure S1: Sample Determination Flowchart

Figure S2: Adjusted Grades by Sex

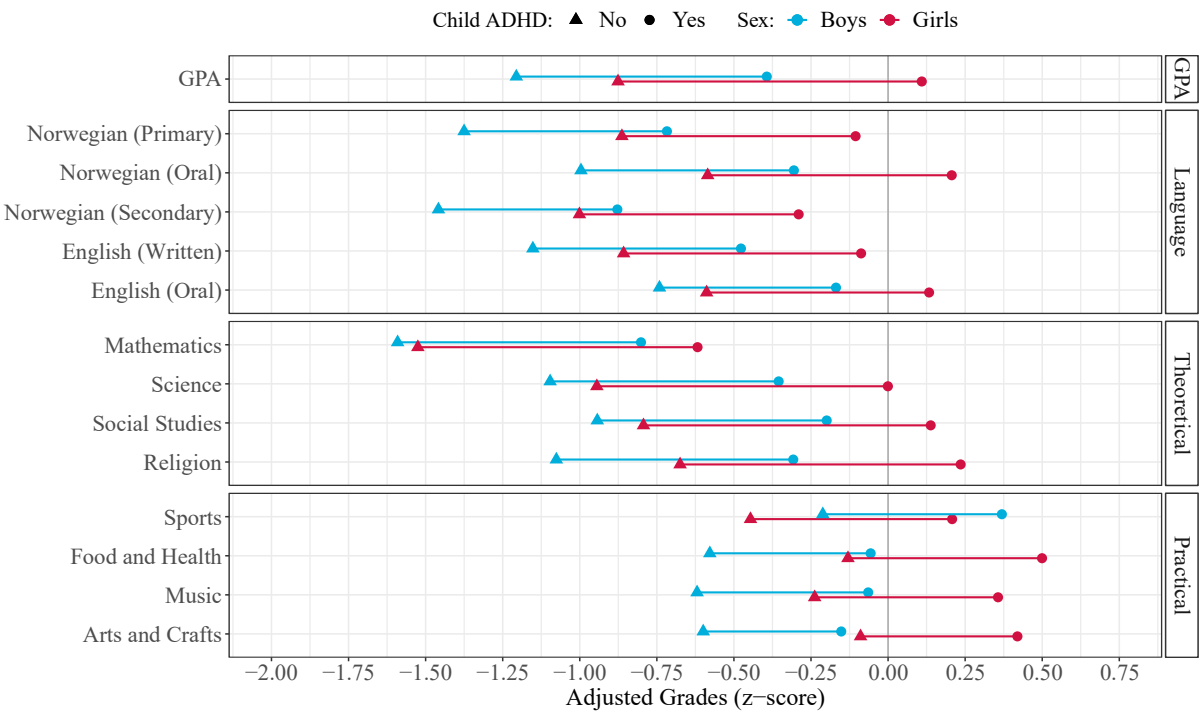
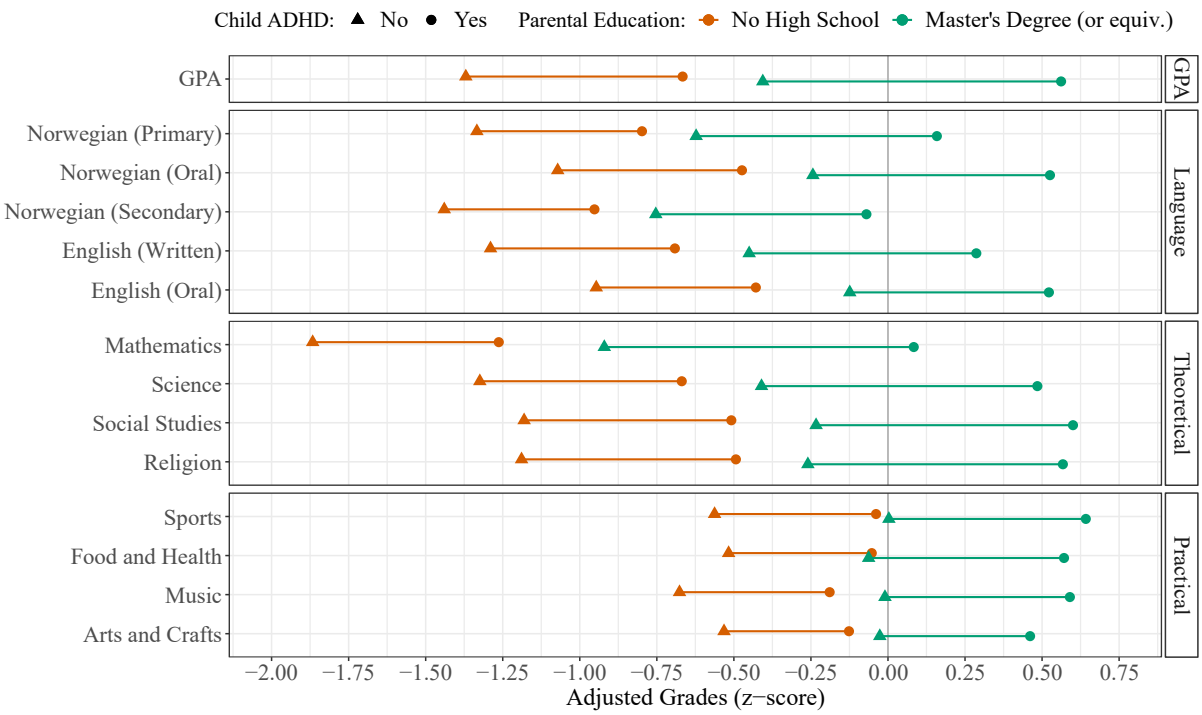


Figure S2: Adjusted mean grades (z-scores) for those with and without ADHD in a selection of subjects stratified by sex.

Figure S3: Adjusted Grades by Parental Education



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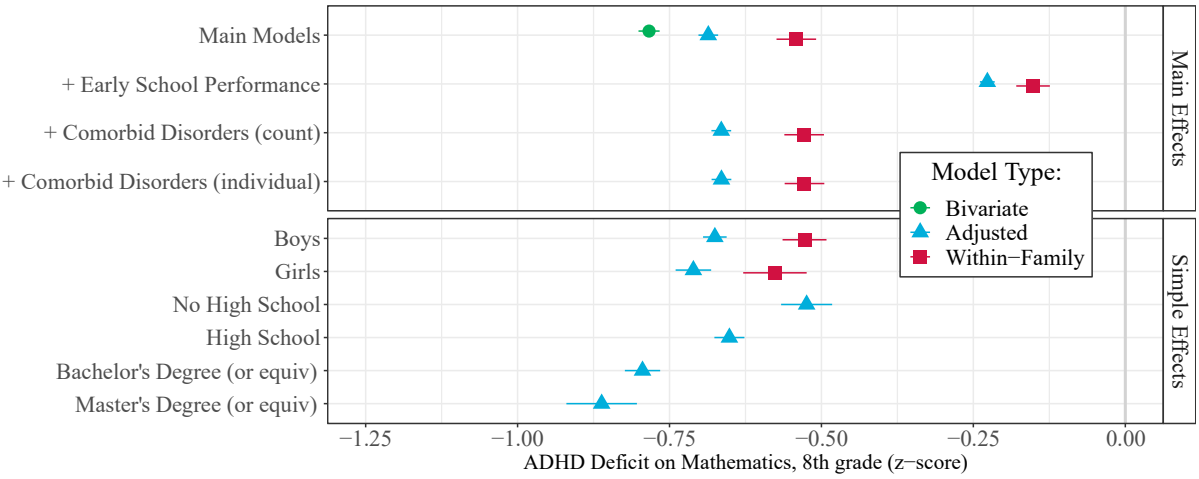

Figure S4: Coefficients (with 95% CIs) showing the ADHD deficit on standardized mathematics tests in 8th grade (z-scores) bivariate and adjusted for sex, parental education, birth year, parity, and birth month, and additionally adjusted for early school performance and comorbid disorders. The lower panel shows the ADHD deficit by sex and parental education. As most full siblings will have equally educated parents, we did not include parental education in the within-family models (hence no interaction between parental education and ADHD in the within-family model).

Figure S5: Reading, 8th Grade

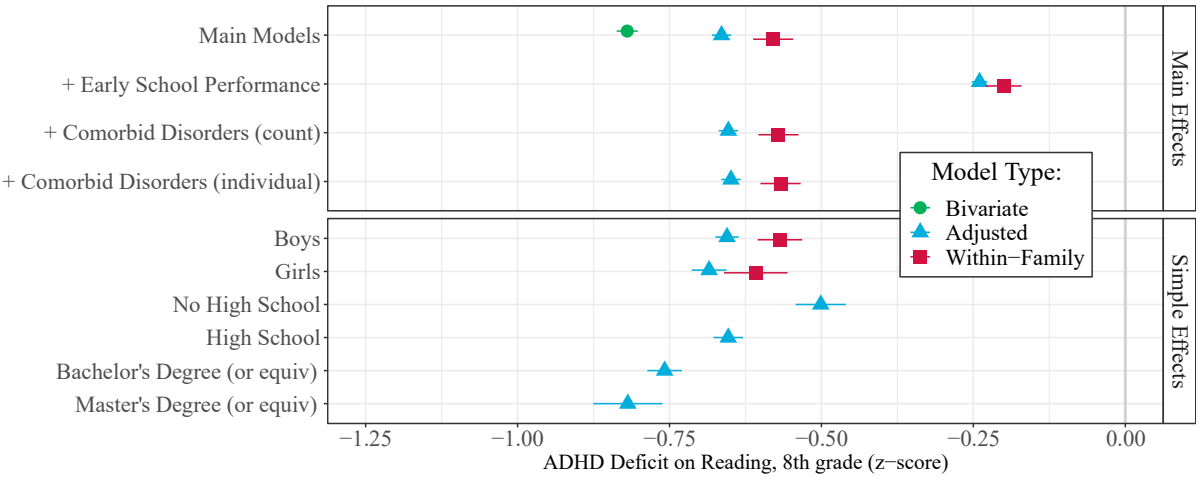

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Figure S6: Mathematics, 9th Grade

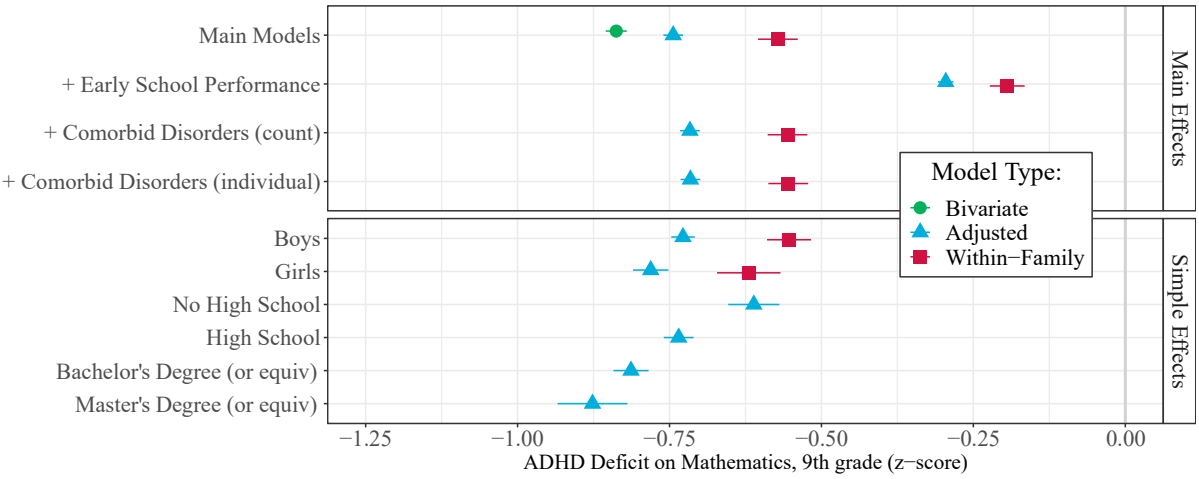

Figure S6: Coefficients (with 95% CIs) showing the ADHD deficit on standardized mathematics tests in 9th grade (z-scores) bivariate and adjusted for sex, parental education, birth year, parity, and birth month, and additionally adjusted for early school performance and comorbid disorders. The lower panel shows the ADHD deficit by sex and parental education. As most full siblings will have equally educated parents, we did not include parental education in the within-family models (hence no interaction between parental education and ADHD in the within-family model).

Figure S7: Reading, 9th Grade

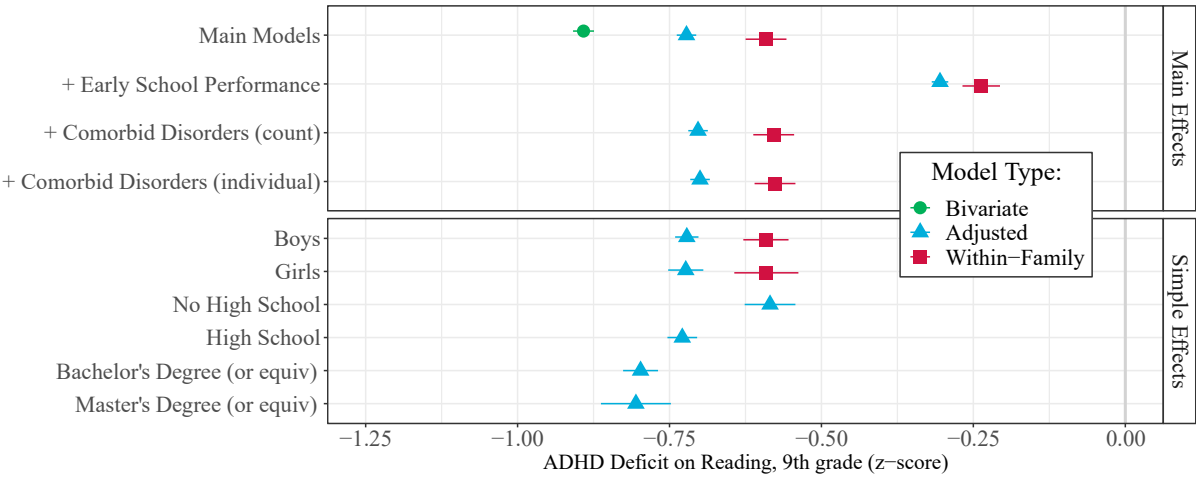

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Figure S8: Registered GPA (Logistic Regressions)

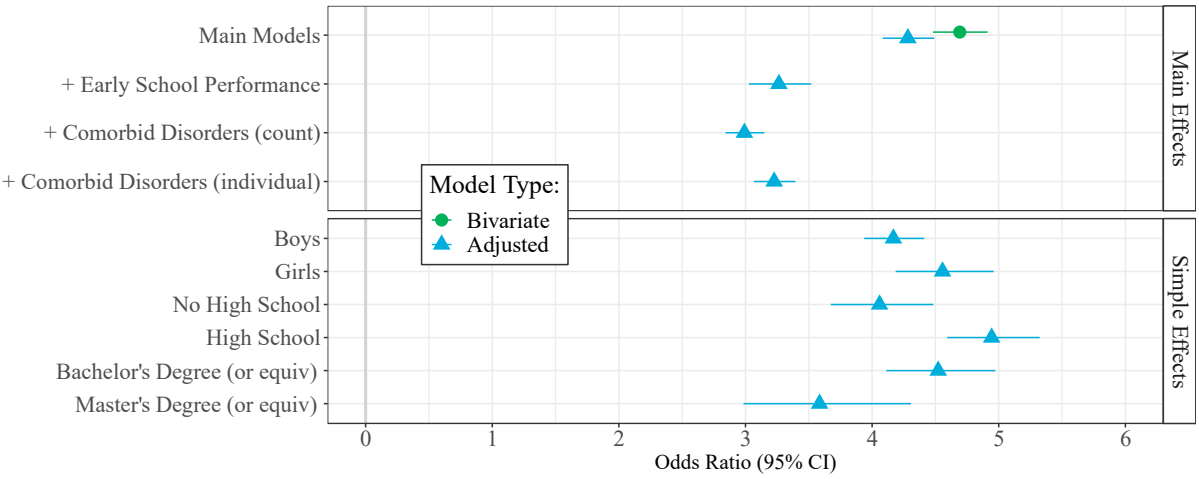

Figure S8: Odds Ratios (with 95% CIs) showing how much more likely children with ADHD are to not have registered GPA (i.e. registered GPA = 0, not registered GPA = 1), bivariate and adjusted for sex, parental education, birth year, parity, and birth month, and additionally adjusted for early school performance and comorbid disorders. The lower panel shows the odds ratios stratified by sex and parental education.

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Table S3 through S18 are large html-tables, and therefore not included here.
The can be downloaded here:
https://acamh.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fjcv2.12064&file=jcv212064-sup-0001-suppl-data.zip

Link to paper:

Table S1: List of School Subjects and Grades

Table S1
List of School Subjects and Grades*

	Mean	*SD*
GPA	4.12	0.83
Language		
Norwegian (Primary)*	3.88	1.02
Norwegian (Secondary)	3.68	1.00
Norwegian (Oral)	4.25	1.04
English (Written)	3.97	1.08
English (Oral)	4.25	1.04
Theoretical		
Mathematics	3.58	1.23
Science	4.14	1.15
Social Studies	4.27	1.11
Religion	4.24	1.13
Practical		
Sports	4.57	0.92
Food and Health	4.52	0.87
Arts and Crafts	4.40	0.92
Music	4.43	0.96
*Combined Mean***	*4.17*	*1.08*

**This list only includes the school subjects that all pupils normally would have. The GPA also comprise school subjects that varies between pupils, such as electives and foreign language subjects. Some pupils take French, others take German. Additionally, grades from final exams are also included in the GPA. However, pupils only take two final exams (one written, one oral) in randomly selected subjects, meaning they vary between pupils.*

*** Norway has two official written versions of Norwegian ("Bokmål" and "Nynorsk"), and pupils receive a grade in both. Which one is considered primary depends on the pupils main language form and/or geographical area. (Read more at Wikipedia)*

**** The mean and SD of all subjects combined were used for standardization. The SD is larger for the overall mean than for the GPA because the GPA will tend to regress towards the mean resulting in fewer extreme grades and consequently less variation around GPA.*

Table S2: Prevalence of Different Disorders

Table S2

Prevalence of Different Disorders

ICPC-2 Code	Name	Prevalence*	Included**
P70	Dementia	0.00 %	No
P71	Organic Psychosis Disorder	0.02 %	No
P72	Schizophrenia	0.01 %	No
P73	Affective Psychosis	0.05 %	No
P74	**Anxiety Disorder / Anxiety State**	**1.09 %**	**Yes**
P75	**Somatization Disorder**	**0.30 %**	**Yes**
P76	**Depressive Disorder**	**2.43 %**	**Yes**
P77	**Suicide / Suicide Attempt**	**0.30 %**	**Yes**
P78	Neuraesthenia / Surmenage	0.07 %	No
P79	**Phobia / Compulsive Disorder**	**0.85 %**	**Yes**
P80	**Personality Disorder**	**0.13 %**	**Yes**
P81	**Hyperkinetic Disorder**	**4.01 %**	**Yes**
P82	**Post-Traumatic Stress Disorder**	**0.18 %**	**Yes**
P85	Mental Retardation	0.06 %	No
P86	**Anorexia Nervosa / Bulimia**	**0.19 %**	**Yes**
P98	Psychosis NOS / Other	0.05 %	No
P99	**Psychological Disorders, Other**	**1.26 %**	**Yes**

** At least one registration between age 10 to 16*

*** Disorders with a prevalence > 0.1% (marked in bold) are included as separate indicator variables in the analyses that adjusts for individual comorbid disorders. All diagnoses were included in the analyses that adjusts for number of comorbid disorders.*

Appendix: Comparison with Jangmo et al (2019)

The ADHD deficit in school performance across sex and parental education: a prospective sibling-comparison register study of 344,152 Norwegian adolescents

Hans Fredrik Sunde (*), Thomas H. Kleppestø, Kristin Gustavson, Magnus Nordmo, Bjørn-Atle Reme, Fartein Ask Torvik

Just like our study, Jangmo et al (2019)[1] compared the association between ADHD and grades across different school subjects among similarly aged Swedish adolescents, which they presented in Supplementary Table S3. The list of school subjects differs slightly from our study owing to the differences between the Norwegian and Swedish school systems. For example, Norway have gathered all the natural sciences into one school subject, whereas Sweden has separate school subjects for Biology, Chemistry, Physics, and Technology. To compare our result with those of Jangmo et al, we averaged the coefficients where multiple school subjects in one study matched onto a single school subject in the other (see R script at the end of this document). Jangmo also included weighted tests in their list, which we did not include in our comparison.

The grading system also differs between Sweden and Norway, and because Jangmo et al did not standardize the outcome variables prior to analysis[2], the coefficients are not directly comparable. However, they report means and standard deviations for the ADHD and non-ADHD group, as well as the observed prevalence of ADHD (4.4%). This allows us to easily calculate the combined standard deviations for each school subjects, and hence calculate what the coefficients would have been if they had used a z-score of the outcome variables instead (rounding errors notwithstanding). This allows for a direct comparison of their findings with our findings.

To do this, one must first calculate the combined means, $\bar{X}_c$, of the two groups (ADHD vs. Non-ADHD) for each school subject. This is done my simply weighting the two means by the relative group size:

$$\bar{X}_c = p\bar{X}_1 + (1-p)\bar{X}_2$$

where p is the proportion of people who are in group 1 (i.e., prevalence of ADHD, 0.044) and $\bar{X}_1$ and $\bar{X}_2$ are the means of each group. We can then calculate the combined standard deviations, σ_c, for each school subject with the following equation:

$$\sigma_c = \sqrt{p(\sigma_1^2 + (\bar{X}_1 - \bar{X}_c)^2) + (1-p)(\sigma_2^2 + (\bar{X}_2 - \bar{X}_c)^2)}$$

where σ_1 and σ_2 are the standard deviations of each group.

[1] Jangmo et al (2019). Attention-Deficit/Hyperactivity Disorder, School Performance, and Effect of Medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, *58*(4), 423-432. https://doi.org/10.1016/j.jaac.2018.11.014

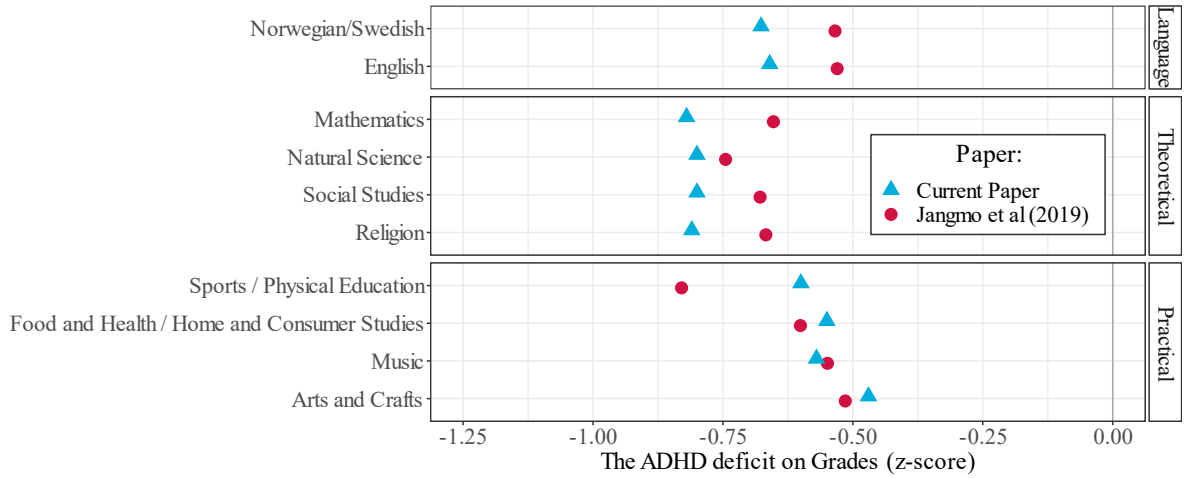
[2] They did also report standardized coefficients, but not in a way that makes them directly comparable to our coefficients.

In our study, we standardized using the mean and standard deviation for all grades regardless of school subject, which allowed us to retain information on relative performance in each school subject. To make the coefficients from Jangmo et al (2019) comparable, we first took the average standard deviation of the grades in all school subjects (excluding the weighted tests), before dividing the unstandardized adjusted coefficients by this average:

$$\beta_{z_i} = \frac{\beta_i}{\bar{\sigma}_c}$$

where i is the different school subjects, β_i is the original coefficient, β_{z_i} is the new, standardized coefficient, and $\bar{\sigma}_c$ is the average standard deviation of all grades regardless of school subject.

We then plotted their transformed coefficients together with the corresponding coefficients in our study (reported in Supplementary Table S5). We find that the associations are similar in strength, but with less systematic variation between school subjects.



To reproduce this figure, see the R script in the accompanying supplementary materials (zip-file)

Paper 2

Sunde, H. F., Eilertsen, E. M., Kinge, J. M., Kleppestø, T. H., Nordmo, M., Caspi, A., Moffitt, T., & Torvik, F. A. Parental income and mental disorders from age 10 to 35: a genetically informative population study (*Submitted*)

2

Paper 3

Sunde, H. F., Eftedal, N. H., Cheesman, R., Corfield, E. C., Kleppestø, T. H., Seierstad, A. C., Ystrøm, E., Eilertsen, E. M., & Torvik, F. A. Genetic similarity between relatives provides evidence on the presence and history of assortative mating (*Submitted*)

3

Genetic similarity between relatives provides evidence on the presence and history of assortative mating

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Conflicts of Interest: None

Word Count: 4132 (excl. methods)

Keywords: Assortative mating, Homogamy, Genetics, Polygenic index, MoBa

Summary

Assortative mating – the non-random mating of individuals with similar traits – is known to increase trait-specific genetic variance and genetic similarity between relatives[1-7]. However, empirical evidence is limited for many traits, and the implications hinge on whether assortative mating has started recently or many generations ago. Here we show theoretically and empirically that genetic similarity between relatives can provide evidence on the presence and history of assortative mating. First, we employed path analysis to understand how assortative mating affects genetic similarity between family members across generations, finding that similarity between distant relatives is more affected than close relatives. Next, we correlated polygenic indices of 47,135 co-parents from the Norwegian Mother, Father, and Child Cohort Study (MoBa) and found genetic evidence of assortative mating in eight out of fifteen examined traits. The same traits show elevated similarity between relatives, especially distant relatives. Five of the eight traits, including educational attainment, showed greater genetic variance among offspring, which is inconsistent with stable assortative mating over many generations. These results suggest an ongoing increase in familial similarity for these traits. The implications of this research extend to genetic methodology and the understanding of social and economic disparities.

Introduction

Assortative mating – the non-random pairing of individuals with similar traits – has long been a challenging topic of interest across various fields, including genetics[1-5,8-11], sociology[12-14], and economics[15,16]. Consequences of assortative mating are wide-ranging, affecting topics such as genetic research methods[17,18], relationship quality[12,19,20], and the perpetuation of social and economic inequalities[12,15,16]. Although partner similarity have been documented for numerous characteristics[17,18,21], it remains uncertain to what extent these similarities result from assortative mating or other processes, such as convergence over time[20,22]. Hence, the genetic consequences are unknown. Recent advances in data availability have enabled empirical investigation into the genetic consequences of assortative mating, wherein two are of key interest: First, partners should exhibit genetic similarity for assorted traits; and second, genetic similarity between relatives should increase for the assorted traits in subsequent generations[1,2,4]. In this paper, we aim to: 1) clarify the theoretical consequences of assortative mating on genetic similarity in extended families; 2) use polygenic indices to assess trait-specific genetic similarity between partners for a range of psychosocial, anthropometric, and health-related traits; 3) investigate whether these traits also exhibit increased genetic similarity among relatives; and 4) use the observed genetic similarity in mother-father-child trios to investigate the stability of assortative mating over many generations.

According to a recent meta-analysis, phenotypic correlations between partners exist for many traits[17]. The correlations are particularly high for cognitive and social traits like educational attainment (0.53) and political values (0.58), but moderate correlations exist for many diverse traits such as height (0.23), depression (0.14), and personality (0.08–0.21). Positive correlations between partners can arise from numerous processes, including convergence (partners becoming more alike over time due to mutual influence), common environments (partners originating from similar environments that affect their traits, but without influencing partner formation), and assortative mating (individuals tending to form partnerships with those having similar traits)[20]. If partner similarity arises because of assortative mating, then this will induce cross-partner correlations between the respective causes of the trait. If the trait is heritable – which most traits are[23,24] – then partners will tend to carry genetic variants with similar effects on the trait. Genetic similarity between partners has been documented for some traits, including height and educational attainment[9,21,25-27]. For example, Yengo, et al. [27] investigated genetic similarity in partners from the UK Biobank across 32 complex traits, but lack of statistical power left the question unresolved for most traits.

If assortative mating leads to genetic similarity between partners, then any resulting offspring are likely to inherit trait-specific genetic variants with similar effects from both parents. This has two important consequences: First, the trait-specific genetic variance in the population will increase because genetic variants with similar effects will tend to co-occur in the same individuals (i.e., variants will be in linkage disequilibrium)[3,4,6,7]. Second, trait-specific genetic similarity between relatives will increase because other family members are likely to inherit genetic variants with similar effects[1-5]. With no assortative mating, genotypic correlations between family members for a trait should correspond to the coefficient of relationship. For example, full siblings (not including monozygotic twins) and parent-offspring pairs are first-degree relatives, with a coefficient of 0.50; aunt/uncle-niece/nephew and grandparent-grandchild pairs are second-degree relatives, with a coefficient of 0.25; and first cousins are third-degree relatives, with a coefficient of 0.125. If assortative mating occurs, however, then the trait-specific genotypic

correlations would be higher than the corresponding coefficients of relationship. Importantly, assortative mating only induces correlations between trait-associated loci and should not be confused with inbreeding, which induces correlations between all loci[28]. With successive generations of stable assortative mating, trait-specific genetic variance and genotypic correlations between relatives increase asymptotically towards an equilibrium, at which point they become constant across generations[3,4,6,7]. We describe this in more detail in the supplementary information.

Whereas earlier theoretical papers have primarily focused on the consequences for phenotypic correlations at equilibrium, our focus is on genotypic correlations and correlations between polygenic indices at both equilibrium and disequilibrium. Our first aim is therefore to derive the expected genotypic correlations and polygenic index correlations using path analysis. In doing so, we establish a general formula for finding such correlations between any two extended family members under assortative mating at equilibrium. Our results imply that genetic similarity between distant relatives should be more affected by assortative mating than similarity between close relatives, which mirrors earlier work[29,30]. Our second aim is to document polygenic index correlations for various traits among partners from the Norwegian Mother, Father, and Child Cohort Study (MoBa)[29,30]. We found genetic evidence of assortative mating for eight out of fifteen investigated traits. Our third aim is to investigate whether genetic similarity between relatives was increased as predicted for these traits. We found that polygenic index correlations among relatives were increased in a way that broadly corresponded to the theoretical expectations. Trait-specific genetic similarity between partners and elevated genetic similarity between relatives indicate that many of the previously observed phenotypic correlations are partly attributable to assortative mating. Our final aim was to use mother-father-child trios to test whether the observations were consistent with equilibrium. Although some traits did not significantly deviate from equilibrium expectations, psychosocial traits like education attainment did. This would imply that that the genetic variance and genetic similarity between relatives for these traits are still increasing across generations.

Results

Fig. 1 shows a theoretical model of similarity in extended families in the presence of assortative mating at intergenerational equilibrium. The model includes eight individuals (i) in three generations (g): two partners in the first generation, their two children in the second generation (who are each other's full sibling) along with their respective partners, and two children in the third generation (who are each other's first cousin). The phenotype that is assorted on is denoted with P_{ig}, whereas trait-associated additive genetic factors and unique environmental factors are denoted with A_{ig} and E_{ig}, respectively. The genotypic correlation between any two individuals is the sum of all valid chains of paths between their respective additive genetic factors and the value of a single chain is the product of its path coefficients[31,32]. Valid chains always begin by tracing backward (←) in relation to the direction of arrows, incorporating exactly one double-headed arrow (↔), after which tracing continues in a forward direction (→). Because the variables in Fig. 1 have unit variances, all valid chains connecting a variable to itself will sum to 1, allowing us to immediately trace in a forward direction (i.e., change direction at once). Copaths (—), which are arrowless paths representing associations arising from assortment[33], link together valid chains per the rules above, forming longer, valid chains. For a more detailed description of path tracing rules involving copaths, see Balbona, et al. [34] or Keller, et al. [35].

Expected genotypic correlations in the nuclear family

There is only one valid chain between partners' respective additive genetic factors (e.g., A_{11} and A_{21}): $h \times \mu \times h$. The genotypic correlation between partners (denoted ρ_g) is thus the phenotypic correlation attributable to assortative mating, μ, weighted by the trait's heritability, h^2:

$$\rho_g = \mu h^2 \tag{1}$$

Similarly, we can trace all valid chains between the additive genetic factors of a parent and their offspring (e.g., A_{11} and A_{22}). There are two valid chains: one directly from parental genetic factors to offspring genetic factors, $\frac{1}{2}$, and one through the other parent via the assorted phenotype: $h \times \mu \times h \times \frac{1}{2}$. The genotypic correlation between parent and offspring is therefore $\frac{1}{2} + \frac{h\mu h}{2}$. With no assortative mating ($\mu = 0$), this reduces to $\frac{1}{2}$. For siblings (A_{22} and A_{23}), there are four valid chains: $\frac{1}{4} + \frac{1}{4} + \frac{h\mu h}{4} + \frac{h\mu h}{4}$, which can be rearranged so that it equals the genotypic parent-offspring correlation. Because they are equal, we can define a common denotation (r_{g_1}) for first-degree relatives. We can also substitute $h \times \mu \times h$ with ρ_g giving us:

$$r_{g_1} = \frac{1 + \rho_g}{2} \tag{2}$$

In other words, the genotypic correlation between first-degree relatives, r_{g_1}, is increased by half the genotypic correlation between partners at equilibrium. Note that the phenotypic correlation will not be the same for siblings and parent-offspring despite the same genotypic correlation[4]. An advantage of using path analysis is how easy path diagrams are to expand. In the supplementary information, we detail how including polygenic indices (section 1, 4 and 5) and relaxing the assumption of equilibrium (section 2, 4, and 5) changes the correlations. During

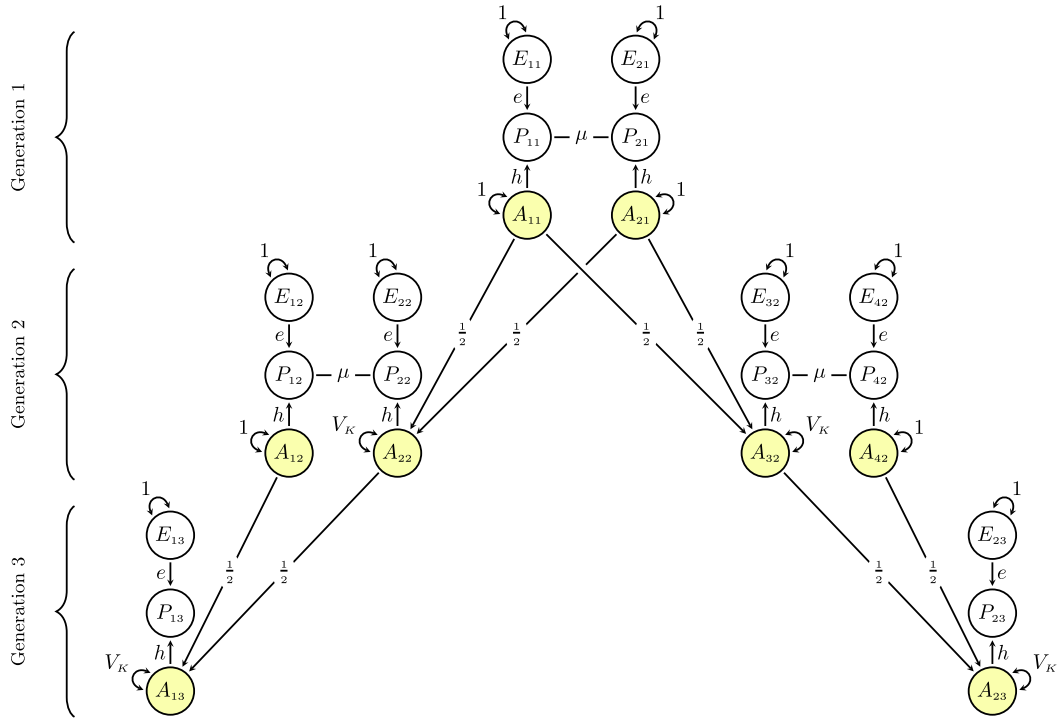

Fig. 1. Path diagram for a model of genetic similarity in extended families under phenotypic assortative mating at intergenerational equilibrium (i.e., equal variance across generations). The partner correlation attributable to assortment is denoted by μ, the recombination variance is denoted by V_K, and h and e denote the effect of additive genetic (A_{ig}) and environmental factors (E_{ig}), respectively, on the phenotype (P_{ig}) of individual i in generation g. All variables have unit variance, meaning $e = \sqrt{1-h^2}$ and $V_K = \frac{1-\mu h^2}{2}$. See the supplementary information for path diagrams representing disequilibrium and including polygenic indices.

disequilibrium, the true correlation will be less than what equation 2 suggests. For polygenic index correlations, one must include a term representing the imperfect correlation between the polygenic index and the true genetic propensity (Supplementary Fig. 1). The polygenic index correlation between partners should therefore be:

$$\rho_{pgi} = \mu h^2 s^2 \tag{3}$$

where s^2 is the shared variance between the polygenic index and the true additive genetic factor (i.e., the genetic signal). If the genetic signal is low, the polygenic index correlation between partners will be biased towards zero compared to the true genotypic correlation[21]. For first-degree relatives, the equation becomes similarly altered, but because the error terms in the polygenic indices are correlated between relatives, the polygenic index correlation will be biased towards the coefficient of relatedness rather than zero:

$$r_{pgi_1} = \frac{1 + \rho_{pgi}}{2} \tag{4}$$

Expected genotypic correlations in the extended family

The model in Fig. 1 has two properties that allow a general algorithm to find the expected genotypic correlation between any two members in extended families. First, all the chains that connect the genotypes of first-degree relatives can readily be continued without breaking path tracing rules. Second, all chains between the genotypes

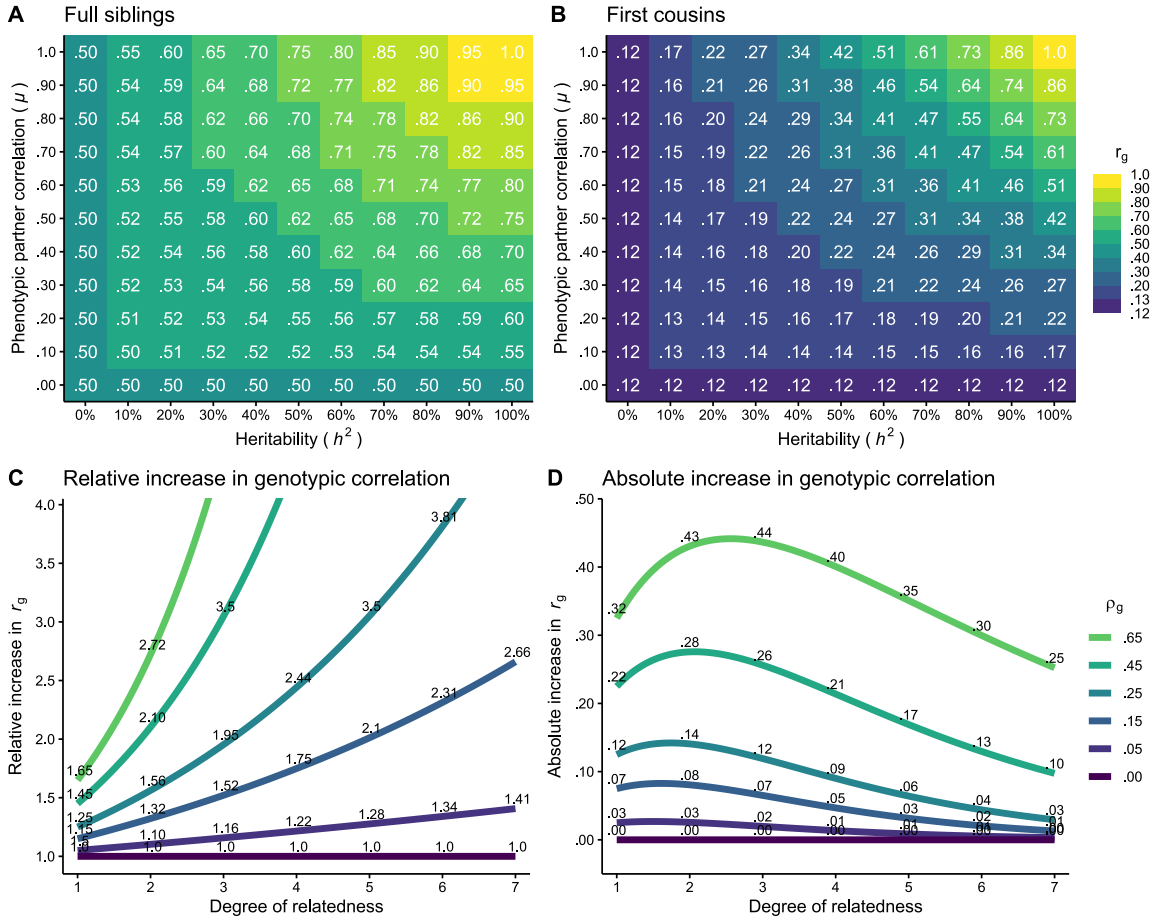

Fig. 2. Assortative mating's effect on genotypic correlations between various relatives. **Top**: The expected genotypic correlation (r_g) at equilibrium between (**A**) full siblings (i.e., first-degree relatives) and (**B**) first cousins (i.e., third-degree relatives) under different combinations of assortment strengths (μ) and heritabilities (h^2). **Bottom**: The relative (**C**) and absolute (**D**) increase in genotypic correlation at equilibrium for various relatives and genotypic correlations between partners (p_g). The reproducible code for this figure is available at https://osf.io/dgw4r/.

of any two related individuals are mediated sequentially through the genotypes of first-degree relatives. The genotypic correlation between k^{th}-degree relatives, denoted r_{g_k}, can thus be attained by raising the genotypic correlation between first-degree relatives to the degree of relatedness:

$$r_{g_k} = r_{g_1}^k = \left(\frac{1+\rho_g}{2}\right)^k \tag{5}$$

For example, the expected genotypic correlation between third-degree relatives like first cousins is $r_{g_1}^3$. This can be verified by manually tracing all valid chains between A_{13} and A_{23} in Fig. 1. The genotypic correlation between non-blood relatives like in-laws, which will be non-zero under assortative mating, can be attained by linking together chains of r_{g_k} and ρ_g (for example, $Corr(A_{12}, A_{42}) = r_{g_1}\rho_g^2$). As for polygenic index correlations, they can be attained by replacing ρ_g with ρ_{pgi} in equation 5 (see supplementary information, section 1).

Fig. 2 shows how assortative mating transforms genotypic correlations between relatives at equilibrium. In Panels A and B, it is evident that assortative mating has a much larger effect on first cousins than full siblings. For

example, for a trait where $\mu = .50$ and $h^2 = 50\%$ (meaning $\rho_g = .25$), siblings (Panel A) will have a correlation of $r_{g_1} = .625$ whereas cousins (Panel B) will have a correlation of $r_{g_3} = .244$, reflecting increases of 25% and 95%, respectively, compared to random mating. Panel C shows how this pattern extends to more distant relatives, with the genotypic correlation between second cousins 3.5 times higher than normal if $\rho_g = .25$ ($r_{g_5} = .095$ *vs.* $.031$). The larger relative increase is not merely because the correlations are smaller to begin with: Panel D shows that the largest absolute increase typically occurs in second-degree relatives like uncles/aunts and nephews/nieces.

The relatively greater increase in correlation between cousins is because third-degree relatives are affected by three assortment processes: Mother-father, uncle-aunt, and grandfather-grandmother partnerships are all correlated under assortative mating and contribute to the increased correlation (Fig. 1). For each additional degree of relatedness, there is an additional assortment process opening pathways for relatives to correlate. This pattern extends to unrelated individuals like siblings-in-laws, who would have a genotypic correlation of $\rho_g r_{g_1} = .157$ if $\rho_g = .25$. It is evident that assortative mating has a relatively larger impact on the genotypic correlation between distant relatives compared to close relatives, and that heritable traits subject to strong assortment can produce significant genotypic correlations between family members who would otherwise be virtually uncorrelated.

Empirical polygenic index correlations between partners and relatives

Fig. 3 shows polygenic index correlations between family members for a range of traits. Eight out of fifteen traits were significantly correlated between partners (Panel A), including height (.07), body mass index (.05), intelligence (.04), and educational attainment (.14). When educational attainment was split into cognitive and non-cognitive factors (GWAS-by-subtraction[36]), we find roughly equal partner correlations for both components. Psychiatric traits like ADHD, depression, cross-psychiatric disorder, and bipolar disorder exhibited no significant correlations between partners. Keep in mind that the correlations will be biased downwards to the extent the genetic signal is poor (ref. equation 3).

Panels B, C, and D show polygenic index correlations between full siblings, parents and offspring, and first cousins, respectively (see Supplementary Fig. 9 for other relatives). The vertical dashed lines are the expected correlations under random mating and the black crosses are the expected correlations at equilibrium given the partner correlation. All traits with significant correlations between partners had significantly higher parent-offspring correlations than would be expected under random mating, and we observed similar patterns for higher-degree relatives. For example, the correlation between polygenic indices for educational attainment was 0.56 (instead of 0.50) between full siblings and 0.20 (instead of 0.125) between first cousins.

Testing intergenerational equilibrium

We fitted structural equation models using mother-father-child to see if a model constrained to equal variance across generations (i.e., equilibrium) resulted in significantly worse fit (see supplementary information, section 6). Five out of eight traits were significantly different from equilibrium. We also investigated two consequences of disequilibrium, namely greater variance in the offspring generation (Fig 4A) and smaller-than-expected parent-offspring correlations (Fig. 4B). During disequilibrium, the ratio of offspring polygenic index variance to parental polygenic index variance should be positive: $Q_{pgi} = \frac{Offspring\ Variance}{Parental\ Variance}$ (see supplementary information, section 2 and 4). However, this ratio is quite sensitive to the genetic signal of the polygenic index, and therefore provides

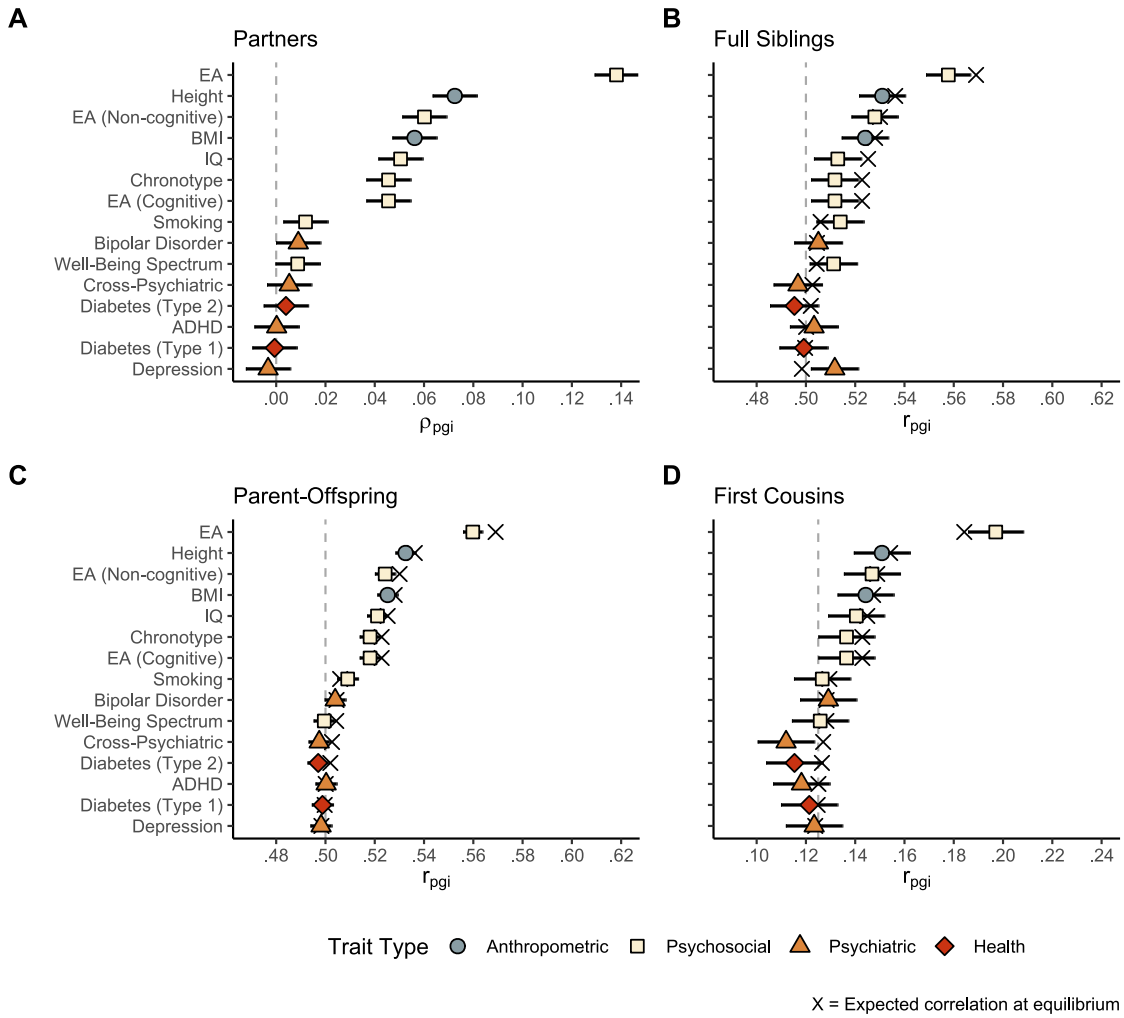

Fig. 3: Polygenic index correlations for various traits between various family members: (**A**) partners, (**B**) full siblings, (**C**) parent-offspring, and (**D**) first cousins. The vertical dashed lines are the expected correlation under random mating (i.e., the coefficient of relatedness), and the black crosses are the expected correlation at equilibrium given equation 5. Abbreviations: EA = educational attainment; BMI = body mass index; IQ = intelligence; ADHD = attention-deficit hyperactivity disorder. Error bars are 95% confidence intervals. The summary statistics and reproducible code for this figure is available at https://osf.io/dgw4r/.

limited information about the history of assortative mating beyond demonstrating disequilibrium. An alternative measure that is less sensitive to the genetic signal is the observed increase in polygenic index correlation as a percentage of the expected increase[21]: $U_{pgi} = \frac{Observed\ Increase}{Expected\ Increase}$ (see supplementary information, section 3 and 5). This provides a measure of how close the trait is to equilibrium. By comparing U_{pgi} to reference values under various heritabilities and assortment strengths, it is possible to infer the equivalent number of generations of stable assortative mating. If the parental generation was the first generation to mate assortatively, we would expect a $U_{pgi} \approx 70\%$, while we would expect $U_{pgi} = 100\%$ if the trait was in equilibrium.

Height and body mass index did not deviate from equilibrium: There was no significant difference between the parental and offspring variance nor between the observed and expected correlations. Psychosocial traits, on the other hand, deviated from equilibrium: For example, the polygenic index variance for educational attainment was 2.4% greater in the offspring generation compared to the parental generation. The true genetic variance ratio is likely much larger: For example, if the polygenic index captures one third of the true genetic factor ($s^2 = 1/3$),

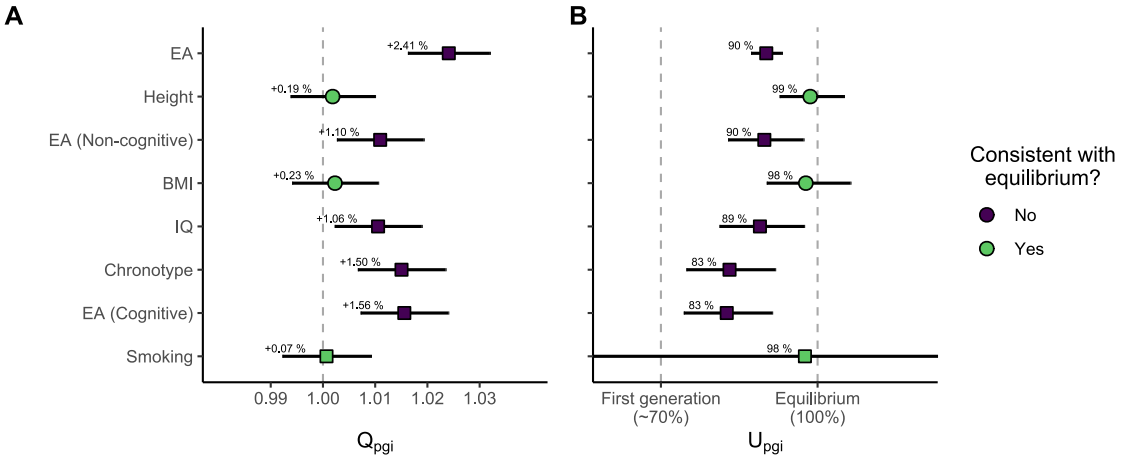

Fig. 4: (**A**) Ratio of offspring polygenic index variance to parental polygenic index variance (Q_{pgi}, see supplementary information, section 2 and 4). A value above 1 would indicate that the variance is greater in the offspring generation compared to the parental generation, as expected during disequilibrium. (**B**) Observed increase in parent-offspring correlation compared to expected increase at equilibrium (U_{pgi}, see supplementary information, section 3 and 5). A value of about 70% would indicate that the parent generation was the first generation to assort on this trait, whereas 100% would indicate that the trait is in intergenerational equilibrium. Only traits with significant correlations between partners are shown. Abbreviations: EA = educational attainment; BMI = body mass index; IQ = intelligence. Error bars are 95% confidence intervals. The summary statistics and reproducible code for this figure is available at https://osf.io/dgw4r/.

then the true variance ratio would be approximately 7.2% (see supplementary information, section 4). The parent-offspring polygenic index correlation was also slightly but significantly lower than expected at equilibrium ($U_{pgi} = 90\%$, 95% CIs: 87–93%), with similar results for the other psychosocial traits. When we compared this to calculations of what the observed increase would have been after successive generations of stable assortment, we found that $U_{pgi} = 90\%$ is equivalent to approximately three generations of stable assortative mating (see supplementary information, section 3 and 5).

Discussion

In this study, our goal was to clarify the theoretical consequences of assortative mating on genetic similarity in extended families and assess empirical measures of genetic similarity to provide insights into the presence and history of assortative mating. We first employed path analysis to deduce the expected polygenic index correlations between relatives under assortative mating. We then presented empirical evidence that assortative mating is present for many traits, leading to significantly increased genetic similarity among relatives for those traits. Finally, we showed that – while assortative mating does not appear to be a recent phenomenon for most traits – genetic similarity is still increasing across generations for psychosocial traits. Here, we discuss the implications of our findings.

Aim 1: Theoretical expectations

Our first aim was to clarify the theoretical consequences of assortative mating. Our key finding is the stronger impact of assortative mating on genotypic correlations between more distant relatives. Although not a novel discovery – even Fisher mentioned it offhandedly in his seminal paper[1] – this effect has been largely overlooked in the literature (cf. [37]). This is despite important implications. A Swedish economics paper reported that nearly one-third of persistence in inequality across generations – traditionally attributable to parent-offspring relationships – is attributable to the extended family[38]. Assortative mating's effects on similarity in extended families may be key to understanding these issues. Similar logic may also apply to environmentally mediated sources of similarity.

Aim 2: Genetic similarity between partners

The second aim of this study was to investigate which traits show genetic evidence of assortative mating. One key challenge when evaluating the pervasiveness of assortative mating is that phenotypic partner similarity can come about from multiple processes. Genotypic similarity, on the other hand, can more confidently be attributed to assortative mating. Most anthropometric traits and psychosocial traits had significant polygenic index correlations between partners. The largest correlation was for educational attainment (.14), which adds to the growing list of evidence that variants associated with educational attainment is undergoing assortative mating[9,21,25,27,39].

Somewhat surprisingly, psychiatric traits did not show evidence of assortative mating despite pervasive phenotypic partner correlations[17,18]. The findings are in line with a recent study that found no genetic partner similarity on general risk for psychopathology (i.e., the "p-factor")[40]. This could indicate that phenotypic partner similarity are caused by processes other than assortative mating, such as convergence[22]. On the other hand, they could also be false negatives resulting from inadequate polygenic indices. As highlighted in equation 3, the polygenic index correlation between partners should be the product of the phenotypic correlation attributable to assortative mating (μ), the heritability (h^2), and the genetic signal (s^2). If the polygenic index fail to adequately measure the relevant genetic factors (meaning $s^2 \approx 0$), for example due to lack of statistical power or other measurement issues[41] in the underlying genome-wide associations study (GWAS), then the polygenic index correlation will be biased towards zero. The highest observed correlations were for educational attainment and height, which are among the traits with the largest sample sizes in the underlying GWAS. A corollary is that the correlations reported here do not quantify the exact degree of assortative mating because it is confounded by the quality of the polygenic index.

Aim 3: Genetic similarity between relatives

Our third aim was to investigate whether relatives were more genetically similar for traits that exhibit evidence of assortative mating. Our findings broadly correspond to theoretical expectations: Traits with significant polygenic index correlations between partners showed increased similarity between relatives, whereas traits with no correlations between partners broadly exhibit patterns as expected under random mating. These empirical patterns demonstrate the theoretical expectations derived earlier, meaning we should expect distant relatives to be highly correlated for traits under strong assortment. The correlations reported here are underestimated by the quality of the polygenic index, meaning the true genotypic correlations between relatives are likely much larger. Our findings have at least two implications. First, genetic variants associated with traits undergoing assortment, such as educational attainment, cluster in extended families, thus increasing or maintaining societal stratification by families[38] (i.e. between-family variation); and second, genetic studies that unknowingly involve numerous distantly related individuals may be biased if the genotypic correlations between them are not negligible.

Aim 4: Intergenerational equilibrium

Our fourth aim was to investigate the history of assortative mating. Our findings differed across traits: Height and body mass index did not deviate from equilibrium expectations, whereas psychosocial traits such as educational attainment did. This was evident in both lower-than-expected parent-offspring polygenic index correlations and greater variance in the offspring generation. Whether or not a trait is in intergenerational equilibrium has important implications for the consequences of assortative mating because it decides whether differences are increasing across generations or merely maintained. We found that polygenic index variance was stable across generations for height and body mass index (as well as for traits not undergoing assortative mating). However, psychosocial traits have greater variance in the offspring generation, implying that the traits are in disequilibrium and that assortative mating is currently leading to *increased* genetic differences in these traits. Although the non-genetic consequences may differ, assortative mating may therefore play a key role in explaining recent increases in inequality[12,15].

Despite being in disequilibrium, the evidence does not suggest that the parental generation was the first to assort on educational attainment. Instead, it appears that the trait is quite near equilibrium. This would also explain the discrepancy between our conclusion and that in Torvik, et al. [21], who found no significant deviation from equilibrium using an earlier version of data from the same cohort. We attribute the change in result from an increase in statistical power, stemming from more genotyped individuals available in the current sample. In this paper, we estimate that the evidence for educational attainment corresponds to approximately three generations of stable assortative mating, but the exact history of assortment may be longer if the strength of assortment has varied over time or if the heritability increased for other reasons[42].

Methodological implications

Many genetic research methods assume random mating, but our findings suggest that such assumptions are unwarranted for many traits. Accounting for assortative mating poses its own challenges, as the genetic consequences and corresponding methods needed depend on whether assortative mating started recently or has reached intergenerational equilibrium. Studies on the genetics of educational attainment especially – or the many traits that correlate with educational attainment[43] – may therefore be biased unless this is properly accounted for.

Twin and family studies that account for assortative mating typically assume equilibrium[35]. Conversely, Kong, et al. [44], who investigated genetic nurture effects of educational attainment in an Icelandic sample, assumed no assortment prior to their parental generation. Our findings imply that, for some traits, neither of these assumptions are valid. Although the patterns and history of assortment may be different across populations, future research should investigate how the conclusions from Kong, et al. [44] and related papers depend on these assumptions[45,46].

Newer genetic methods that can account for disequilibrium are being developed[34]. When these methods are impractical, the potential biases induced by different assumptions must be considered on a case-by-case and method-by-method basis. Different methods will be biased in different ways. For example, assortative mating leads to underestimated heritability in classical twin designs[35,47] and overestimated heritability in molecular designs[48], with the corollary that the missing heritability problem may be larger than previously assumed[49,50]. Overall, researchers must carefully consider what impacts the presence and history of assortative mating would have on their results.

Limitations and future directions

Despite our large sample size, our results are limited by low-quality polygenic indices, which results in lower partner correlations and consequently less power to detect assortative mating. This is amplified for the tests of equilibrium, where smaller polygenic index correlations between partners result in less statistical power to detect deviations from equilibrium. Our tests for equilibrium are therefore less conclusive for traits with small polygenic index correlations, such as smoking.

Another concern is that our results may be confounded by population stratification[51], where (1) the trait in question happens to be more common within certain strata (e.g., subcultures or geographical areas), (2) some genetic variants are randomly present at higher frequencies in these strata, and (3) individuals are more likely to mate within these strata. The combination of the first two phenomena would result in a spurious correlation between those genetic variants and the trait, and when coupled with the third phenomenon, similar spurious correlations could emerge between partners. While we controlled for 20 principal components in our analysis, which is the standard method for addressing stratification[52], this approach may not fully account for this phenomenon[53]. However, the evidence we present aligns well with predictions given assortative mating. It is also not obvious how population stratification could explain increased variance in the offspring generation. Consequently, our results should be considered indicative of assortative mating until a more compelling alternative explanation is offered. Future theoretical work should investigate how the consequences of assortative mating and population stratification differ so that they can better be distinguished in future research.

There are several interesting research avenues that could follow from this work. First, we did not consider shared environmental effects or gene-environment correlations in our models, which may affect the genetic consequences of assortative mating. Second, there may be some selection bias in the cohort study our results are based on. Future work using population-wide phenotypic data might provide insights into how much this matters. Third, patterns of assortative mating are likely to vary between populations[54,55], meaning that our empirical findings may not be universally generalizable. Replicating these results in other populations will therefore be beneficial. Fourth, future research may want to investigate which phenotypes mediate the polygenic index correlations between partners, as it may not always be attributable to the phenotype that the polygenic index supposedly measures.

Methods

Sample

We used data from the Norwegian Mother, Father and Child Cohort Study (MoBa)[29]. MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 41% of the pregnancies. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth[56]. The cohort includes approximately 114,500 children, 95,200 mothers and 75,200 fathers. The current study is based on version 12 of the quality-assured data files released for research in January 2019. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (2017/2205).

For the correlations, the sample included 47,135 unique mother-father dyads (i.e., partners) where both had been genotyped and passed quality control [30]. As described in Corfield, et al. [30], relatedness relationships in MoBa were inferred from genetic data by applying KING programs[57] to a subset of single nucleotide polymorphisms (SNPs) with call rate < 98% and minor allele frequency (MAF) < 5%. KING accurately infers monozygotic twin or duplicate pairs (kinship coefficient > 0.3540), first-degree (parent-offspring, full siblings, dizygotic twin pairs; kinship coefficient range 0.1770 - 0.3540), second-degree (half siblings, grandparent-offspring, avuncular relationships; kinship coefficient range 0.0884 – 0.1770), and third-degree (first cousins; kinship coefficient range 0.0442 – 0.0884) relationships. This method identified 117,041 parent-offspring dyads, 22,575 full sibling dyads, 35,923 second-degree dyads (e.g., uncle-nephew), 28,330 third-degree dyads (e.g., first cousins), 9,392 fourth-degree dyads, and 235,209 dyads of unrelated family members (e.g., in-laws, nephews–uncles' spouses, partners, etc.,) where both members of the dyads had been genotyped and passed quality control.

To test equilibrium, we used mother-father-child trios from MoBa. After randomly selecting one offspring from each nuclear family, we were able to construct a sample of 81,145 genotyped mothers, 54,550 genotyped fathers, and 71,544 genotyped offspring, resulting in a total of 93,767 families. Of these, 36,764 were complete trios, whereas 10,371 included only partners, 24,659 included only mother-offspring dyads, and 4,914 included only father-offspring dyads.

Measures

We used beta weights from large, publicly available up-to-date genome-wide association studies listed the supplementary information, section 8. Polygenic indices were calculated using LDPred[58], a Bayesian approach that uses a prior on the expected polygenicity of a trait (assumed fraction of non-zero effect markers) and adjusts for linkage disequilibrium (LD) based on a reference panel to compute SNPs weights. Genotypes were coordinated with the summary statistics, with the number of overlapping SNPs reported in supplementary information, section 8. LD adjustment was performed using the European subsample of the 1000 Genomes genotype data as LD reference panel[59]. The weights were estimated based on the heritability explained by the markers in the GWAS summary statistics and the assumed fraction of markers with non-zero effects. For each GWAS trait we created

LDpred PGI with the –score command in plink2[60]. Prior to calculating correlations between partners and relatives, we residualised the polygenic indices by regressing out the first 20 principal components of genetic ancestry, as well as chip, imputation, and batch number.

Statistics

The polygenic index correlations were attained by correlating the residualised polygenic indices between partners and relatives using *cor.test* in R. 4.0.3[61]. We tested whether the observed correlations were consistent with equilibrium by fitting structural equation models to mother-father-child trio covariance matrices, and testing whether a model constrained to equilibrium via equal variance across generations resulted in significantly worse fit. We describe this procedure in more detail in the supplementary information, section 6.

Acknowledgements

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References

1 Fisher, R. A. The Correlation between Relatives on the Supposition of Mendelian Inheritance. *Transactions of the Royal Society of Edinburgh* **52**, 399-433 (1918). https://doi.org:10.1017/s0080456800012163

2 Wright, S. Systems of mating. III. Assortative Mating based on Somatic resemblance. *Genetics* **6**, 144-161 (1921). https://doi.org:10.1093/genetics/6.2.144

3 Bulmer, M. G. *The Mathematical Theory of Quantitative Genetics*. (Oxford University Press, 1980).

4 Lynch, M. & Walsh, B. *Genetics and Analysis of Quantitative Traits*. (Sinauer Associates, Inc., 1998).

5 Nagylaki, T. The correlation between relatives with assortative mating. *Annals of Human Genetics* **42**, 131-137 (1978). https://doi.org:10.1111/j.1469-1809.1978.tb00938.x

6 Gimelfarb, A. Quantitative characters under assortative mating: Gametic model. *Theoretical Population Biology* **25**, 312-330 (1984). https://doi.org:10.1016/0040-5809(84)90012-1

7 Hayashi, T. Genetic variance under assortative mating in the infinitesimal model. *Genes & Genetic Systems* **73**, 397-405 (1998). https://doi.org:10.1266/ggs.73.397

8 Gimelfarb, A. A general linear model for the genotypic covariance between relatives under assortative mating. *Journal of Mathematical Biology* **13**, 209-226 (1981). https://doi.org:10.1007/bf00275215

9 Robinson, M. R. *et al.* Genetic evidence of assortative mating in humans. *Nature Human Behaviour* **1**, 0016 (2017). https://doi.org:10.1038/s41562-016-0016

10 Robert Plomin, Eva Krapohl & F. O'Reilly, P. Assortative Mating—A Missing Piece in the Jigsaw of Psychiatric Genetics. *JAMA Psychiatry* **73**, 323 (2016). https://doi.org:10.1001/jamapsychiatry.2015.3204

11 Yengo, L. Mate choice through a genomic lens. *Nature Reviews Genetics* (2023). https://doi.org:10.1038/s41576-023-00605-w

12 Schwartz, C. R. Trends and Variation in Assortative Mating: Causes and Consequences. *Annual Review of Sociology* **39**, 451-470 (2013). https://doi.org:10.1146/annurev-soc-071312-145544

13 Mare, R. D. Five Decades of Educational Assortative Mating. *American Sociological Review* **56**, 15-32 (1991). https://doi.org:10.2307/2095670

14 Birkelund, G. E. & Heldal, J. Who marries whom? Educational homogamy in Norway. *Demographic Research* **8**, 1-30 (2003). https://doi.org:10.4054/DemRes.2003.8.1

15 Greenwood, J., Guner, N., Kocharkov, G. & Santos, C. Marry Your Like: Assortative Mating and Income Inequality. *American Economic Review* **104**, 348-353 (2014). https://doi.org:10.1257/aer.104.5.348

16 Eika, L., Mogstad, M. & Zafar, B. Educational Assortative Mating and Household Income Inequality. *Journal of Political Economy* **127**, 2795-2835 (2019). https://doi.org:10.1086/702018

17 Horwitz, T. B., Balbona, J. V., Paulich, K. N. & Keller, M. C. *Correlations between human mating partners: a comprehensive meta-analysis of 22 traits and raw data analysis of 133 traits in the UK Biobank* (BioRxiv, 2023).

18 Nordsletten, A. E. *et al.* Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders. *JAMA Psychiatry* **73**, 354 (2016). https://doi.org:10.1001/jamapsychiatry.2015.3192

19 Luo, S. & Klohnen, E. C. Assortative Mating and Marital Quality in Newlyweds: A Couple-Centered Approach. *Journal of Personality and Social Psychology* **88**, 304-326 (2005). https://doi.org:10.1037/0022-3514.88.2.304

20 Luo, S. Assortative mating and couple similarity: Patterns, mechanisms, and consequences. *Social and Personality Psychology Compass* **11**, e12337 (2017). https://doi.org:https://doi.org/10.1111/spc3.12337

21 Torvik, F. A. *et al.* Modeling assortative mating and genetic similarities between partners, siblings, and in-laws. *Nature Communications* **13** (2022). https://doi.org:10.1038/s41467-022-28774-y

22 Sjaarda, J. & Kutalik, Z. Partner choice, confounding and trait convergence all contribute to phenotypic partner similarity. *Nature Human Behaviour* (2023). https://doi.org:10.1038/s41562-022-01500-w

23 Turkheimer, E. Three Laws of Behavior Genetics and What They Mean. *Current Directions in Psychological Science* **9**, 160-164 (2000). https://doi.org:10.1111/1467-8721.00084

24 Polderman, T. J. C. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics* **47**, 702-709 (2015). https://doi.org:10.1038/ng.3285

25 W. Domingue, B., J. Fletcher, D. Conley & D. Boardman, J. Genetic and educational assortative mating among US adults. *Proceedings of the National Academy of Sciences* **111**, 7996-8000 (2014). https://doi.org:10.1073/pnas.1321426111

26 Okbay, A. *et al.* Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nature Genetics* **54**, 437-449 (2022). https://doi.org:10.1038/s41588-022-01016-z

27 Yengo, L. *et al.* Imprint of assortative mating on the human genome. *Nature Human Behaviour* **2**, 948-954 (2018). https://doi.org:10.1038/s41562-018-0476-3

28 Wright, S. Systems of mating. II. The effects of inbreeding on the genetic composition of a population. *Genetics* **6**, 124-143 (1921). https://doi.org:10.1093/genetics/6.2.124

29 Magnus, P. *et al.* Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology* **45**, 382-388 (2016). https://doi.org:10.1093/ije/dyw029

30 Corfield, E. C. *et al. The Norwegian Mother, Father, and Child cohort study (MoBa) genotyping data resource: MoBaPsychGen pipeline v.1* (BioRxiv, 2022).

31 Wright, S. Correlation and Causation. *Journal of Agricultural Research* **20**, 557-585 (1921).

32 Wright, S. The Method of Path Coefficients. *The Annals of Mathematical Statistics* **5**, 161-215 (1934).

33 Cloninger, C. R. Interpretation of intrinsic and extrinsic structural relations by path analysis: theory and applications to assortative mating. *Genetical Research* **36**, 133-145 (1980). https://doi.org:10.1017/s0016672300019765

34 Balbona, J. V., Kim, Y. & Keller, M. C. Estimation of Parental Effects Using Polygenic Scores. *Behavior Genetics* **51**, 264-278 (2021). https://doi.org:10.1007/s10519-020-10032-w

35 Keller, M. C. *et al.* Modeling Extended Twin Family Data I: Description of the Cascade Model. *Twin Research and Human Genetics* **12**, 8-18 (2009). https://doi.org:10.1375/twin.12.1.8

36 Demange, P. A. *et al.* Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. *Nature Genetics* **53**, 35-44 (2021). https://doi.org:10.1038/s41588-020-00754-2

37 Yengo, L. & Visscher, P. M. Assortative mating on complex traits revisited: Double first cousins and the X-chromosome. *Theoretical Population Biology* **124**, 51-60 (2018). https://doi.org:10.1016/j.tpb.2018.09.002

38 Adermon, A., Lindahl, M. & Palme, M. Dynastic Human Capital, Inequality, and Intergenerational Mobility. *American Economic Review* **111**, 1523-1548 (2021). https://doi.org:10.1257/aer.20190553

39 Abdellaoui, A., Borcan, O., Chiappori, P.-A. & Hugh-Jones, D. Trading Social Status for Genetics in Marriage Markets: Evidence from UK Biobank (working paper). *HCEO Working Paper Series* (2022).

40 Ayorech, Z. *et al.* (PsyArXiv, 2023).

41 Fried, E. I., Flake, J. K. & Robinaugh, D. J. Revisiting the theoretical and methodological foundations of depression measurement. *Nature Reviews Psychology* (2022). https://doi.org:10.1038/s44159-022-00050-2

42 Heath, A. C. *et al.* Education policy and the heritability of educational attainment. *Nature* **314**, 734-736 (1985). https://doi.org:10.1038/314734a0

43 Brendan Bulik-Sullivan *et al.* An atlas of genetic correlations across human diseases and traits. *Nature Genetics* **47**, 1236-1241 (2015). https://doi.org:10.1038/ng.3406

44 Kong, A. *et al.* The nature of nurture: Effects of parental genotypes. *Science* **359**, 424-428 (2018). https://doi.org:doi:10.1126/science.aan6877

45 Nivard, M. G. *et al. Neither nature nor nurture: Using extended pedigree data to elucidate the origins of indirect genetic effects on offspring educational outcomes.* (2022).

46 Demange, P. A. *et al.* Estimating effects of parents' cognitive and non-cognitive skills on offspring education using polygenic scores. *Nature Communications* **13** (2022). https://doi.org:10.1038/s41467-022-32003-x

47 Knopik, V. S., Neiderhiser, J. M., DeFries, J. C. & Plomin, R. *Behavioral Genetics*. 7th edn, (Worth Publishers, 2017).

48 Border, R. *et al.* Assortative mating biases marker-based heritability estimators. *Nature Communications* **13** (2022). https://doi.org:10.1038/s41467-022-28294-9

49 Young, A. I. Solving the missing heritability problem. *PLOS Genetics* **15**, e1008222 (2019). https://doi.org:10.1371/journal.pgen.1008222

50 Manolio, T. A. *et al.* Finding the missing heritability of complex diseases. *Nature* **461**, 747-753 (2009). https://doi.org:10.1038/nature08494

51 Abdellaoui, A., Verweij, K. J. H. & Zietsch, B. P. No evidence for genetic assortative mating beyond that due to population stratification. *Proceedings of the National Academy of Sciences* **111**, E4137-E4137 (2014). https://doi.org:10.1073/pnas.1410781111

52 Price, A. L. *et al.* Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics* **38**, 904-909 (2006). https://doi.org:10.1038/ng1847

53 Blanc, J. & Berg, J. J. *Testing for differences in polygenic scores in the presence of confounding* (Cold Spring Harbor Laboratory, 2023).

54 Yamamoto, K. *et al.* Genetic footprints of assortative mating in the Japanese population. *Nature Human Behaviour* (2022). https://doi.org:10.1038/s41562-022-01438-z

55 Verweij, K. J. H. & Abdellaoui, A. Partner-choice genetics in Japan. *Nature Human Behaviour* (2022). https://doi.org:10.1038/s41562-022-01439-y

56 Paltiel, L. *et al.* The biobank of the Norwegian Mother and Child Cohort Study – present status. *Norsk Epidemiologi* **24** (2014). https://doi.org:10.5324/nje.v24i1-2.1755

57 Manichaikul, A. *et al.* Robust relationship inference in genome-wide association studies. *Bioinformatics* **26**, 2867-2873 (2010). https://doi.org:10.1093/bioinformatics/btq559

58 Vilhjálmsson, J., Bjarni *et al.* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *The American Journal of Human Genetics* **97**, 576-592 (2015). https://doi.org:10.1016/j.ajhg.2015.09.001

59 Chou, W.-C. *et al.* A combined reference panel from the 1000 Genomes and UK10K projects improved rare variant imputation in European and Chinese samples. *Scientific Reports* **6**, 39313 (2016). https://doi.org:10.1038/srep39313

60 Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience* **4** (2015). https://doi.org:10.1186/s13742-015-0047-8

61 R: A language and environment for statistical computing. (R Foundation for Statistical Computing, Vienna, Austria, 2022).

Paper 3
Supplementary Information

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Supplementary information

Genetic similarity between relatives provides evidence on the presence and history of assortative mating

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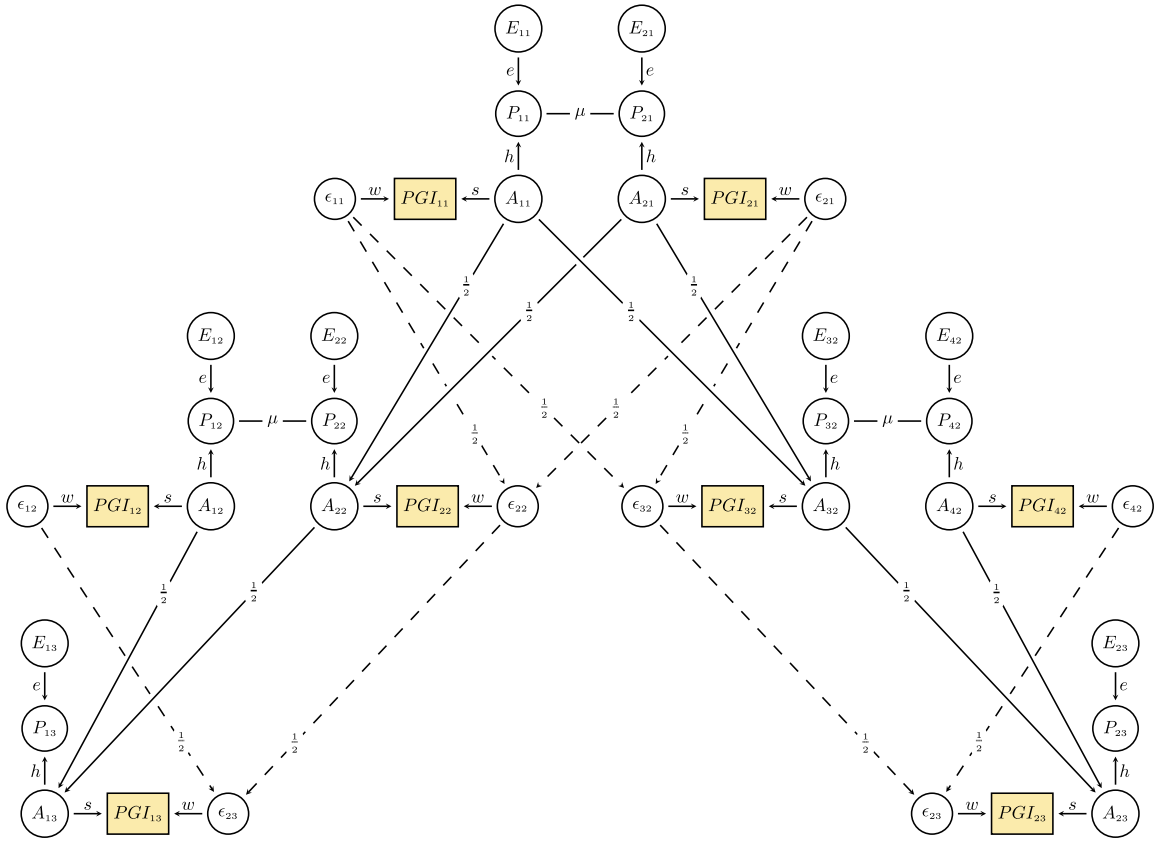
Contents

1. Polygenic index correlations at equilibrium



Supplementary Fig. 1: *Path diagram of associations between relatives' polygenic indices (PGI).*

Supplementary Fig. 1 is an extension of Fig. 1 and represents the associations between various family members' polygenic indices at equilibrium. The equilibrium assumption is instantiated via equal variances across generations. All variables have unit variances, and the variance terms (↔) are not drawn to remove clutter. We assume polygenic indices are composed of true genetic factors (A) and noise (ϵ). The correlation between the true genetic factors and the polygenic indices is denoted s, meaning the genetic signal – the shared variance between the polygenic index and the true genetic factor – is s^2. To keep all variables at unit variances, the effect of noise will be $w = \sqrt{1 - s^2}$ (similar to how $e = \sqrt{1 - h^2}$). Because the error in the polygenic index primarily results from misestimated effects and not mismeasured genotypes, the errors will be inherited just like the phenotype-related genotype (dashed lines). By path tracing, we see that the polygenic index correlation between partners (e.g., PGI_{11} and PGI_{21}) should be:

$$\rho_{pgi} = s \times h \times \mu \times h \times s = \mu h^2 s^2 \qquad (S1.1)$$

If one suspects that the genetic signal is poor, it is possible to do a back-of-the-envelope calculation to find the approximate value of ρ_g. For example, the polygenic index from the most recent genome-wide association study for educational attainment explained between 12% and 15% of the variance in holdout samples[1], whereas a meta-analysis of twin studies on educational attainment[2] estimated the mean heritability to be about 45%. Obviously, these values are likely to vary by population and cohort, but if we take these at face value, the polygenic index captures $s^2 = \frac{15}{45} = 33\%$ of the true additive genetic variance. We observe a polygenic index

correlation of .14 between partners for educational attainment, but if that polygenic index has a genetic signal of about 33%, then the true genotypic correlation is likely somewhere around $\rho_g = \frac{\rho_{pgi}}{s^2} = .42$. (Remember that the confidence intervals would also be similarly inflated). If you think the genetic signal is higher or lower, you can repeat the calculation with numbers of your choice.

The polygenic index correlation between any two relatives can be thought to be composed of two components: the error-related genotype and the phenotype-related genotype. The error term correlation should equal the coefficient of relatedness, whereas the phenotype-related genotypic correlation will equal the true genotypic correlation. These two components will be weighted by w^2 and s^2, respectively:

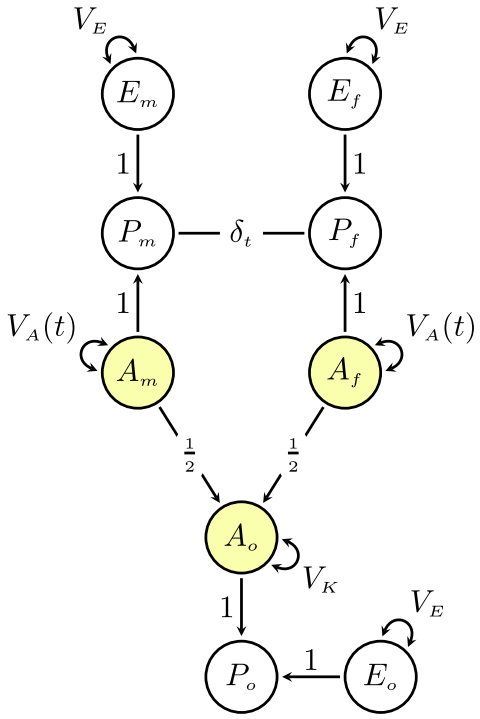
$$r_{pgi_k} = w^2 \left(\frac{1}{2}\right)^k + s^2 \left(\frac{1+\rho_g}{2}\right)^k \quad (S1.2)$$

This can be verified by tracing all chains between any two relatives in Supplementary Fig. 1.

Equation S1.2 simplifies to:

$$r_{pgi_k} = \left(\frac{1+\rho_{pgi}}{2}\right)^k \quad (S1.3)$$

2. Genetic variance across generations during disequilibrium



Supplementary Fig. 2: *Path diagram illustrating genetic similarity in mother-father-child trios during disequilibrium.*

Because assortative mating will change genetic variance before equilibrium, we can no longer assume unit variances as we did in Fig. 1. Supplementary Fig. 2 therefore uses explicit variance components. This changes how we derive correlations, because tracing all valid chains between two variables will give us the covariance, not the correlation. To turn a covariance into a correlation, we need to divide by the geometric mean of the two variables' variances. To find the variances, we must trace all valid chains leading from the two variables back to themselves.

$$\frac{Cov(X,Y)}{\sqrt{Var(X) \times Var(Y)}} \tag{S2.1}$$

Before we understand how the correlation increases in successive generations under disequilibrium, we must first understand how the variance changes. The equations are available elsewhere[3-5], but because we will be extending the model to see how polygenic indices are affected, it will be useful to re-derive them from first principles using path analysis.

We let t denote the number of *prior* generations of assortative mating, where $t = 0$ is the generation where partners first match on the phenotype. Note that this would imply that partners in generation $t = 1$ would be the *second* generation to assort on the phenotype. Supplementary Fig. 2 shows a mother-father-offspring trio (subscripted m, f, and o, respectively) where the parents are in generation t. The genetic variance in

generation t is denoted $V_A(t)$, and the recombination variance is denoted V_K. The recombination variance will depend on the genetic variance in the base population (before assortative mating) and will be[3-6]:

$$V_K = \frac{V_A(0)}{2} \quad (S2.2)$$

The genetic and environmental *effects* are, for simplicity's sake, assumed to be constant across generations and therefore set to 1. We are also assuming that the environmental variance, denoted V_E, is constant across generations. If you want to relax these assumptions, you can replace them by appropriate parameters (e.g., $V_E(t)$) and redo the path tracing with these changes.

As always, the heritability in generation t is the genetic variance over the phenotypic variance:

$$h^2(t) = \frac{V_A(t)}{V_A(t) + V_E} \quad (S2.3)$$

The partner similarity is slightly more complicated because the co-path coefficient is neither the covariance nor the correlation between partners when variances are not equal to one. Instead, it is a special coefficient denoting the strength of assortment. Because we have already defined μ as the phenotypic *correlation*, the assortment strength in generation t is now denoted δ_t to avoid confusion. We can use path tracing to find the phenotypic partner correlation:

$$\mu = \frac{\delta_t(V_A(t) + V_E)^2}{V_A(t) + V_E} = \delta_t(V_A(t) + V_E) \quad (S2.4)$$

We can apply similar logic to the genotypic correlation between partners:

$$\rho_g(t) = \frac{\delta_t V_A^2(t)}{V_A(t)} = \delta_t V_A(t) \quad (S2.5)$$

Because heritability will change across generations, all else being equal, so will the genotypic correlation between partners – even when keeping μ constant. Note also that we can transform equation S2.5 using equation S2.3 and equation S2.4 and find that $\rho_G(t) = \mu h^2(t)$, thus matching equation 1 in the main paper. Finally, to keep μ constant while V_A increases, δ_t will have to decrease accordingly. It is an open question whether it is more realistic to keep μ or δ_t constant when investigating assortative mating across generations, but here we follow previous work and let μ be constant[3,7]. This does not affect the equations, but it would change the resulting figures somewhat.

We are now ready to derive the genetic variance in the offspring generation. We do that by tracing all paths leading from A_o back to itself:

$$V_A(t+1) = Var(A_o)$$

$$= V_K + \frac{V_A(t)}{4} + \frac{V_A(t)}{4} + \frac{\delta_t V_A^2(t)}{4} + \frac{\delta_t V_A^2(t)}{4}$$

$$= V_K + V_A(t)\frac{1 + \delta_t V_A(t)}{2} \quad (S2.6)$$

If we substitute S2.2 and S2.5 into S2.6, we get:

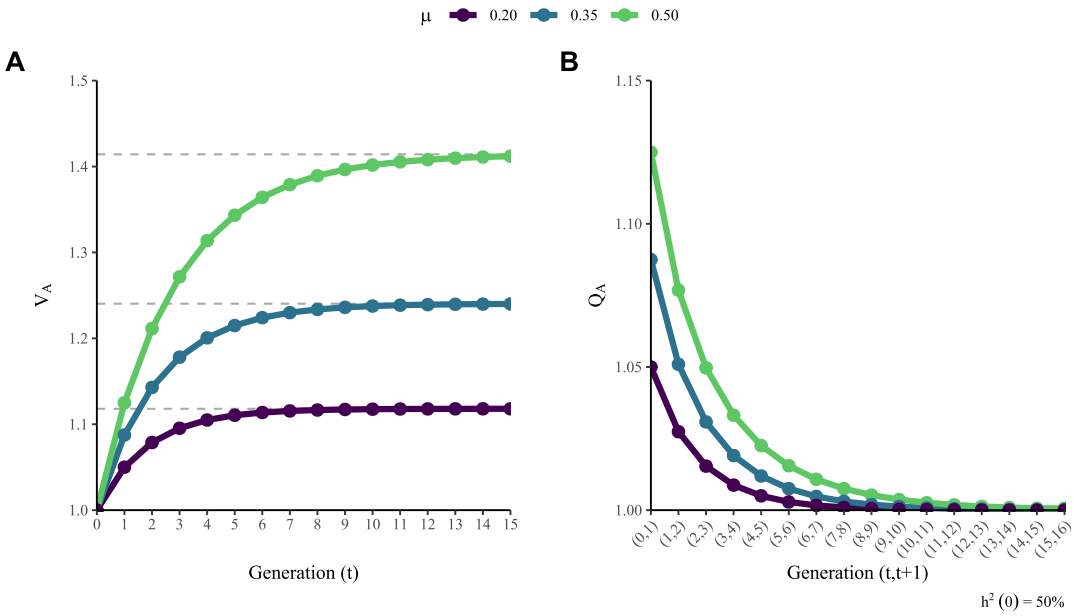
$$V_A(t+1) = \frac{V_A(0)}{2} + V_A(t)\left(\frac{1 + \rho_g(t)}{2}\right) \quad (S2.7)$$

This equation matches what is reported in other sources[3-5].

We will also define the intergenerational genetic variance ratio, $Q_A(t)$, as we will refer to that later:

$$Q_A(t) = \frac{V_A(t+1)}{V_A(t)} \quad (S2.8)$$

We can now apply equation S2.7 recurrently to see how genetic variance changes across generations under different scenarios. For simplicity's sake, we will assume the heritability is 50% before assortment in all plots presented hereafter.



Supplementary Fig. 3: *Genetic variance in successive generations of assortative mating.*

In Supplementary Fig. 3, we see how the genetic variance (V_A) increases in successive generations of assortative mating following equation S2.7 for three different phenotypic partner correlations. Panel A shows how the variance increases asymptotically towards equilibrium (indicated by the dashed lines), and Panel B shows the intergeneration variance ratio (Q_A). Overall, variance increases in the initial generations of assortment before reaching equilibrium after between 6 to 10 generations, practically speaking, depending on assortment strength. Larger partner correlations lead to more generations in disequilibrium in part because increased genetic variance leads to increased heritability (all else equal), which in turn leads to an increased genotypic correlation between partners, which in turn increases the variance further.

Note that we can simplify equation S2.8 further if we are interested in the first generation of assortment, where $V_A(t) = V_A(0)$, or the equilibrium variance, where $V_A(t) = V_A(t+1) = V_A(\infty)$:

$$V_A(1) = V_A(0)\left(1 + \frac{\rho_g(0)}{2}\right) \quad (S2.9a)$$

$$V_A(\infty) = \frac{V_A(0)}{1 - \rho_g(\infty)} \quad (S2.9b)$$

These simplifications match equations reported elsewhere[3,8].

3. The genotypic correlation between parents and offspring under disequilibrium

Because we have many more parent-offspring dyads in our data compared to other dyads, this correlation will be estimated with high precision. We will therefore only focus on the parent-offspring correlation under disequilibrium. To find the correlation, we must know the variance (which we derived in the last section) and the covariance. To find the covariance, we apply path tracing rules to find all valid chains between A_m (or A_f) and A_o in Supplementary Fig. 3, and simplify accordingly:

$$\begin{aligned} Cov(A_m, A_o) &= \frac{V_A(t)}{2} + \frac{\delta_t V_A^2(t)}{2} \\ &= V_A(t)\left(\frac{1+\rho_g(t)}{2}\right) \end{aligned} \quad (S3.1)$$

Because the genotypic covariance is a function of the genetic variance in the parent generation, the genotypic covariance too will increase together with the variance in successive generations of assortative mating. To find the correlation, we divide the covariance by the pooled variance:

$$r_g(t) = Corr(A_m, A_o) = \frac{V_A(t)\left(\frac{1+\rho_g(t)}{2}\right)}{\sqrt{V_A(t)V_A(t+1)}} \quad (S3.2)$$

The purple line Supplementary Fig. 4A shows how the genotypic correlation between parents and offspring increases with successive generations of assortative mating (assuming $h^2(0) = 50\%$ and $\mu = .50$). Note that, because the parent-offspring correlation is an intergenerational correlation, the number of prior generations of assortative mating will not be the same for parents and offspring. We will keep denoting the parental generation as generation t (and therefore the offspring generation as $t+1$). We see that the correlation increases immediately and keeps increasing towards an equilibrium just like how the variance increases.

The green dotted line is the expected genotypic correlation if we assumed equilibrium and used equation 2 from the main paper ($r_g = \frac{1+\rho_g}{2}$). We see that it only matches the actual correlation when the trait is in equilibrium. Otherwise, it overestimates the correlation. A mismatch between the true correlation and expected correlation between relatives is therefore evidence of a trait in disequilibrium.

The reason for this mismatch is directly attributable to different variances across generations. Equation two in the main paper implicitly assumes that the variance is equal across generations, but during disequilibrium, the pooled variance (the denominator) is slightly more than the variance in the parent generation (part of the numerator). This leads to a smaller correlation than equation 2 would predict. When we rearrange equation S2.8 and substitute that into the denominator of equation S3.2, the variance terms cancel out and we can express the correlation as:

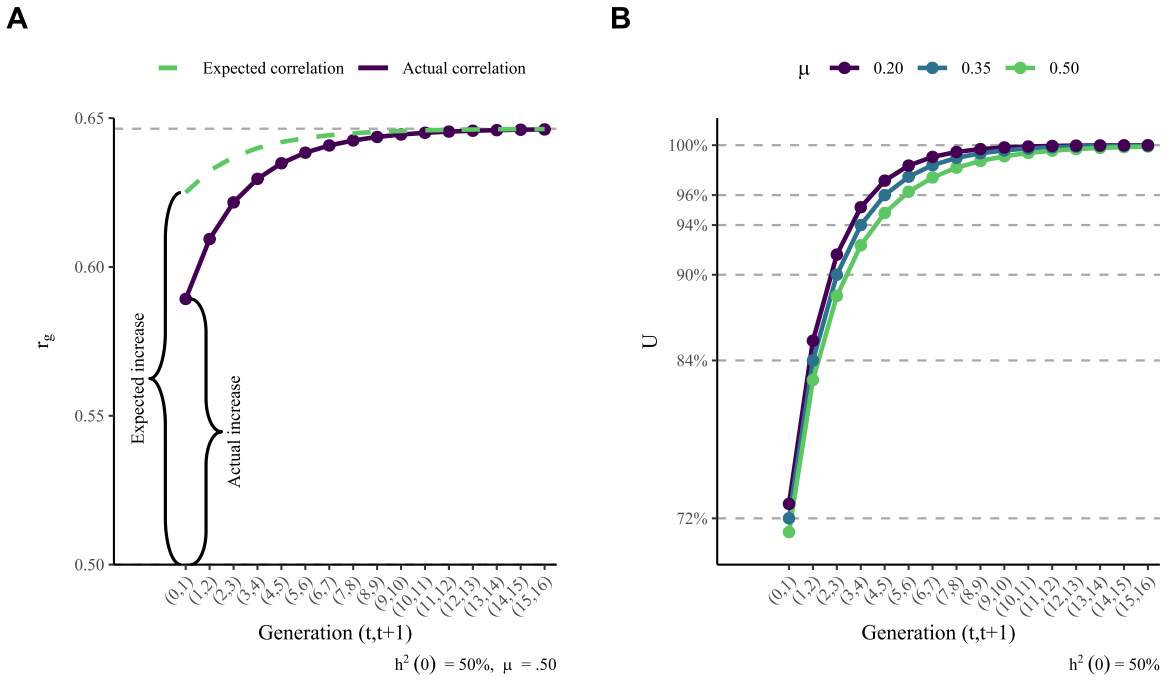
$$r_g(t) = \frac{1+\rho_g(t)}{2\sqrt{Q(t)}} \quad (S3.3)$$

The *degree* of mismatch depends on the number of generations since assortative mating began. It should therefore be possible to infer the history of assortment by quantifying the degree of mismatch in the parent-

offspring correlation. Torvik, et al. [9] defined U as the ratio of observed increase in correlation to the expected increase in correlation at equilibrium given the current genotypic correlation between partners. In other words, it is the observed increase as a percentage of the expected increase at equilibrium, where 100% would indicate equilibrium:

$$U(t) = \frac{Actual\ Increase}{Expected\ Increase} = \frac{r_g(t) - 0.5}{\left(\frac{1 + \rho_g(t)}{2}\right) - 0.5} \qquad (S3.4)$$

Note that U is specific to each relationship and will not be the same for full siblings or other relatives. Here, we are using it for the genotypic parent-offspring correlation. Panel B in Supplementary Fig. 4 plots how U develops in successive generations of assortative mating depending on the phenotypic correlation between partners. We see that it is approximately 72% after one generation, 84% after two generations, 90% after three generations, etc., For traits under stronger assortment, U increases slightly slower (and vice versa), but the differences are not large.

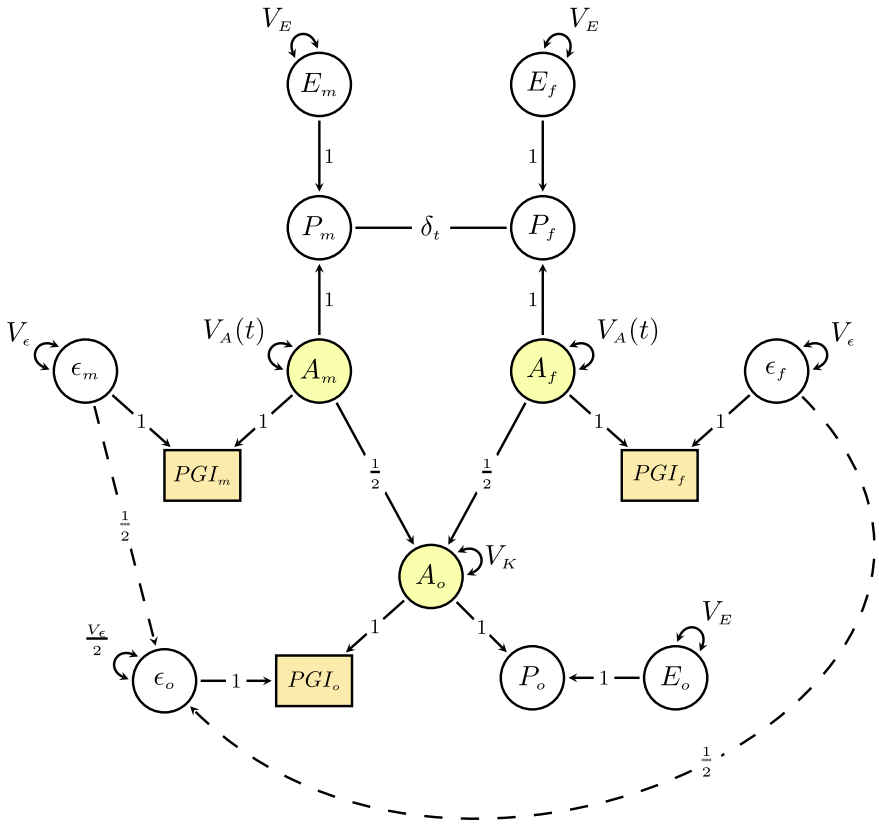


Supplementary Fig. 4: *The dynamics of the genotypic parent-offspring correlation during disequilibrium.*

By comparing an observed U-value with Supplementary Fig. 4B, it is possible to infer how the numbers of generations since assortative mating began. Obviously, this would involve making assumptions such as constant environmental variance and constant partner correlations (preceded by no partner correlation), which is unlikely to reflect reality. For this reason, we do not deem it worthwhile to develop a more accurate estimation of t beyond looking up a rough estimate in the figure (although it is perfectly possible to calculate $U(t)$ with other assumptions). A given U can be said to be *equivalent* to an approximate t, which is to say that a population with no assortative mating prior to t generations of constant assortment would yield a similar U value. It is important to note, though, that multiple other processes could give rise to the same U value, such as changing assortment strengths or changes in environmental and genetic effects across generations.

Note that U calculated with polygenic indices roughly tracks the true heritability and true genotypic partner correlation of the sorted phenotype (see section 5), not the polygenic index correlation between partners (which is confounded by s^2). Given that educational attainment appears to be roughly 50% heritable[2,10] and exhibits a strong phenotypic correlation between partners[9,11], we can search for its observed U-value ($U = 90\%$) along the green line in Supplementary Fig. 4B. We find the U-value roughly matches what we would expect at $t = 2$, indicating two prior generations of assortment. In other words, our result for educational attainment matches what we would expect if the parental generation was the *third* generation to mate assortatively on educational attainment.

4. Polygenic index variance during disequilibrium



Supplementary Fig. 5: *Path diagram illustrating polygenic index similarity under disequilibrium.*

Supplementary Fig. 5 extends Supplementary Fig. 2 by including polygenic indices. Because we are no longer assuming unit variances, the genetic signal is now indicated by the relative importance of true genetic variance, $V_A(t)$, and error variance, V_ϵ (not to be confused with V_E!) in the polygenic index. Because the initial variance in the polygenic index is arbitrary, we will for simplicity's sake not scale the variance. Applying path tracing rules, we find that the variance in the polygenic index is:

$$V_{pgi}(t) = Var(PGS_m) = V_A(t) + V_\epsilon \tag{S4.1}$$

Because genetic variance initially increases with successive generations of assortative mating, the variance in the polygenic index also increases. This has the slightly odd effect of making the genetic signal higher in successive generations (assuming the error term is constant). We must therefore give the genetic signal generation-specific notation:

$$s^2(t) = \frac{V_A(t)}{V_A(t) + V_\epsilon} \tag{S4.2}$$

When using polygenic indices as proxies for the true genetic factor, we must understand how the genetic signal affects Q and U. We will consider U in the next section. Let us first consider how the polygenic index variance changes across generations. Because we already know how the genetic variance changes, we can combine equation S4.1 and S2.7 and get:

$$V_{pgi}(t+1) = V_A(t+1) + V_\epsilon \tag{S4.3}$$

Likewise, we change adapt equation S2.8 and obtain the intergenerational variance ratio for the polygenic index:

$$Q_{pgi}(t) = \frac{V_{pgi}(t+1)}{V_{pgi}(t)} \tag{S4.4}$$

Because the polygenic index variance contains noise that presumably stays constant across generations, the intergenerational variance ratio for polygenic indices will always be closer to one than the true variance ratio, meaning it will underestimate the increased variance in the offspring generation under positive assortative mating:

$$\left|1 - Q_{pgi}\right| \leq |1 - Q_A| \tag{S4.5}$$

Put another way, the polygenic index variance will not increase to the same extent as the true genetic variance. If the genetic signal is known, then it is possible to calculate the true intergenerational variance ratio (Q_A) given the variance ratio for polygenic indices (Q_{pgi}). Before that, we must do some rearranging. For simplicity's sake, I will not use the generation-specific notation in the following equations if the parameter is from generation t.

First, we rearrange equation S4.2 to give us the V_ϵ using s^2:

$$V_\epsilon = V_A \frac{(1 - s^2)}{s^2} \tag{S4.6}$$

We then rearrange equation S2.8 to give us $V_A(t+1)$ using Q_A:

$$V_A(t+1) = Q_A V_A \tag{S4.7}$$

We can now substitute S4.6 and S4.7 into equations S4.1 and S4.3 and simplify accordingly:

$$\begin{aligned} V_{pgi} &= V_A + V_A \frac{(1 - s^2)}{s^2} \\ &= \frac{V_A}{s^2} \end{aligned} \tag{S4.8a}$$

$$\begin{aligned} V_{pgi}(t+1) &= Q_A V_A + V_A \frac{(1 - s^2)}{s^2} \\ &= V_A \left(Q_A + \frac{1}{s^2} - 1 \right) \end{aligned} \tag{S4.8b}$$

Which we in turn can substitute into S4.4 and simplify accordingly:

$$\begin{aligned} Q_{pgi} &= \frac{V_A(Q_A + 1/s^2 - 1)}{V_A/s^2} \\ &= Q_A s^2 + 1 - s^2 \end{aligned} \tag{S4.9}$$

Solving for Q_A gives us:

$$Q_A(t) = 1 + \frac{Q_{pgi}(t) - 1}{s^2(t)} \quad (S4.10)$$

We can continue using educational attainment as an example, where the polygenic index variance was $Q_{pgi} = 1.024$ times greater in the offspring generation than in the parental generation. If we keep assuming the genetic signal is 33% (see section 1), the true genetic factor has 1.072 times greater variance in the offspring generation than the parent generation.

5. The polygenic index correlation between parents and offspring under disequilibrium

The polygenic index covariance between parents and offspring consists of two components: The true genotypic covariance and the covariance attributable to the shared error terms. Because we did not scale the variance, the polygenic index covariance is simply the sum of these two components:

$$Cov(PGI_m, PGI_o) = V_A(t)\left(\frac{1+\rho_g(t)}{2}\right) + \frac{V_\epsilon}{2} \quad (S5.1)$$

You can double-check this by tracing all valid chains in Supplementary Fig. 5. To get the correlation, we must divide by the pooled variance:

$$r_{pgi}(t) = Corr(PGI_m, PGI_o) = \frac{V_A(t)\left(\frac{1+\rho_g(t)}{2}\right) + \frac{V_\epsilon}{2}}{\sqrt{V_{pgi}(t)V_{pgi}(t+1)}} \quad (S5.2)$$

Because the genetic signal changes from generation to generation, it is not straightforward to reduce S5.1 or S5.2 to simpler equations (nor is it necessary here). Instead, we can calculate what the observed correlation would be under various assumptions and see how it behaves compared to the true genotypic correlation. It will also be useful to see how it behaves compared to the expected correlation given the polygenic index correlation between partners.

The polygenic index correlation between partners will still equal equation S1.1 (i.e., $\rho_{pgi} = \rho_g s^2$), which you can double check by tracing all valid chains between PGS_m and PGS_m and divide by the polygenic index variance:

$$\rho_{pgi}(t) = \frac{\delta_t V_A^2(t)}{V_A(t)/s^2(t)} = s^2(t)\delta_t V_A(t) = \rho_g(t)s^2(t) \quad (S5.3)$$

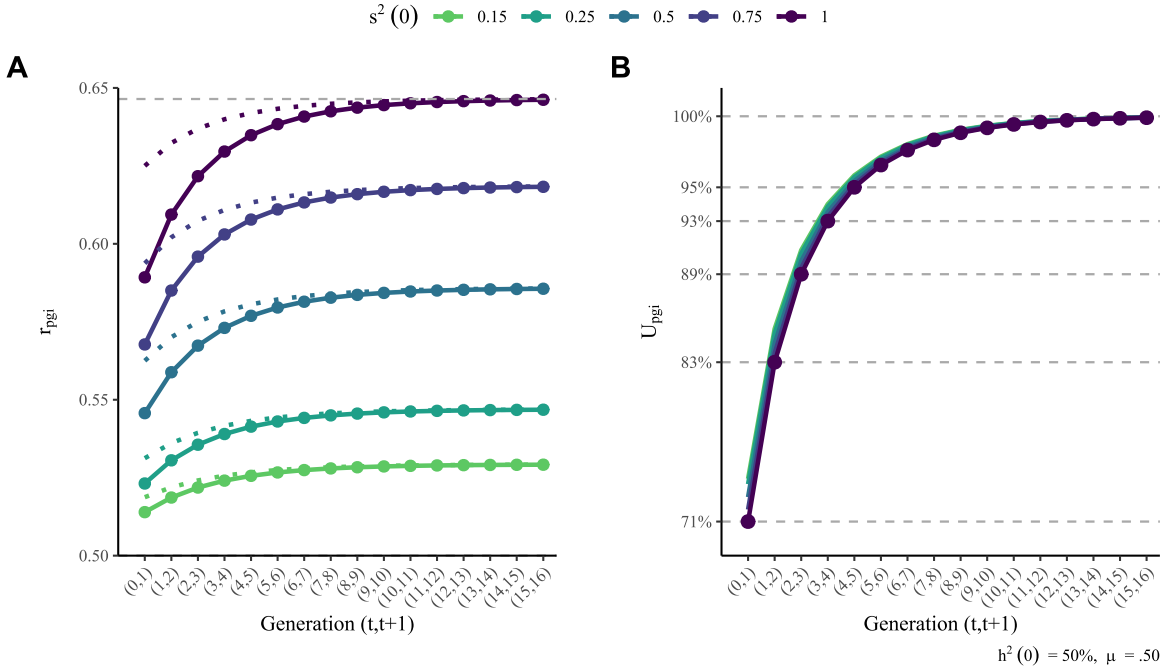
We can also define the polygenic index equivalent of U (i.e., the ratio of actual to expected increase):

$$U_{pgi}(t) = \frac{r_{pgi}(t) - 0.5}{\left(\frac{1+\rho_{pgi}(t)}{2}\right) - 0.5} \quad (S5.4)$$

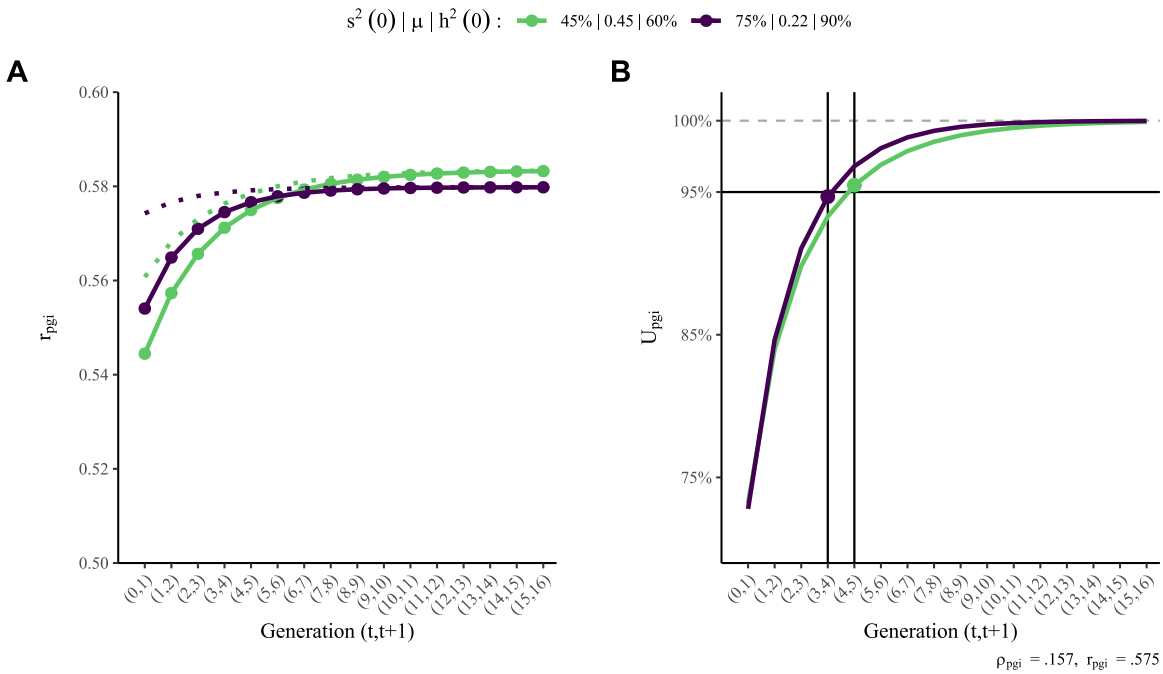
Supplementary Fig. 6A shows how various degrees of genetic signal (s^2) affects the polygenic index correlation between parents and offspring in successive generations of assortative mating (assuming $h^2(0) = 50\%$ and $\mu = .50$). The solid lines are the actual correlations, whereas the dotted lines are what you would predict using $\frac{1+\rho_{pgi}(t)}{2}$. We see that less genetic signal (i.e., lower s^2) results in a lower polygenic index correlation between parents and offspring. However, we see in Panel B that U_{pgi} is almost unaffected by the genetic signal. There is a small change where lower s^2 results in slightly higher U_{pgi}, but overall, U_{pgi} will approximately equal U.

An important consideration, therefore, is that U_{pgi} depends on the true genotypic partner correlation, not the polygenic index correlation. The latter will be confounded by s^2, meaning one cannot use the observed

correlation to infer how many generations of assortment has occurred. In Supplementary Fig. 7, we show two scenarios that would be indistinguishable if one only had access to polygenic index correlations ($\rho_{pgi} = .157, r_{pgi} = .575, U_{pgi} = 95\%$). Without making assumptions about the true heritability and partner correlation, it would be impossible to say this indicated three or four generations since assortment began. To infer t based on U, one must therefore make assumptions about the likely true heritability and true assortment strength and look at the relevant line in Supplementary Fig. 4 (or calculate it manually).

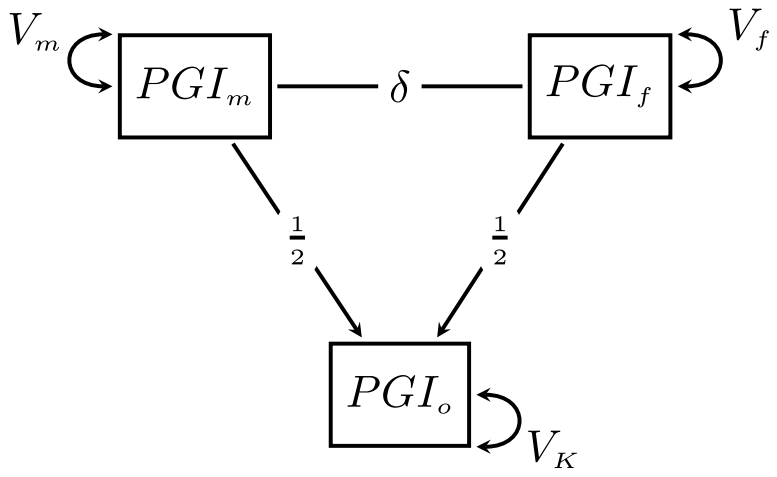


Supplementary Fig. 6: *Dynamics of polygenic score correlations with varying genetic signal strengths*



Supplementary Fig. 7: *Similar polygenic index correlations can result from different processes.*

6. Empirically testing intergenerational equilibrium



Supplementary Fig. 8: *Structural equation model used to test intergenerational equilibrium.*

Whether a trait is consistent with equilibrium can be quickly gauged by seeing if the confidence intervals for the correlations in Fig. 3 overlaps with the expected correlations (the black crosses). To perform a more formal test of equilibrium, we fitted structural equation models (Supplementary Fig. 8) to the mother-father-offspring covariance matrix for each trait and used a log-likelihood test to check if constraining the model to equilibrium resulted in significantly poorer fit. This approach also allowed us to compute Q_{pgi} and U_{pgi} with confidence intervals, which offer two alternative ways to check for equilibrium: First, whether the observed parent-offspring correlation was smaller than expected given the partner correlation (i.e., if $U_{pgi} \neq 1$, ref. equation S5.4). Second, whether the variance in the offspring generation was greater than in the parental generation (i.e., $Q_{pgi} \neq 1$, ref. equation S4.4). Note that these are not independent tests, but rather transformations of each other that highlight different aspects of disequilibrium. The models were instantiated in OpenMx[12] in R[13].

To avoid putting needless constraints on the model, the maternal and paternal variance (V_m and V_f, respectively) were allowed to differ. The partner covariance is therefore $V_m \delta V_p$, whereas the parent-offspring covariances are $\frac{V_m + V_m \delta V_p}{2}$ and $\frac{V_f + V_m \delta V_p}{2}$, respectively (For U_{pgi} and Q_{pgi}, we used the pooled variance, see below). The offspring variance is slightly more complicated: $V_K + \frac{V_m}{4} + \frac{V_f}{4} + \frac{V_m \delta V_f}{2}$. Note that these equations are the same as those presented in section 2, only adapted for varying maternal and paternal variance.

Both the parent-offspring correlations and the intergenerational variance ratio will depend on the recombination variance (V_K). The recombination variance will be half the genetic variance in the parent generation in the absence of assortative mating (equation S2.2). For a trait at equilibrium, V_K can be found by rearranging equation S2.9b and substituting it into equation S2.2. To estimate how much the recombination variance deviated from what would be expected at equilibrium, we added a new freely estimated parameter (x) to this equation:

$$V_K = \frac{\sqrt{V_f V_m} + V_m \delta V_f + x}{2} \quad (S6.1)$$

This parameter allows the variance in the offspring generation to differ from the parent generation. If x is significantly different from zero, then the trait is not consistent with equilibrium. This can be tested by constraining x to 0 and seeing if it results in significantly worse fit (see Supplementary Tables 1 through 15 below).

We also defined Q_{pgi} and U_{pgi} in the model, which is how we obtained confidence intervals for these parameters. If $x > 0$, then $Q_{pgi} > 1$ and $U_{pgi} < 1$. To define U_{pgi}, we also needed to define the partner correlation (ρ_{pgi}) and the pooled parent-offspring correlation (r_{pgi}). Note again that these equations are the same as those presented earlier, only adapted for varying maternal and paternal variance:

$$\rho_{pgi} = \sqrt{V_m V_f} \times \delta \quad (S6.2)$$

$$r_{pgi} = \frac{\left(\sqrt{V_m V_f} + V_m \delta V_p\right)/2}{\sqrt{\sqrt{V_m V_f} \times Var(PGI_o)}} \quad (S6.3)$$

$$U_{pgi} = \frac{r_{pgi} - 0.5}{\left(1 + \rho_{pgi}\right)/2 - 0.5} \quad (S6.4)$$

$$Q_{pgi} = \frac{Var(PGI_o)}{\sqrt{V_m V_f}} \quad (S6.5)$$

We report U_{pgi} and Q_{pgi} for traits with significant partner correlations in Fig. 4 in the main paper.

We also used this modelling approach as an alternative test for significant partner similarity (i.e., assortative mating) by testing whether constraining δ to 0 resulting in significantly worse fit (after construing the model to equilibrium). None of the models contradicted the results reported in the main paper. We further compared a model where we constrained V_f to equal V_m (i.e., sex invariant variance). Significant differences would indicate that men and women have different selection bias into the sample. We found this to be the case for chronotype (p = .005), smoking (.022), IQ (<.001), and EA (cognitive) (.005).

Supplementary Table 1: Model Comparisons for ADHD

Base	Comparison	*k*	-2LL	df	*Δ*2LL	*Δ*df	*p*
Full		4	553,901.6	207,235			
Full	Equilibirium	3	553,902.0	207,236	0.333	1	0.5637
Equilibirium	No_Assortment	2	553,902.0	207,237	0.002	1	0.9668
No_Assortment	Sex_Invariant	1	553,903.0	207,238	1.077	1	0.2995

Supplementary Table 2: Model Comparisons for Bipolar Disorder

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	554,059.5	207,235			
Full	Equilibirium	3	554,065.0	207,236	5.470	1	0.0193
Equilibirium	No_Assortment	2	554,067.3	207,237	2.304	1	0.1291
No_Assortment	Sex_Invariant	1	554,067.5	207,238	0.256	1	0.6130

Supplementary Table 3: Model Comparisons for BMI

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	551,232.0	207,235			
Full	Equilibirium	3	551,232.3	207,236	0.302	1	0.5829
Equilibirium	No_Assortment	2	551,440.7	207,237	208.388	1	0.0000
No_Assortment	Sex_Invariant	1	551,440.8	207,238	0.117	1	0.7327

Supplementary Table 4: Model Comparisons for Chronotype

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	552,232.4	207,235			
Full	Equilibirium	3	552,245.0	207,236	12.575	1	0.0004
Equilibirium	No_Assortment	2	552,359.3	207,237	114.305	1	0.0000
No_Assortment	Sex_Invariant	1	552,367.3	207,238	8.051	1	0.0045

Supplementary Table 5: Model Comparisons for Smoking

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	553,115.7	207,235			
Full	Equilibirium	3	553,115.7	207,236	0.025	1	0.8752
Equilibirium	No_Assortment	2	553,129.9	207,237	14.205	1	0.0002
No_Assortment	Sex_Invariant	1	553,135.2	207,238	5.282	1	0.0216

Supplementary Table 6: Model Comparisons for EA (Cognitive)

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	552,280.5	207,235			
Full	Equilibirium	3	552,294.0	207,236	13.483	1	0.0002
Equilibirium	No_Assortment	2	552,407.8	207,237	113.825	1	0.0000
No_Assortment	Sex_Invariant	1	552,415.6	207,238	7.729	1	0.0054

Supplementary Table 7: Model Comparisons for Cross-Psychiatric

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	554,911.1	207,235			
Full	Equilibirium	3	554,914.3	207,236	3.197	1	0.0738
Equilibirium	No_Assortment	2	554,914.5	207,237	0.228	1	0.6329
No_Assortment	Sex_Invariant	1	554,916.1	207,238	1.596	1	0.2065

Supplementary Table 8: Model Comparisons for EA

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	546,524.6	207,235			
Full	Equilibirium	3	546,562.0	207,236	37.394	1	0.0000
Equilibirium	No_Assortment	2	547,761.8	207,237	1,199.877	1	0.0000
No_Assortment	Sex_Invariant	1	547,763.8	207,238	2.007	1	0.1565

Supplementary Table 9: Model Comparisons for Height

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	550,305.2	207,235			
Full	Equilibirium	3	550,305.4	207,236	0.202	1	0.6531
Equilibirium	No_Assortment	2	550,666.1	207,237	360.636	1	0.0000
No_Assortment	Sex_Invariant	1	550,666.5	207,238	0.406	1	0.5239

Supplementary Table 10: Model Comparisons for IQ

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	551,813.9	207,235			
Full	Equilibirium	3	551,820.1	207,236	6.253	1	0.0124
Equilibirium	No_Assortment	2	551,970.7	207,237	150.579	1	0.0000
No_Assortment	Sex_Invariant	1	551,983.1	207,238	12.431	1	0.0004

Supplementary Table 11: Model Comparisons for EA (Non-cognitive)

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	551,402.0	207,235			
Full	Equilibirium	3	551,408.7	207,236	6.762	1	0.0093
Equilibirium	No_Assortment	2	551,605.0	207,237	196.313	1	0.0000
No_Assortment	Sex_Invariant	1	551,605.8	207,238	0.722	1	0.3954

Supplementary Table 12: Model Comparisons for Depression

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	554,680.7	207,235			
Full	Equilibirium	3	554,680.8	207,236	0.065	1	0.7990
Equilibirium	No_Assortment	2	554,682.7	207,237	1.932	1	0.1645
No_Assortment	Sex_Invariant	1	554,682.9	207,238	0.132	1	0.7162

Supplementary Table 13: Model Comparisons for Diabetes (Type 1)

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	554,096.4	207,235			
Full	Equilibirium	3	554,097.4	207,236	1.045	1	0.3068
Equilibirium	No_Assortment	2	554,097.4	207,237	0.000	1	0.9948
No_Assortment	Sex_Invariant	1	554,097.5	207,238	0.081	1	0.7759

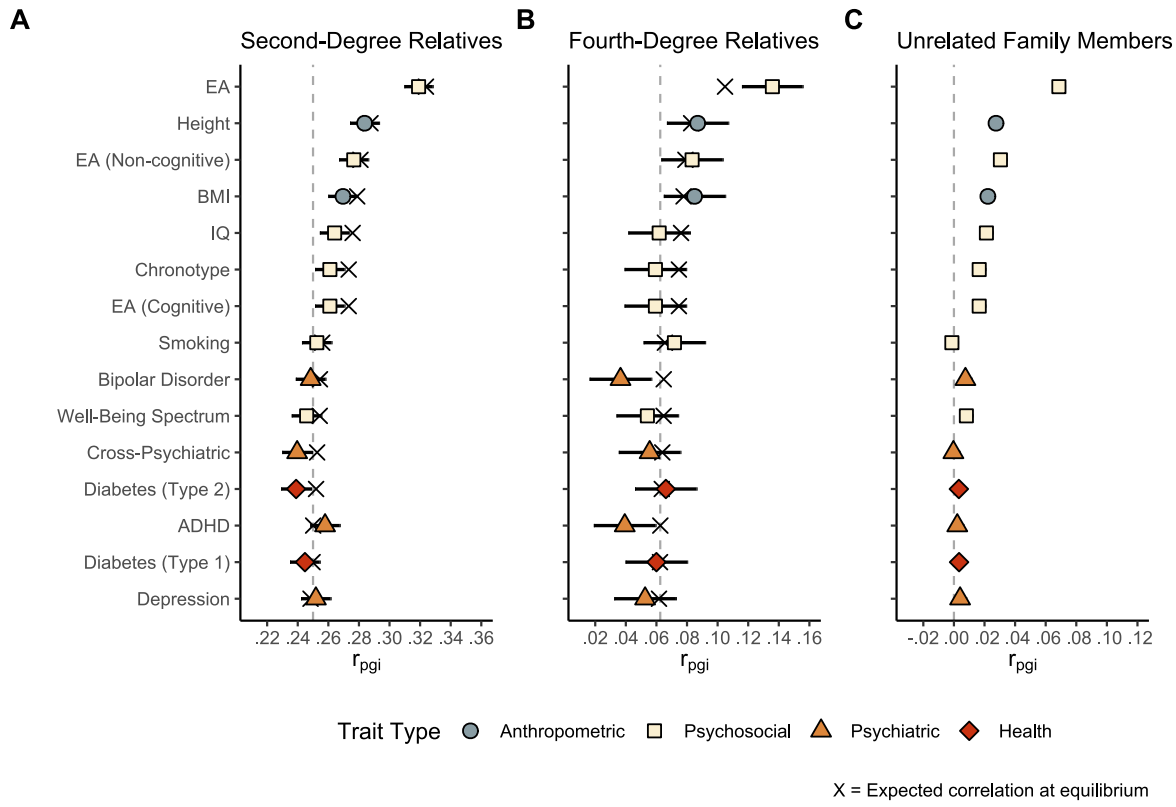
Supplementary Table 14: Model Comparisons for Diabetes (Type 2)

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	554,656.5	207,235			
Full	Equilibirium	3	554,659.9	207,236	3.347	1	0.0673
Equilibirium	No_Assortment	2	554,659.9	207,237	0.003	1	0.9535
No_Assortment	Sex_Invariant	1	554,659.9	207,238	0.000	1	0.9976

Supplementary Table 15: Model Comparisons for Well-Being Spectrum

Base	Comparison	*k*	-2LL	df	*Δ2*LL	*Δ*df	*p*
Full		4	554,631.7	207,235			
Full	Equilibirium	3	554,632.6	207,236	0.889	1	0.3459
Equilibirium	No_Assortment	2	554,633.3	207,237	0.670	1	0.4131
No_Assortment	Sex_Invariant	1	554,633.7	207,238	0.393	1	0.5305

7. Polygenic index correlations between other relatives



Supplementary Fig. 9: *Polygenic index correlations between second-degree, fourth-degree, and unrelated family members*

Supplementary Fig. 9 shows the polygenic index correlations (95% CIs) among relatives that were not included in Fig. 3 in the main paper. Unrelated family members include all dyads in extended families that are not genetically related (i.e., relations that are mediated by a partner, such as in-laws, non-genetic uncles/aunts, partners, etc.).

The summary statistics and reproducible code for this figure is available at https://osf.io/dgw4r/.

8. Information about the polygenic indices

Supplementary Table 16: Polygenic indices

Trait	GWAS sample size	Overlapping SNPs
Educational Attainment (EA)[1]	765283	908380
Non-Cognitive EA[14]	510795	879419
Cognitive EA[14]	257700	879419
Intelligence[15]	269867	911938
Well-Being Spectrum[16]	2311180	800700
Height[17]	4080687	1041747
Body Mass Index (BMI)[18]	695648	802341
Cigarettes per day (Smoking)[19]	245876	907384
Type 1 Diabetes[20]	520580	911412
Type 2 Diabetes[21]	659316	827710
Cross-Psychiatric Disorders[22]	734126	688620
Bipolar Disorder[23]	413466	912724
Broad Depression[24]	500199	256913
ADHD[25]	225534	902783
Chronotype[26]	697828	879419

Overlapping SNPs refers to the number of single nucleotide polymorphisms (SNP) that were available in both the GWAS summary statistics and in the genotype data in MoBa. It is therefore the number of SNPs used to calculate the polygenic indices. Non-cognitive EA and cognitive EA are based on GWAS-by-subtraction as described here[14]. In short, the polygenic index for educational attainment is split into that related to intelligence and that unrelated to intelligence.

9. Supplementary references

1 Okbay, A. *et al.* Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nature Genetics* **54**, 437-449 (2022). https://doi.org:10.1038/s41588-022-01016-z

2 Silventoinen, K. *et al.* Genetic and environmental variation in educational attainment: an individual-based analysis of 28 twin cohorts. *Scientific Reports* **10** (2020). https://doi.org:10.1038/s41598-020-69526-6

3 Bulmer, M. G. *The Mathematical Theory of Quantitative Genetics*. (Oxford University Press, 1980).

4 Hayashi, T. Genetic variance under assortative mating in the infinitesimal model. *Genes & Genetic Systems* **73**, 397-405 (1998). https://doi.org:10.1266/ggs.73.397

5 Gimelfarb, A. Quantitative characters under assortative mating: Gametic model. *Theoretical Population Biology* **25**, 312-330 (1984). https://doi.org:10.1016/0040-5809(84)90012-1

6 Rogers, A. Assortative mating and the segregation variance. *Theoretical Population Biology* **23**, 110-113 (1983). https://doi.org:https://doi.org/10.1016/0040-5809(83)90007-2

7 Nagylaki, T. The correlation between relatives with assortative mating. *Annals of Human Genetics* **42**, 131-137 (1978). https://doi.org:10.1111/j.1469-1809.1978.tb00938.x

8 Lynch, M. & Walsh, B. *Genetics and Analysis of Quantitative Traits*. (Sinauer Associates, Inc., 1998).

9 Torvik, F. A. *et al.* Modeling assortative mating and genetic similarities between partners, siblings, and in-laws. *Nature Communications* **13** (2022). https://doi.org:10.1038/s41467-022-28774-y

10 Polderman, T. J. C. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics* **47**, 702-709 (2015). https://doi.org:10.1038/ng.3285

11 Horwitz, T. B., Balbona, J. V., Paulich, K. N. & Keller, M. C. *Correlations between human mating partners: a comprehensive meta-analysis of 22 traits and raw data analysis of 133 traits in the UK Biobank* (BioRxiv, 2023).

12 Neale, M. C. *et al.* OpenMx 2.0: Extended Structural Equation and Statistical Modeling. *Psychometrika* **81**, 535-549 (2016). https://doi.org:10.1007/s11336-014-9435-8

13 R: A language and environment for statistical computing. (R Foundation for Statistical Computing, Vienna, Austria, 2022).

14 Demange, P. A. *et al.* Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. *Nature Genetics* **53**, 35-44 (2021). https://doi.org:10.1038/s41588-020-00754-2

15 Savage, J. E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nature Genetics* **50**, 912-919 (2018). https://doi.org:10.1038/s41588-018-0152-6

16 Baselmans, B. M. L. *et al.* Multivariate genome-wide analyses of the well-being spectrum. *Nature Genetics* **51**, 445-451 (2019). https://doi.org:10.1038/s41588-018-0320-8

17 Yengo, L. *et al.* A saturated map of common genetic variants associated with human height. *Nature* **610**, 704-712 (2022). https://doi.org:10.1038/s41586-022-05275-y

18 Yengo, L. *et al.* Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Human Molecular Genetics* **27**, 3641-3649 (2018). https://doi.org:10.1093/hmg/ddy271

19 Liu, M. *et al.* Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nature Genetics* **51**, 237-244 (2019). https://doi.org:10.1038/s41588-018-0307-5

20 Chiou, J. *et al.* Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. *Nature* **594**, 398-402 (2021). https://doi.org:10.1038/s41586-021-03552-w

21 Xue, A. *et al.* Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nature Communications* **9** (2018). https://doi.org:10.1038/s41467-018-04951-w

22 Lee, P. H. *et al.* Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* **179**, 1469-1482.e1411 (2019). https://doi.org:10.1016/j.cell.2019.11.020

23 Mullins, N. *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nature Genetics* **53**, 817-829 (2021). https://doi.org:10.1038/s41588-021-00857-4

24 Howard, D. M. *et al.* Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience* **22**, 343-352 (2019). https://doi.org:10.1038/s41593-018-0326-7

25 Demontis, D. *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics* **55**, 198-208 (2023). https://doi.org:10.1038/s41588-022-01285-8

26 Jones, S. E. *et al.* Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. *Nature Communications* **10** (2019). https://doi.org:10.1038/s41467-018-08259-7