Genetic Architecture of ADHD and Overlap With Other Psychiatric Disorders And Cognition-Related Phenotypes

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) co-occurs with many other psychiatric disorders and traits. In this review, we summarize and interpret the existing literature on the genetic architecture of these comorbidities based on hypothesis-generating approaches. Quantitative genetic studies indicate that genetic factors play a substantial role in the observed co-occurrence of ADHD with many different disorders and traits. Molecular genetic correlations derived from genome-wide association studies and results of studies based on polygenic risk scores confirm the general pattern but provide effect estimates that are smaller than those from twin studies. The

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; ANO, Anorexia nervosa; ASD, Austism spectrum disorder; CAUSE, Causal Analysis Using Summary Effect estimates; CD, Conduct disorder; CNV, Copy number variant; DBD, Disruptive behavior disorder; DZ, Dizygotic; GWAS, Genome-wide association study; ID, Intellectual disability; IQ, Intelligence quotient; LCV, Latent causal variable; MDD, Major depressive disorder; MR, Mendelian randomization; MZ, Monozygotic; NGS, Next generation sequencing; OCD, Obsessive-compulsive disorder; ODD, Oppositional defiant disorder; OR, Odds ratio; PGC, Psychiatric Genomics Consortium; PI-PTV, Protein truncating variants - intolerant genes; PTSD, Post-traumatic stress disorder; PTV, Protein truncating variants; SCZ, Schizophrenia; SNP, Single nucleotide polymorphism; SNV, Single nucleotide variant; SUD, Substance use disorder; TS, Tourette syndrome; WES, Whole-exome sequencing; WGS, Whole-genome sequencing.

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identification of the specific genetic variants and biological pathways underlying co-occurrence using genome-wide approaches is still in its infancy. The first analyses of causal inference using genetic data support causal relationships between ADHD and comorbid disorders, although bidirectional effects identified in some instances point to complex relationships. While several issues in the methodology and inferences from the results are still to be overcome, this review shows that the co-occurrence of ADHD with many psychiatric disorders and traits is genetically interpretable.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattentive, hyperactive, and impulsive behaviors (Faraone et al., 2015). According to DSM-5 and ICD-11 criteria, ADHD has an onset during childhood before 12 years and can persist into adulthood (Diagnostic and statistical manual of mental disorders, 2013; World Health Organization, 2018). Its prevalence in children and adolescents from the general population is estimated as 5–6% (Polanczyk et al., 2007) and is around 2.8% in adults (Fayyad et al., 2017). The clinical picture of ADHD symptoms changes from childhood to adulthood, with overt hyperactivity of childhood being replaced by inner restlessness and being talkative in adulthood. Adults with ADHD show continued attentional problems and disorganization (Kooij et al., 2019). Although life trajectories of people with ADHD are highly variable, the disorder is, overall, associated with an increased risk of functional and psychosocial difficulties that can lead to serious personal and societal costs. ADHD impacts multiple aspects of daily life, including academic achievement, performance at work, and interpersonal relationships (Bernardi et al., 2012; Kooij et al., 2019).

In recent years, ADHD has become more and more conceptualized as the extreme on dimensions of attention problems and hyperactivity/impulsivity that have a continuous distribution in the general population (Larsson et al., 2012; Levy et al., 1997). While the diagnostic threshold for the presence or absence of ADHD as defined in DSM-5 or ICD-11 is required for clinical decision making, what is known about causes, concomitants, and consequences of ADHD fits better with this dimensional view of symptom severity than with qualitative differences above and below the diagnostic threshold.

2. Comorbidity

ADHD is frequently comorbid with other diseases including psychiatric disorders and also non-mental conditions, which are explained in detail in another review article in this special issue (Kittel-Schneider et al., 2022). Up to 70–80% individuals with ADHD have comorbid psychiatric disorders across the lifespan (Kessler et al., 2014). There are strong associations between ADHD and lifetime occurrence of oppositional defiant disorder (ODD; ~45%), conduct disorder (CD; ~20%), personality disorders (up to ~60% in adults), major depressive disorder (MDD)/dysthymia (~40%), bipolar disorder (BD; ~15%), anxiety disorders (~35%), substance use disorders (SUD; ~25%), and eating disorders (~10%) (Kessler et al., 2014). Also, ADHD is highly comorbid with other neurodevelopmental disorders, such as the autism spectrum (up to ~65%; Clark et al., 1999), reading disabilities (up to ~50%; Langer et al., 2019), and tic disorders (~20%; Banaschewski et al., 2007). The range of disorders listed here is not exhaustive, and it is important to note that estimates of comorbidity vary strongly from one study to the next and depend on the population studied (e.g., general population or patients with ADHD; children or adults) and the instruments used (e.g. semi-standardized clinical or fully standardized trained research-staff interviews). A detailed analysis of comorbidity patterns with respect to age and sex, coming from large registries and cohorts, is provided in another review article in this special issue (Hartman et al., 2023).

In addition to the disorders mentioned above, multiple continuously distributed traits that are not part of the core diagnostic criteria of ADHD also covary with ADHD symptom severity. For example, emotional dysregulation problems, like mood swings, temper outbursts, and irritability are frequently co-occurring (Shaw et al., 2014). Furthermore, individuals with ADHD often have poor performance in one or more cognitive domains including attention regulation and executive functions, reward and temporal information processing (Kooij et al., 2019; Marx et al., 2021; Willcutt et al., 2005; Zheng et al., 2020).

The presence of comorbid psychiatric conditions and high scores on co-ocurring emotional and cognitive problems have a strong impact on the outcomes of ADHD. Moreover, comorbidity is one of the major factors that contributes to the persistence of the disorder from childhood into adulthood (Roy et al., 2016). The presence of comorbid disorders can also complicate detection, diagnosis and correct treatment of ADHD (Hartman et al., 2023; Kooij et al., 2019). Furthermore, the presence of comorbid conditions in individuals with ADHD goes hand in hand with stronger symptom severity and impairments, as well as increased mortality (Dalsgaard et al., 2015; Elwin et al., 2020; Kessler et al., 2005b; Kooij et al., 2019; Sun et al., 2019).

Given the clinical implications, it is important to understand the causes of the widespread co-occurrence of ADHD with psychiatric disorders and related traits. One possible explanation for the widespread comorbidity with common disorders in adulthood (i.e., mood disorders, anxiety disorders and substance use disorders) is the continued burden of ADHD and related emotional and cognitive traits and their link to psychosocial and functional stressors in daily life (Hartman et al., 2019; Kessler et al., 2005a; Rychik et al., 2021; Wymbs et al., 2021; Zendarski et al., 2020). Alternatively, psychiatric comorbidity may also be a direct expression of shared genetic liabilities among ADHD, comorbid conditions, and associated emotional, cognitive and behavioral features, rather than having their onset through these exposures. For example, genetic and phenotypic co-occurrence of ADHD with other childhood early-onset neurodevelopmental disorders such as autism spectrum disorder (ASD) or reading disability are indicative of a shared genetic background (Polderman et al., 2014; Satterstrom et al., 2019; Wadsworth et al., 2015), although shared genetic liability may also hold for adult-onset disorders (Anttila et al., 2018). A combination of both pathways may be most likely in many cases, given that the psychosocial and functional stressors that patients with ADHD are exposed to in their daily life are partly genetically driven as well, including low educational attainment, risk taking, and so forth (Karlsson Linnér et al., 2019; Morris et al., 2019; Wendt et al., 2021).

In the subsequent sections, we review the current literature on hypothesis-generating approaches to testing the involvement of genetic mechanisms in the co-occurrence of ADHD with other psychiatric disorders and related traits. In this, we took along quantitative genetic twin studies as well as molecular genetic methods at genome-wide scale exploring the role of common and rare genetic variants. As will become clear, some co-occurring disorders and traits have received more research attention than others. Regardless, the field agrees on the important role of genetics in explaining the association of ADHD with comorbid psychiatric disorders and co-occurring traits (Brikell et al., 2021; Du Rietz et al., 2020).

3. Quantitative genetics

Twin studies have demonstrated that the liability to ADHD is largely

genetic in origin. The mean heritability across 37 twin studies of ADHD was recently estimated as 74% (Faraone and Larsson, 2019). Twin studies, if based on cross-informant ratings and clinically diagnosed ADHD, have shown that the heritability is similar in magnitude in children, adolescents, and adults, although it drops to up to ~40% when based only on self-report ratings of ADHD (Brikell et al., 2015). Twin studies have also demonstrated that the heritability is largely similar in males and females and for the inattentive and hyperactive-impulsive components of ADHD (Faraone and Larsson, 2019). Importantly, heritability was also shown to be similar for categorical, clinical definitions of ADHD and continuous measures of ADHD symptoms in the general population (Faraone and Larsson, 2019).

The genetic contribution to ADHD and psychiatric comorbidity has been addressed in several twin studies. A recent meta-analysis of multivariate twin studies suggested substantial genetic overlaps of ADHD symptoms with other neurodevelopmental disorder symptoms, as well as with broader concepts of other externalizing and internalizing disorder symptoms (genetic correlations 0.49–0.56; Andersson et al., 2020). Most of the quantitative genetic studies on ADHD overlap with neurodevelopmental disorders have focused on ASD; in those studies, both clinical and population samples have been examined. A UK study of over 6000 twin pairs reported genetic correlations larger than 0.50 between autistic-like-traits and ADHD-traits in the general population (Ronald et al., 2008). An even stronger genetic overlap was found in a study of parent-rated ASD and ADHD symptoms from 16,858 Swedish twins, where the genetic correlation was 0.80 (Lichtenstein et al., 2010). Evidence for shared genetic risk between clinically diagnosed ASD and ADHD has also been reported in a recent, large-scale family study (N = 1,899,654), where a highly elevated familial risk for comorbidity of ADHD and ASD was seen in monozygotic (MZ) twins (odds ratio (OR) = 17). The risk for comorbidity among those disorders decreased along with decreasing relatedness (dizygotic (DZ) twin OR = 4.33; full-sibling OR = 4.59), as expected from a genetically mediated relationship (Ghirardi et al., 2018). Faraone and coworkers studied the genetic association of ADHD and intellectual disability (ID) in the Swedish medical registry data, and model fitting analyses attributed 91% of the correlation between the liabilities to ADHD and ID to genetic factors (Faraone et al., 2017). Several additional quantitative genetic studies focused on externalizing symptoms, with studies demonstrating genetic overlap of ADHD with ODD symptoms (Nadder et al., 2002), CD (Faraone et al., 2000), antisocial behaviour (Kuja-Halkola et al., 2015), and substance use problems (Capusan et al., 2015; Chang et al., 2012; Skoglund et al., 2015). Few quantitative genetic studies have explored how genetic factors contribute to the co-occurrence between ADHD and internalizing disorders and symptoms, but one twin study demonstrated that shared genetic factors explain the overlap between ADHD and depression (Cole et al., 2009).

In addition to studies of genetic overlap between ADHD (symptoms) and individual disorder or symptom domains, there has been an increased quantitative genetic research interest into a latent general psychopathology factor that captures phenotypic and genetic covariation across several psychiatric conditions, including ADHD. Those studies have shown explained variances between 10% and 57% (Allegrini et al., 2020; Caspi et al., 2014; Lahey et al., 2011; Pettersson et al., 2016; Selzam et al., 2018; Waldman et al., 2016). Building on such work, a recent quantitative genetic study demonstrated that ADHD is more strongly linked genetically to a neurodevelopmental construct than to externalizing and internalizing constructs, after accounting for a general psychopathology factor (Du Rietz et al., 2020).

Beyond the behavioural traits and psychiatric disorders co-occurring with ADHD mentioned above, quantitative genetic studies have also explored how genetic factors contribute to associations between ADHD and cognitive phenotypes related to comorbid learning difficulties (Faraone et al., 2017; Kuntsi et al., 2004). For example, Kuntsi et al. (2004) found that the association between ADHD (assessed via ADHD symptoms or ADHD diagnosis) and low intelligence quotient (IQ) was largely due to genetic factors (Kuntsi et al., 2004), while Faraone et al. (2017) found that individuals with a diagnosis of ID were at increased risk for ADHD and relatives of individuals with ID had an increased risk for ADHD compared with relatives of those without ID. A few twin studies have also established that genetic factors of ADHD correlate with genetic factors of mathematical (Greven et al., 2014) and reading ability (Daucourt et al., 2020).

In summary, quantitative genetic studies indicate that genetic factors play a substantial role in the co-occurrence of ADHD with other psychiatric disorders and related traits. While such analyses provide estimates for the extent of a genetic involvement, they are not informative about the actual model underlying this co-occurrence such as whether one disorder/trait influences the risk of developing the other (vertical pleiotropy), or whether pleiotropy exists for the molecular genetic factors underlying both disorders/traits (horizontal pleiotropy). Genome-wide molecular studies, reviewed in the next section, have provided evidence of the polygenic nature of psychiatric conditions and can provide more detailed information on the nature of this genetic overlap. Derived methods, such as Mendelian randomization, and the functional interpretation of findings from the genome-wide association studies (GWASs) are also starting to shed some light on the underlying comorbidity models and mechanisms.

4. Molecular genetics

Molecular genetic studies have been performed for both common and rare genetic variants in ADHD. The initial analyses primarily concentrated on specific candidate genes chosen on the basis of existing knowledge in the field. However, this review emphasizes hypothesis-free analyses that investigate the genome on a larger scale, such as GWASs or whole-exome sequencing studies, among others (e.g. Demontis et al., 2023, 2019b; Satterstrom et al., 2019). These studies contribute to our understanding of the genetic architecture not only of ADHD but also of its overlap with other psychiatric disorders and phenotypes, and they enable the identification of individual genetic variants and molecular pathways contributing to the overlap.

4.1. Common variants

Common genetic variants associated with ADHD have been studied through GWASs for the last 15 years. Through a collaboration between the Psychiatric Genomics Consortium (PGC) and the Danish iPSYCH initiative, the first 12 genome-wide significant loci were identified in a sample of 20,183 individuals with ADHD and 35,191 controls (Demontis et al., 2019b). The proportion of heritability explained by these common variants (SNP-based heritability) was approximately 22% (Demontis et al., 2019b). Recently, a new GWAS meta-analyis of ADHD based on expanded data from iPSYCH, deCODE genetics and the PGC have analysed around twice as many ADHD cases as in the previous GWAS meta-analysis (38,691 individuals with ADHD and 186,843 controls) and have increased the number of genome-wide significant loci to 27 (Demontis et al., 2023). The SNP-based heritability estimated by Demontis et al. (2023) was 14%, which is lower than the previously reported by Demontis et al. (2019b). However, when the SNP-based heritability was estimated for the separated cohorts, results from iPSYCH (23%) was in line with the previous finding, but lower SNP-based heritability was observed for PGC (12%) and deCODE (8.1%) (Demontis et al., 2023).

These studies paved the way to (a) the estimation of the genetic overlap (section 4.1.1), (b) the assessment of causal relationships (section 4.1.2) and (c) the identification of common genetic variants (section 4.1.3) between ADHD and other psychiatric disorders and traits.

4.1.1. Genetic correlations and polygenic risk scores

A widely used approach trying to estimate the genetic overlap of ADHD with other phenotypes is to estimate the genetic correlation (rg),

which gives an estimate of the average correlation of genetic effects across the genome of the two phenotypes. Another approach is to perform polygenic risk score (PRS) analyses. In this approach, effect sizes from a well-powered GWAS are used as weights in calculations of PRS in a target sample, and subsequently it can be tested whether the PRS is associated with an outcome of interest. Thus, the results can give an estimate of how the polygenic risk burden (of e.g. ADHD) relates to the risk of other disorders/phenotypes.

Assessing common variants genome-wide, ADHD shows genetic correlation with numerous disorders and traits (Fig. 1), including substantial correlation with several psychiatric disorders (Anttila et al., 2018; Cabana-Domínguez et al., 2019; Demontis et al., 2019b; Grotzinger et al., 2022; Johnson et al., 2020; Kranzler et al., 2019; Lee et al., 2019). The highest (positive) correlation is seen with post-traumatic stress disorder (PTSD; rg = 0.78; Grotzinger et al., 2022), cannabis use disorder (rg = 0.53; Johnson et al., 2020), cocaine use disorder (rg = 0.50; Cabana-Domínguez et al., 2019), MDD (rg = 0.45; Als et al., 2023; Grotzinger et al., 2022) and ASD (rg = 0.36; Grove et al., 2019), while obsessive compulsive disorder (OCD) appears to be the only psychiatric disorder consistently showing a negative correlation with ADHD (rg = −0.17; Grotzinger et al., 2022). Regarding the correlation with ASD, it is noteworthy that analysis within a relatively homogenous nationwide Danish cohort showed a correlation as high as rg = 0.50, which remained substantial when excluding individuals diagnosed with both ADHD and ASD (rg = 0.40; Mattheisen et al., 2022).

Studies investigating the genetic correlation between ADHD and behavioural traits have also been carried out. The genetic correlation between ADHD symptoms in the general population and diagnosed ADHD is very high (rg = 0.97; Demontis et al., 2019b) and supports that ADHD can be viewed as the extreme end of a continuum of symptoms. Additionally, behavioural phenotypes related to core symptoms of ADHD have been studied in population-based data (23andMe) where ADHD demonstrated significant positive genetic correlations with delay discounting (a measure of reward processing with the tendency to discount the value of delayed versus current rewards; rg = 0.37; Sanchez-Roige et al., 2018) and measures of impulsivity (e.g. lack of premeditation; rg = 0.43; Sanchez-Roige et al., 2019a). These findings also support that the biological mechanism underlying ADHD-related behaviours in the general population overlap with the mechanisms underlying the behaviours in individuals with diagnosed ADHD.

Also, strong genetic correlations have recently been reported between ADHD and aggression in children (rg = 0.74; Demontis et al., 2021; Ip et al., 2021), and increased polygenic risk scores (PRS) for ADHD (PRS-ADHD) have been reported in patients with ADHD and comorbid disruptive behavior disorders (DBDs; Demontis et al., 2021; Hamshere et al., 2013). In addition, the PRS-ADHD also increased the risk for developmental dyslexia (Gialluisi et al., 2020; Kember et al., 2021).

Information on shared genetics between ADHD and SUD and related substance use behaviors is extensive, consistent with the high prevalence of these comorbidities in ADHD (Hartman et al., 2023). The shared genetic backgound might involve variants affecting externalizing behaviors increasing SUD risk, in line with a study by Sanchez-Roige and coworkers (Sanchez-Roige et al., 2019a) that reported a positive genetic correlation of ADHD with drug experimentation (rg = 0.28). This study showed that impulsive personality traits are genetically associated with substance use and ADHD, suggesting that impulsivity may be an endophenotype contributing to these psychiatric conditions. In line with this notion, a recent study which evaluated the role of impulsivity in ADHD comorbidity, found an adventurous-hyperactive subtype with high

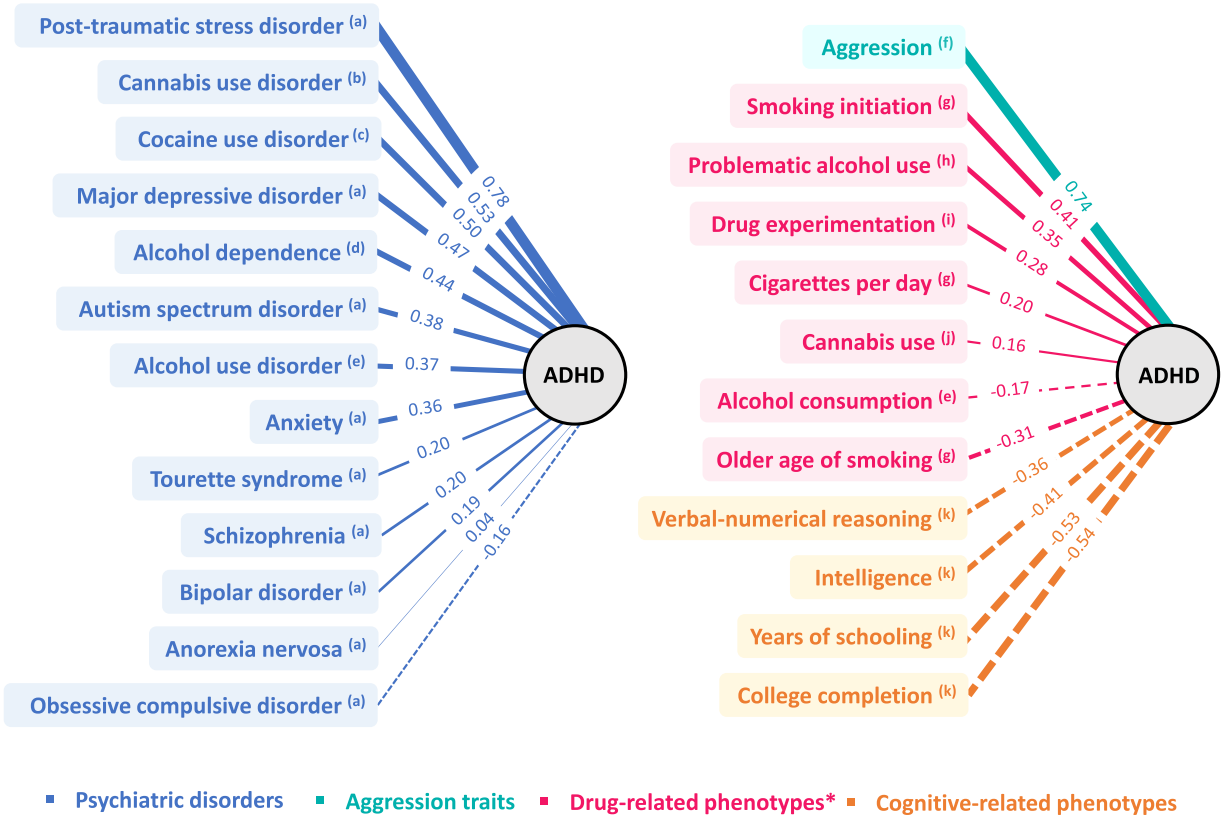


Fig. 1. Schematic representation of genetic correlations reported between ADHD and other psychiatric disorders (left panel) and behavioural and cognitive traits (right panel). Positive correlations are presented in solid lines and negative correlations in dashed lines. The line width corresponds to the strength of the correlation. [(a)] Grotzinger et al. (2022); [(b)] Johnson et al. (2020); [(c)] Cabana-Domínguez et al. (2019); [(d)] Walters et al. (2018); [(e)] Kranzler et al. (2019); [(f)] Demontis et al. (2021); [(g)] Liu et al. (2019); [(h)] Zhou et al. (2020); [(i)] Sanchez-Roige et al. (2019a) [(j)] Pasman et al. (2018); [(k)] Demontis et al. (2019b). *Drug-related phenotypes not involving a clinical diagnosis.

genetic load (Grimm et al., 2020). Also, genetic variants associated with cognition phenotypes that are negatively correlated with ADHD may be involved in the susceptibility to SUD (see below).

Positive genetic correlation between ADHD and alcohol dependence (rg = 0.44; Walters et al., 2018) or problematic alcohol use (rg = 0.35; Zhou et al., 2020) have also been reported. The genetic overlap of ADHD with alcohol consumption, however, seems to demonstrate a consistently different pattern. Two studies, one based on the UK Biobank and 23andMe cohorts (N = 141,932; Sanchez-Roige et al., 2019b) and one based on participants of the Million Veteran Program (N = 274,424; Kranzler et al., 2019), investigated the genetic architectures of a measure of alcohol consumption (AUDIT-C scores) and problematic alcohol use (AUDIT-P and alcohol use disorder (AUD)). These studies found a positive genetic correlation of ADHD with severe alcohol use phenotypes (rg = 0.23 (AUDIT-P; Sanchez-Roige et al., 2019b), rg = 0.37 (AUD; Kranzler et al., 2019)), but a negative genetic correlation with continuous measures of alcohol consumption (rg = −0.10; rg = −0.17 (AUDIT-C)). Since ADHD has a negative genetic correlation with measures of cognitive abilities (Demontis et al., 2019b) (see below) and alcohol consumption has a positive genetic correlation with cognitive abilities (Kranzler et al., 2019; Sanchez-Roige et al., 2019b), it might be hypothesized that the shared genetic component of ADHD and alcohol consumption involves cognition-associated variants (i.e variants which increase ADHD risk but decrease cognitive performance (and thus decrease alcohol consumption).

In addition to alcohol-related phenotypes, ADHD has also shown positive genetic correlation with smoking-related phenotypes (e.g. smoking initiation (rg = 0.41), cigarettes per day (rg = 0.20)), and negative correlation with age of smoking initiation (rg = −0.31), in which lower scores reflect earlier ages of initiation (Liu et al., 2019)). Significant genetic correlations have also been reported with illicit drug use such as cannabis use (rg = 0.16; Pasman et al., 2018) or cannabis and cocaine use disorders as mentioned above. PRS analyses support the results of these genetic correlation analyses. For example, PRS-ADHD was significantly associated with risk of cannabis use disorder in the Danish iPSYCH cohort (2387 cases, 48,985 controls; Demontis et al., 2019a), with cocaine use disorder in a combined data of cocaine use disorder (2085 cases, 4293 controls; Cabana-Domínguez et al., 2019), and with current smoking in a PRS-pheWAS of UK Biobank samples (N = 334,976; Leppert et al., 2020). However, it is worth noticing that the studies found PRS-ADHD to explain only a fraction of the variance in the analysed phenotypes. Additionally, PRS-ADHD was associated with increased risk of SUD among individuals with ADHD in the iPSYCH cohort (N = 13,116 individuals with ADHD), and also in this study the PRS-ADHD only explained a small amount of variance in the phenotype, as 0.2% of the overall risk of comorbid SUD could be attributed to the ADHD polygenic risk (Wimberley et al., 2020).

In the GWAS meta-analysis of ADHD by Demontis et al. (2019b), phenotypes related to cognitive traits demonstrated consistent, substantial, negative genetic correlations with ADHD (e.g. intelligence (rg = −0.41), college completion (rg = −0.54), verbal-numerical reasoning (rg = −0.36), and years of schooling (rg = −0.53)). The strong negative correlation of ADHD with years of schooling was confirmed using the GWAS Atlas tool, using results from an updated, more recent GWAS of educational attainment (N = 76,6345, 23andMe excluded; rg = −0.52; Lee et al., 2018). Interestingly, a recent study dissected the shared and distinct genetic architecture between ADHD and ASD and found that the genetic correlation of the shared liability across ASD-ADHD was strong for other psychiatric phenotypes while the ASD-ADHD differentiating genetic liability correlated most strongly with cognitive traits (Mattheisen et al., 2022).

Several studies have also used the GWAS meta-analysis of ADHD by Demontis et al. (2019b) to estimate PRS and explore the impact of the common ADHD risk variant burden on measures of cognition (Alemany et al., 2019; Klein et al., 2019). Such studies have found PRS-ADHD was associated with executive functioning, as PRS-ADHD was significantly associated with inhibitory control in Chinese children and adolescents (N = 963; Chang et al., 2020). While no association with working memory was found in this study, another study did report an association of PRS-ADHD with working memory (N = 514; Nigg et al., 2018); also, a third study found an association between PRS-ADHD and verbal working memory in children from a Spanish cohort (N = 1555; Aguilar-Lacasaña et al., 2020). PRS-ADHD has also been linked to language-related abilities in the ALSPAC cohort (N = 5919; Verhoef et al., 2019) and was strongly associated with educational attainment (university degree) in a PRS-pheWAS of the UK Biobank sample (N = 334,976; Leppert et al., 2020). In the latest GWAS meta-analysis of ADHD (Demontis et al., 2023), associations of ADHD-PRS with cognitive measures were assessed in the Philadelphia Neurodevelopmental Cohort (N = 4973). ADHD-PRS were negatively associated with neurocognitive domains including attention and working memory (Demontis et al., 2023).

Brain-related phenotypes have also been studied for their genetic overlap with ADHD. Using the ENIGMA GWAS of different brain volumes, Klein et al. reported a genetic correlation of ADHD with intracranial volume (rg = −0.22), where genetic variants associated with a smaller intercranial volume were associated with increased ADHD risk (Klein et al., 2019). None of the subcortical brain volumes known to be associated with ADHD had significant genetic correlations with ADHD (Grasby et al., 2020; Hoogman et al., 2017; Klein et al., 2019). A subsequent ENIGMA study on brain cortical phenotypes of surface area and thickness also reported a negative genetic correlation with total cortical surface area (rg = −0.16), but not with other cortical phenotypes (Grasby et al., 2020). Through PRS analyses, PRS-ADHD was, however, associated with a smaller caudate volume in children (N = 1139) and smaller total brain volume in children and adolescents with and without ADHD (N = 511; Alemany et al., 2019).

Overall, evidence from epidemiological studies on the phenotypic co-occurrence of ADHD with psychiatric disorders and traits are (largely) supported by the genetic associations found based on genetic correlation estimates and PRS analyses.

4.1.2. *Establishing causality*

Understanding whether there is a causal relationship between ADHD and co-occurring psychiatric disorders and traits and inferring the direction of this causality may play an important role in developing strategies to improve the lives of individuals with ADHD. In observational studies, causal relationships are hard to infer due to the potential effect of confounding factors affecting the results or to the possible presence of reverse causality. Different strategies have been developed to overcome these inference problems (Box 1). To date, a number of studies have assessed the causal relationship between ADHD and comorbid conditions, mainly focused on SUD and smoking-related traits. So far, results remain inconclusive.

Longitudinal analyses in twins have reported conflicting results on the causal relationship between ADHD and smoking, cannabis and alcohol use (Elkins et al., 2020, 2018; Treur et al., 2015). Treur and coworkers reported an effect for smoking, leading to higher attention problem scores later in life, whereas Elkings and coworkers did not detect an effect for smoking, alcohol or cannabis misuse on later ADHD (Elkins et al., 2020; Treur et al., 2015). Also, Elkings and coworkers did not detect a causal effect for ADHD on alcohol or cannabis use either, but a subsequent study in the same sample reported increased substance problems, to a greater degree for women than men, for individuals with ADHD in early adulthood (Elkins et al., 2020, 2018).

Mendelian randomization (MR) studies have consistently reported a positive causal effect of ADHD genetic liability on ever smoking, as well as a significant effect in the opposite direction (Fluharty et al., 2018; Jang et al., 2020; Treur et al., 2019; Vilar-Ribó et al., 2020). Treur and collegues, who undertook further follow-up analyses, suggested a high probability of horizontal pleiotropy influencing the effect of ever smoking on ADHD in their MR analysis (Treur et al., 2019), consistent

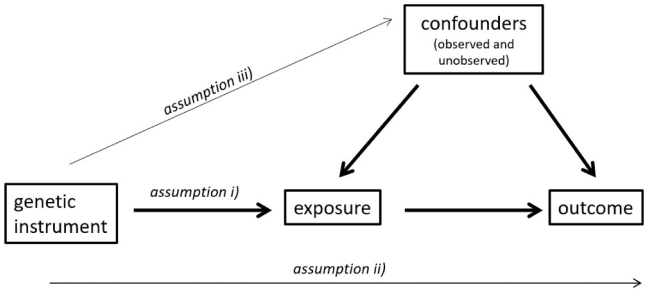
Box 1
Summary Of Methods Used To Infer Causality.

Longitudinal designs with multiple measures avoid reverse causality effects, however data collection for many different variables in large enough sample sizes is very costly and unmeasured confounders can still be an issue in these studies.

Twin study designs are used to account for factors that may confound a potential causal relationship, by implicitly controlling for all factors shared within a twin-pair even when they are unmeasured. An issue in this kind of studies arises in the presence of non-shared confounding factors, particularly when they are also unmeasured.

Randomized controlled trials (RCT) avoid the effect of unmeasured confounding factors, by randomly allocating individuals to different groups and balancing this way the distribution of measured and unmeasured factors across groups. In a RCT each group is treated differently and then the effect of each treatment is measured and compared. This design avoids both confounding and reverse causality issues, however there are clear ethical issues in their application for certain disciplines.

Mendelian randomization (MR) is based in a RCT design. This technique makes use of genetic variants, whose alleles have been randomly allocated during meiosis to individuals in the population, creating this way two groups (in the case of a biallelic variant) with a supposedly balanced distribution of confounding factors, similarly to an RCT. In MR, genetic variants are used as instrumental variables (genetic instruments), serving as a proxy for an exposure and their effect in an outcome is tested. A significant association with the outcome would provide evidence for a causal relationship only if the genetic instrument meets the following assumptions: *i)* robust association with the exposure, *ii)* association to the outcome only through the exposure and *iii)* independence of confounding factors that affect the exposure and the outcome. Currently, MR is of particular interest because it can be easily undertaken using summary statistics for traits analyzed in different sets of individuals in large scale genetic studies, which are now available for a wide range of traits. The challenges that MR analyses present are mostly related to the assumptions it makes and the interpretation of the findings. MR assumptions are hard to test, for this reason a number of MR methods using different variations of the assumptions required have been developed, such as bidirectional MR (Pickrell et al., 2016) or Causal Analysis Using Summary Effect estimates (CAUSE) (Morrison et al., 2020) designed to be more robust to different kinds of horizontal pleiotropy. The general recommendation is to run a combination of these methods and look for consistency in the results.



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Latent Causal Variable (LCV) model is also designed, using a similar approach to bidirectional MR, to infer causality using genetic data and avoiding biases due to horizontal pleiotropy. This method takes two traits which are genetically correlated and uses the fact that if trait 1 is partially genetically causal for trait 2 most SNPs affecting trait 1 will have a proportional effect on trait 2, but no vice versa (O'Connor and Price, 2018).

with a recent MR study that found significant results for current smoking only when ADHD was used as exposure (Soler Artigas et al., 2023). Latent Causal Variable (LCV) analyses undertaken in the same study provided evidence for genetic liability to smoking initiation being causal for ADHD, but not for the reverse direction (Treur et al., 2019). Regarding cigarettes per day, smoking cessation, age of smoking and lifetime smoking, significant results using MR showed the expected direction of effect, where ADHD increases the risk for these smoking-related traits (Jang et al., 2020; Treur et al., 2019; Vilar-Ribó et al., 2020). A bidirectional negative effect has also been reported for the genetic liability of ADHD and past tobacco smoking for non-heavy smokers, indicating lower frequency of smoking in the past for individuals who were not heavy smokers when asked (Soler Artigas et al., 2023). However, no evidence for a causal relationship between ADHD genetic liability and nicotine dependence was identified, perhaps due to limited power according to the authors (Vink et al., 2020).

Also, a positive causal effect of ADHD genetic liability on lifetime cannabis use, and also in the opposite direction, was reported using MR, but no causal relationship in any direction was found using LCV (Soler Artigas et al., 2020; Treur et al., 2019; Vilar-Ribó et al., 2020). Regarding alcohol use, suggestive evidence using MR was found for a positive causal effect of ADHD genetic liability on alcohol dependence and no evidence in the other direction, however LCV provided evidence for a causal role of alcohol dependence on ADHD and not on the reverse direction (Treur et al., 2019). MR analyses have also been undertaken for ADHD and cocaine dependence and addiction to illicit drugs, with no significant results, probably due to the still limited sample sizes of these studies (Vilar-Ribó et al., 2020).

A recent study reported MR analyses, as well as bidirectional MR and LCV analyses, and concluded that overall vertical pleiotropy, at least a single causal direction, may not explain the well-known high rate of co-occurrence among ADHD and substance use, and that horizontal pleiotropy, or more complex forms of phenotypic causation, may be responsible for this (Jang et al., 2020). They also stated that cyclical feedback loops between ADHD, smoking-related behaviors, lifetime cannabis use and alcohol use may exist to some degree and that this type of causality can evade LCV and bidirectional MR but would still be detected by other MR methods to some extent (Jang et al., 2020). Given that the authors used a more limited subset of genetic variants (half of the reported associations in the case of ADHD) in their study, we cannot

discard limited power in their MR analyses to detect the significant findings on cigarettes per day, smoking cessation and lifetime cannabis use that studies described above identified in the same datasets (Treur et al., 2019).

Several studies have also assessed the causal relationship between ADHD and MDD or intelligence. A study using both a longitudinal design and MR analyses suggested that ADHD increases the risk of depression later in life, which is consistent with a causal effect of ADHD genetic liability on subsequent MDD (Riglin et al., 2020). The MR findings of the authors, however, were different for more broadly defined depression, for which a causal relationship in the opposite direction suggested that genetic liability for a broad definition of depression may have a causal effect on ADHD (Riglin et al., 2020). A recent MR study including additional sensitivity analyes, such as Causal Analysis Using Summary Effect estimates (CAUSE), replicated these findings for MDD (Soler Artigas et al., 2023). In addition, evidence of a negative bidirectional relationship between ADHD and intelligence has been described using both MR and a longitudinal design in twins (Rommel et al., 2015; Savage et al., 2018).

Results from the current literature, overall, are not conclusive and are partly hard to interpret. The relationship between ADHD and other co-occurring comorbid disorders may not be explained just by simple causation in one direction and may point to more complex relationships. The different methods available to assess causality have their own strengths and limitations and require different sets of assumptions to hold; for instance, unmeasured confounders may be an issue in longitudinal studies and horizontal pleiotropy may be an issue in MR studies. Study characteristics, such as sample size, must be also considered when interpreting the results; for instance, a negative MR finding may be due to the limited sample size of GWAS where the genetic variants were identified. Recent guidelines to aid in the design and interpretation of MR studies (Burgess et al., 2020; Smith et al., 2019), novel methods to assess causality (Darrous et al., 2020; Morrison et al., 2020), and additional studies triangulating evidence across different methods and samples will contribute to a better understanding of the temporal relationship between ADHD and adverse health outcomes.

4.1.3. Cross-disorder analyses

The studies investigating genetic architecture through genetic correlations and PRS analyses using common genetic variation described above clearly show that the co-occurrence of ADHD with other psychiatric disorders and traits is at least partly based on genetic variants. Researchers have now started to perform studies to identify the underlying individual genetic variants by performing cross-disorder analyses. A summary of these analyses, explained in detail below, is shown in Table 1.

The field was jump-started by an early study of the Psychiatric Genomics Consortium's cross-disorder working group published in 2013, in which overlap between five psychiatric disorders, including ADHD, ASD, schizophrenia (SCZ), MDD, and BD, was investigated in 33,332 cases and 27,888 controls (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). In this study, four genome-wide significant loci were identified (close to genes *ITIH3, AS3MT, CACNB2* and *CACNA1C*), with the first three also appearing relevant for ADHD in model selection analysis. Pathway analysis suggested a role for calcium channel signalling genes for all five disorders. The second study of the PGC's cross-disorder working group extended the cross-disorder meta-analyses to eight mental disorders (ADHD, ASD, SCZ, BD, MDD, Tourette syndrome (TS), anorexia nervosa (ANO), and OCD) and 232,964 cases and 494,162 controls (Lee et al., 2019). A total of 146 independent lead single nucleotide polymorphisms (SNPs) were identified; of those, 109 (75%) showed pleiotropic effects involving at least two of the eight disorders. Seventeen of the 109 pleiotropic loci were found relevant for ADHD plus at least one additional disorder using a Bayesian statistical framework to estimate the posterior probability of association with each disorder. Interestingly, authors found 11 pleiotropic loci that showed opposite effects on the risk of different disorders. Of them, three showed association with ADHD, one presenting opposite effects in SCZ and the other two in ANO. The most pleiotropic SNPs implicated *RBFOX1*, encoding a splicing regulator mainly expressed in neurons and involved in neuronal migration as well as synapse formation (Fernàndez-Castillo et al., 2020), and *DCC,* which encodes a protein with important roles in axonal guidance during neurodevelopment (Bendriem and Ross, 2017). More generally, enrichment of expression of pleiotropic genes was seen for multiple brain tissues, and specifically in neurons. These pleiotropic risk loci were enriched for genes involved in neurogenesis, regulation of nervous system development, and neuron differentiation. Spatio-temporal gene expression patterns of the genes implicated through the 109 pleiotropic risk loci showed peak expression around the second trimester of prenatal life; after birth, gradually increasing gene expression was seen until adulthood.

An update of the meta-analysis of the five disorders (ADHD, ASD, SCZ, MDD and BD) analysed together in the PGC study published in 2013 was also recently reported, including strongly increased sample sizes (Wu et al., 2020). Based on Multi-Trait Analysis of GWAS (MTAG) methodology, eight genes were found being associated with at least four out of the five conditions, namely *SORCS3*, *GABBR1*, *GLT8D1*, *HIST1H1B, HIST1H2BN, HIST1H4L, KCNB1*, and *DCC* (Jia et al., 2019). The findings strongly overlapped with those reported in the larger PGC eight-disorder analysis described above (Lee et al., 2019).

Genetic sharing was also investigated in a subgroup of the eight disorders, those with typical symptom onset in childhood (ADHD, ASD, OCD, and TS), in a separate study of 41,983 cases and 51,311 controls

Table 1
Summary of the cross-disorder/trait studies that include ADHD. ADHD: Attention-deficit/hyperactivity disorder; ASD: Autism spectrum disorder; BD: Bipolar disorder, MDD: Major depressive disorder; SCZ: Schizophrenia; ANO: Anorexia nervosa; OCD: Obsessive compulsive disorder; TS: Tourette syndrome; DEP: Depression; ALCH: Problematic alcohol use; ANX: Anxiety; PTSD: Post-traumatic stress disorder; EA: Educational attainment; IQ: Intelligence quotient.

Disorders/Traits	Sample size	Reference
Psychiatric disorders		
ADHD, ASD, BD, MDD, SCZ	33,332 cases and 27,888 controls	Cross-Disorder Group of the Psychiatric Genomics Consortium (2013)
ADHD, BD	14,259 cases and 21,363 controls	van Hulzen et al. (2017)
ADHD, ANO, ASD, BD, MDD, OCD, SCZ, TS	232,964 cases and 494,162 controls	Lee et al. (2019)
ADHD, ASD, OCD, TS	41,983 cases and 51,311 controls	Yang et al. (2021)
ADHD, BD	39,451 cases and 65,552 controls	O'Connell et al. (2019)
ADHD, ASD, BD, DEP, SCZ	92,119 cases, 117,225 controls and 688,809 continuous score (DEP)	Wu et al. (2020)
ADHD, ALCH, ANO, ANX, ASD, BD, MDD, OCD, PTSD, SCZ, TS	462,483 cases, 1114,731 controls, 147,267 continuous score (ALCH)	Grotzinger et al. (2022)
ADHD, ASD	34,462 cases and 41,201 controls	Mattheisen et al. (2022)
Behavioural and cognitive traits		
ADHD, EA	ADHD (2064 trios, 896 cases, and 2455 controls), EA (328,917)	Shadrin et al. (2018)
ADHD, EA	ADHD (19,099 cases, 34,194 controls), EA (842,499)	O'Connell et al. (2020)
ADHD, IQ	ADHD (19,099 cases and 34,194 controls), general intelligence (269,867)	O'Connell et al. (2020)
ADHD, lifetime cannabis use	ADHD (19,099 cases and 34,194 controls), lifetime cannabis use (14,374 cases and 17,956 controls)	Soler Artigas et al. (2020)

(Yang et al., 2021). Through genomic structural equation modelling, a common factor was identified, on which ADHD, ASD and TS loaded. Subsequently, by performing SNP- and gene-based meta-analyses of the three disorders, seven independent pleiotropic loci and 18 genes were identified, respectively (including *ST3GAL3, MANBA, SORCS3, DUSP6, WNT3 and XRN2,* among others). Most of the findings had not been observed in the earlier eight-disorder meta-analysis, suggesting a role in early onset of mental illness. Enrichment analyses based on the 200 top-findings from the SNP- and gene-based analyses of pleiotropy highlighted pathways involved in neuronal development, axonogenesis, and synaptic structure and organization, among the most significant ones. Tissue-specificity analysis for the expression of genes in the pleiotropic loci prominently and predominantly implicated the frontal cortex, basal ganglia, hypothalamus, cerebellum, amygdala, and hippocampus. In particular, the fetal brain appeared to be implicated.

Finally, the latest study of the PGC's cross-disorder working group extended cross-disorder analyses to 11 psychiatric disorders (Grotzinger et al., 2022). In addition to the eight disorders in the former study (Lee et al., 2019), the following were added: PTSD, anxiety, and problematic alcohol use. This study primarily focused on the validity of the cross-disorder genetic structure in terms of the etiological, diagnostic and therapeutic utility of genomic factors, determining if risk mechanisms operate at the disorder-specific level or at the more aggregated-factor level (e.g. at the level of ADHD, the latent neurodevelopmental factor level, or latent general factor level). One of the main conclusions of the study was that the neurodevelopmental disorder factor comprised by ADHD, ASD, PTSD, and to a lesser extent MDD, was not valid in terms of capturing the genetic relationships with external biobehavioral traits and functional genomic and molecular levels of analysis. Instead, strong heterogeneity in the genetic associations with both external biobehavioral traits and individual SNPs was found at the disorder-specific level, particularly between ASD and the other disorders comprised by the neurodevelopmental factor including ADHD. Thus, the previously described cross-disorder behavioral genetic finding reporting the strongest similarity between ASD and ADHD does not extend to these molecular genetic findings, at least with respect to common variants. The inconsistent pattern of results from the recent behavioral and molecular genetic studies emphasizes the need for further large-scale cross-disorder studies.

In addition to the meta-analyses across several disorders, pairwise meta-analyses have also been performed for several ADHD-comorbid disorder combinations. A recent study investigated shared genetic risk for ADHD and ASD by cross-disorder analyses of large data sets, totaling 34,462 cases and 41,201 controls (Mattheisen et al., 2022). This study identified seven loci shared by the disorders, two of them had not been identified before as shared between ADHD and ASD. The two novel associations were located in a highly pleiotropic multigene locus on chromosome 1 (including *PTPRF*, *KDM4A*, *ST3GAL3* and *MIR6079*) and at the *MANBA* gene locus on chromosome 4. Both were also identified in the analyses across ADHD, ASD and TS (Yang et al., 2021). To identify and prioritize putative causal shared genes authors performed a transcriptome-wide association study (TWAS) identifying *MANBA*, *MOCS2* and *CCDC71* genes. Gene-based analysis highlighted two additional novel candidate genes (*SORCS3* and *DUSP6*) for shared ADHD and ASD risk, which were also identified by Yang et al. (2021). Interestingly, in addition to shared loci, this study also provided first evidence for several genetic variants that distinguish the two disorders. A study published in 2017 reported on genetic overlap between ADHD and BD, which is strongly supported by clinical and epidemiological studies (Schiweck et al., 2021). With a still limited sample size for ADHD, two genome-wide significant pleiotropic loci were observed, close to the genes *CEP85L* and *TAF9BP2*. Restricting the BD sample based on an early age of onset, one significant pleiotropic locus was seen close to the *ADCY2* gene (van Hulzen et al., 2017). A second study leveraged larger sample sizes for both ADHD and BD and identified five shared loci (close to genes *EMCN, NPAS3, RP11–6N13.1, RP1–84O15.2*, and *CTC-447K7.1*; O'Connell et al., 2019).

Moving beyond the identification of genes pleiotropically involved in at least one additional psychiatric disorder, variation underlying the genetic correlation between ADHD and several behavioral and brain traits is also increasingly being explored. A first example is given by two studies identifying the variants implicated in ADHD, educational attainment (EA) and/or intelligence. In the first study, based on data on just above 3000 patients, they observed three shared loci in the conjunctional analysis for ADHD and EA (*KDMA4*, which lies close to *ST3GAL3* and *PTPRF* in a known ADHD risk locus, *PINK1*, and *MEF2C*). As expected, based on the negative correlation between ADHD and EA, opposite effect directions for the three variants with the strongest association signal for each locus were observed for ADHD and EA (Shadrin et al., 2018). The more recent study by the same authors using the same design benefitted from greatly increased sample sizes that were now available for ADHD (from the 2019 GWAS) and EA (842,499 individuals), and the authors also included data on intelligence (269,867 individuals). The study identified 30 loci shared between ADHD and EA and/or intelligence (close to genes *CALN1, FOXP1, FOXP2, MEF2C, PTPRF* and *SORCS3,* among others); 24 loci were observed for ADHD and EA, of which seven were novel to both phenotypes, and 15 loci were seen for ADHD and intelligence, of which four were novel. Nine of the loci showed association with all three phenotypes. Interestingly, despite the overall negative genetic correlations of ADHD with either trait, both opposite and concordant effect directions were seen for individual shared loci (O'Connell et al., 2020). In an analysis examining the genetic overlap between ADHD and lifetime cannabis use using the 2019 ADHD GWAS and data on 32,330 individuals reporting on cannabis use, the authors identified two pleitropic SNPs as well as the pleitropic genes *WDPCP* and *ZNF251* (Soler Artigas et al., 2020).

In terms of pleiotropy of ADHD risk variants with brain imaging traits, analyses have so far been limited to brain structural traits for which GWAS of sufficient sample size are available. Using the ENIGMA GWAS of subcortical gray matter volumes (Adams et al., 2016; Hibar et al., 2017, 2015), a recent study identified genetic variants underlying the genetic sharing between ADHD and several brain traits. Two loci were found associated with both ADHD risk and intracranial volume, one in chromosome 15 (*SEMA6D*) and one in chromosome 16 (intergenic). Four additional loci were identified for ADHD and volumes of the amygdala (chromosome 3, intergenic), caudate nucleus (chromosome 5, *LINC00461*), and putamen (chromosome 15, *SEMA6D* and chromosome 2, intergenic) (Klein et al., 2019). While still limited in terms of results, such studies might inform us about the biological pathways from gene to disorder involving the brain's structure and functional networks in the future. An interesting novel approach in this direction was most recently published: Taking brain cortical thickness alteration profiles observed across psychiatric disorders as point of departure, the authors took a virtual histology approach to identify gene co-expression modules involved in individual disorders and in groups of disorders correlated through cortical alterations and genetics. For ADHD, negative correlations were seen with gene expression profiles specific for astrocytes, CA1 pyramidal neurons, and microglia. Gene expression profiles specific for the same group of cell types were also related with a principal component of brain structure across the six psychiatric disorders (Patel et al., 2021).

Looking across the studies described in this section, it is clear that the integration of large, international data sources based on innovative statistical and bioinformatic methods can enhance our understanding of the biological processes involved in ADHD and its comorbid psychiatric disorders and traits, and they help to clarify the brain networks and cell types involved.

4.2. Rare variants

The discrepancy between the total heritability of ADHD (74%) based on twin studies, as described above (Faraone and Larsson, 2019), and

the SNP-based heritability of 14–22% estimated on the basis of common variants analyzed in the GWASs on ADHD (Demontis et al., 2023, 2019b), suggests that rare variants, despite being individually infrequent in the population, may additionally play a role in the disorder as they usually have larger effect sizes. Although ADHD is highly heritable and polygenic, rare mutations have received relatively little attention compared to many other similarly heritable and polygenic disorders that include SCZ, ASD and ID. Nonetheless, rare copy number variants (CNVs) have been studied in ADHD for several years (Harich et al., 2020; Jarick et al., 2014; Lesch et al., 2011; Williams et al., 2012, 2010), and a growing number of studies have investigated rare single nucleotide variants (SNVs; frequency < 1%) or low-frequency SNVs (frequency between 1% and 5%) in relation to ADHD using exome-chip approaches or whole-exome sequencing (WES; Al-Mubarak et al., 2020; Corominas et al., 2020; Demontis et al., 2016; Ganna et al., 2018; Satterstrom et al., 2019; Schäfer et al., 2018; Torrico et al., 2020; Zayats et al., 2016). Findings support the existence of pleiotropy for rare variants associated with ADHD and other psychiatric and neurodevelopmental disorders that are frequently comorbid with ADHD, such as ASD. No research so far has focused on cognitive traits related to ADHD (other than the low IQ seen in ID).

The work on CNVs provided the first clues about the extent of rare-variant overlap between ADHD and other disorders. A study in around 300 parent-offspring trios with a child with ADHD identified 14 large (>200 Kb) de novo CNVs, a mutation rate that is four times higher than that found in controls and similar to that observed in ASD, SCZ or TS (Martin et al., 2020). Four of these CNVs had previously been implicated in other neurodevelopmental disorders (ASD, SCZ, TS and developmental delay/ID; Coe et al., 2014; Marshall et al., 2017; Rees et al., 2016; Sanders et al., 2015; Wang et al., 2018). Another study on 6000 children and adults with ADHD prioritized 26 genes in rare and common CNVs, five of which showed gene-based association with a combined measure across eight psychiatric disorders (ADHD, ASD, SCZ, BD, MDD, ANO, TS and OCD; Harich et al., 2020). Finally, a study in 30 parent-offspring trios with ADHD that merged data from SNVs and CNVs identified through WES showed that on average, children with inherited SNV/CNV variants had twice as many comorbidities than children with the novo variants, although these are preliminary results as the sample size was small (de Araújo Lima et al., 2016).

More recently, WES studies have started to provide information on SNVs involved in ADHD comorbidity. First, several studies compared samples of individuals with ADHD with samples of individuals with other psychiatric or neurodevelopmental disorders to detect pleiotropic effects. For example, a WES study in 8000 children with ASD and/or ADHD and 5000 controls showed that these two neurodevelopmental disorders have a similar burden of evolutionary constrained protein-truncating variants, and that these variants occur in similar and overlapping sets of genes (Satterstrom et al., 2019). The top cross-disorder finding from this study was *MAP1A*, a gene highly expressed in the brain and involved in the organization of neuronal microtubules (Fink et al., 1996). An excess of missense variants (i.e. variants that produce an amino acid switch in the protein) in this gene had previously also been reported in ASD and in SCZ (Myers et al., 2011). *GRIN2B*, encoding a member of the glutamate receptor superfamily and involved in excitatory synaptic transmission, has been found mutated through Sanger or next-generation sequencing (NGS) studies in patients with ADHD and in subjects with other neurodevelopmental disorders, including ASD, SCZ, developmental delay or language impairment (Hu et al., 2016). Finally, a WES study of 13 quantitative traits and 10 diseases on 100,000 participants, including ADHD, SCZ, BD and ID, revealed a cross-disorder enrichment of protein truncating variants (PTV) that occur in PTV-intolerant genes (PI-PTV; Ganna et al., 2018). Interestingly, those patients with multiple neurodevelopmental or psychiatric disorders showed a stronger enrichment of PI-PTVs that was not driven by any single disorder. This suggests that the PI-PTVs, as a whole, are likely to be pleiotropic, possibly influencing some core intermediate phenotypes that relate to risk to many neurodevelopmental and psychiatric disorders, although from this work, it cannot be excluded that certain genes have disease-specific effects.

A second source of evidence that SNVs are involved in ADHD comorbidity comes from pedigree studies in which ADHD and other psychiatric disorders or traits co-occurred in individuals that bear a rare mutation in a particular gene. In many cases, those pedigrees were identified based on an additional, non-psychiatric condition. Several genes could be identified in this way for: ADHD and ASD (*YWHAZ*; Torrico et al., 2020), ADHD, OCD, aggression, ID, language impairment, dysmorphic facial features and epilepsy (*PACS1*; Stern et al., 2017), ADHD, ID and congenital cataracts (*KCNA4*; Kaya et al., 2016), ADHD and ID with syndromic retinitis pigmentosa (*SCAPER;* Tatour et al., 2017), ADHD, learning difficulties, fine motor developmental delay and multiple congenital anomalies (*ASH1L*; Shen et al., 2019), ADHD, ASD and insomnia (*CRY1*; Onat et al., 2020), as well as ADHD, global developmental delay, microcephaly, language delay and dysmorphic features (*STAG2*; Mullegama et al., 2017).

As mentioned above, reports now exist linking both rare and common genetic variation in several genes and pathways to (the same or different) psychiatric disorders. Developing approaches that allow the integration of data from different types of genetic variation is therefore likely to be maximally informative about the role of genetic sharing in ADHD and its comorbidities. A first study aiming at such integration used a simple cross-disorder design to investigate genetic sharing between ID and ADHD: based on a list of genes assessed for rare variants causing ID in a diagnostic setting, the authors investigated whether common variants in this set of genes were associated with ADHD (Klein et al., 2020). They indeed found significant associations for the gene set as a whole in two independent samples. The genes most strongly implicated were *ST3GAL3, TRAPPC9* and *MEF2C*. A role in ADHD-like behavior was confirmed in a Drosophila model for the last two genes, while *ST3GAL3* did not have a homologue in this model organism (Klein et al., 2020). Future studies based on genome-wide sequencing will enable more sophisticated integrative methods to be used.

From the above studies on rare variation, no clear picture regarding molecular pathways involved in ADHD comorbidity has yet emerged. However, based on what we currently know, it appears that a majority of genes contributing to ADHD through rare variants are not specific to ADHD and also contribute to other psychiatric and neurodevelopmental disorders. Future studies using larger sample sizes and novel approaches combining common and rare variants will help on clarifying this picture.

5. Outlook

In this paper we reviewed the evidence for the role of genetics in the comorbidity of ADHD with other psychiatric disorders and related traits. We focused on hypothesis-generating approaches, covering quantitative genetic twin and family studies as well as genome-wide molecular-genetic studies of common and rare genetic variants. Hypothesis-driven studies interrogating particular candidate genes or variants were not considered here.

Quantitative genetic studies indicate that genetic factors are involved in the observed co-occurrence of ADHD with different psychiatric disorders and traits. Genome-wide molecular studies and derived methods have provided information on the nature of the genetic overlap observed. Specifically, GWASs have allowed to estimate the molecular genetic overlap, using common genetic variation, of ADHD and these co-occurring disorders and traits. Such studies have shown the existence of substantial genetic correlations between ADHD and several psychiatric disorders, being PTSD, SUD, MDD and ASD the ones presenting the highest correlations, and related traits such as aggression- or alcohol-related phenotypes.

Cross-disorder GWASs have also allowed the identification of common genetic variants shared across ADHD and comorbid disorders/traits. These studies, in combination with other types of large-scale data

sources, are also starting to provide information about the brain regions and cell types involved in ADHD and its comorbidities, through powerful statistical and bioinformatic approaches. Some of the genetic variants that have been identified as shared between disorders show risk-increasing effects on one disorder and protective effects on the other (e.g. Lee et al., 2019). This is seen independent of whether the overall genetic correlation between the disorders involved is positive or negative. In the same vein, same-direction associations with disorders can be observed for variants in pairs of disorders that have an overall negative genetic correlation (e.g. O'Connell et al., 2020). This indicates that the genetic correlations we compute provide only rough estimates of the genetic relationship between two phenotypes. Recently developed methods considering local differences (Guo et al., 2021; Werme et al., 2022; Zhang et al., 2021) might considerably change our current estimates of genetic correlation for ADHD and its comorbid disorders and traits in the near future.

While shared genetics definitely has an important role in ADHD comorbidity, different models could potentially account for the genetic correlations reported in the literature. In this regard, we also reviewed different methods that have been used to establish causality, including longitudinal twin analyses, MR studies and LCV analyses. While distinguishing between possibilities such as horizontal versus vertical pleiotropy has proved challenging to date, such approaches are relatively novel and method developments are still ongoing.

Although this review focuses on the current literature on hypothesis-free approaches, some genes have been widely investigated through candidate-gene association studies yielding positive associations with different psychiatric disorders (including ADHD). However, except for a few cases, these hits have not been replicated by GWAS, which raises questions on how alterations in these genes can actually be causally related to psychiatric conditions, but also on the value of genome-wide significance to nominate causal variation. Genes related to dopaminergic and serotonergic neurotransmission are examples of this, which have been widely studied through candidate-gene studies on the basis of their major role in regulating emotional functions and cognitive processes. A recent study using GWAS data and applying gene-based and pathway analyses supports a pleiotropic contribution of these systems in several psychiatric conditions, including ADHD (Cabana-Domínguez et al., 2022).

Apart from the common genetic risk variants identified so far in ADHD and several of its comorbidities, studies focusing on rare variants also support the existence of pleiotropic rare variants associated with ADHD and other disorders that are frequently comorbid with ADHD. However, the combined role of common and rare genetic variation in ADHD comorbidity is currently insufficiently clear, as analyses of one or the other type of genetic variation have been carried out largely in isolation. This is because we still lack samples of sufficient sample size with both data types to allow meaningful integration. First examples of such integration in neurodevelopmental disorders are starting to find their way into the literature, e.g. with the Deciphering Developmental Disorders (DDD) cohort (Niemi et al., 2018), but the advent of (affordable) whole genome sequencing (WGS) is likely to allow more elegant approaches in the near future. This is of particular importance now that new data suggest that the 'missing heritability' for height and body mass index resides in low-frequency genetic variants that are not well tagged by the currently assessed common genetic variants (Wainschtein et al., 2019). Whether these findings will generalize to ADHD and its comorbid disorders awaits future research.

Also, it has been shown that genes involved in monogenic disorders (identified in the OMIM database) that present with ADHD symptoms contribute to the polygenic forms of ADHD and comorbidities, as shown by association studies performed on GWAS data (Fernàndez-Castillo et al., 2021). Interestingly, many of the mendelian disorders identified in this work, each caused by rare variation in a single gene, present with conditions that are comorbid with ADHD, in addition to the ADHD symptoms, namely aggressive behaviour, anxiety, OCD and ASD.

The integration of common and rare variation will ultimately also lead to more meaningful biological insights. Now, the risk variants that are described in cross-disorder analyses can often not yet be mapped onto molecular-cellular pathways and thus, the present data are currently not maximally informative from the mechanistic point of view. The question whether cross-disorder variants increase the risk for mental disorders in general or whether there is specificity for specific disorder combinations cannot be sufficiently answered yet.

Findings from molecular genetic studies do not yet explain the level of comorbidity which is found in behavioral genetic or epidemiological studies. One partial explanation, which is especially true for rare variants, is the insufficient sample size used so far. Moreover, current studies have not systematically assessed the degree to which comorbidity might be accounted for by shared environmental risk factors or by shared gene by environment interactions. A complicating issue here is gene-environment correlation: the behavioral consequences of ADHD might lead to differential environmental exposures and, consequently, to comorbidity, which is not reflected adequately in genetic studies. One example of gene-environment interaction is related to SUD, where the impulsive symptoms of ADHD may lead to risk-taking behaviors which in turn might conduct to earlier or higher exposure to (especially illicit) drugs. Similarly, repetitive exposure to stress (Hartman et al., 2019; Rychik et al., 2021) or experience of failure (in the educational (Zendarski et al., 2020), professional (Kessler et al., 2005a) or romantic domains (Wymbs et al., 2021)) might increase the risk towards depression via environmental routes. Measuring epigenetic contributions to ADHD comorbidity might provide an interesting future avenue to make progress in understanding the contribution of the environment to ADHD outcome and comorbidity (Mooney et al., 2020).

As mentioned above, for many study designs, the currently available sample sizes for genetic studies of ADHD are still relatively limited. More data is becoming available through international collaborations, such as the PGC and iPSYCH. In addition, both phenotypic and genetic studies suggest that clinically diagnosed ADHD is the extreme of behavioral traits/symptoms present throughout the population and that those symptoms are associated with the same genetic factors as the clinical presentation of ADHD (Demontis et al., 2019b). This provides excellent opportunities to use population samples for genetic studies of ADHD comorbidity. With more and more large-scale population studies coming available, such as the UK Biobank (Sudlow et al., 2015), the Million Veteran Program (Gaziano et al., 2016) and All of Us ("The "All of Us" Research Program, 2019), this should facilitate significant progress in our understanding of the biological underpinnings to be made in the coming years. Of note, more and more datasets collect environmental data in addition to phenotype and genetic data, which will foster combined analyses. However, a critical bottleneck in this is the phenotyping of ADHD symptoms in such cohorts. Because ADHD is still given secondary importance by many researchers it has proven difficult to convince those responsible for developing phenotyping batteries for such cohorts to give ADHD symptom phenotyping priority. If this is not changed, ADHD research will not be able to benefit from the new cohorts to a similar degree as research of other psychiatric disorders and traits will. Changing this situation should be a priority of all scientists involved in ADHD research.

In terms of clinical application, utility of genetic data on ADHD comorbidity is still a bridge too far, given the low variability explained. Currently, genetic studies provide a fascinating first glimpse into the molecular architecture of mental illness. Although the percentage of variance explained is too little to be used for diagnosis, the new wave of GWASs provides validation for clinical studies of comorbidity and is thus useful for educating clinicians and patients. With (1) increasing sample sizes (especially of comorbid cases), (2) the analysis and integration of different forms of risk variants (common and rare), and (3) using more sophisticated bioinformatic and machine-learning methods, (4) in conjunction with the rapid development of low-cost high-throughput genetic analyses, it seems likely that genetic data may become useful for

diagnosis, prognosis and/or prediction of treatment response. Clinicians must therefore be made aware of the current state of knowledge and be trained to integrate it into diagnostic and therapeutic decision trees in the future; secondary and tertiary prevention, such as prevention of substance use or obesity in ADHD cases, might be of special relevance here.

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Declaration of Competing Interest

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Glossary

Confounder: distortion of the association between an exposure and an outcome due to a third variable called a confounder, associated with both the exposure and the outcome.

Genetic correlation: proportion of variance that two traits share due to genetic variants. A genetic correlation of 0 implies that the genetic effects on one trait are independent of the other, while a correlation of 1 implies that all of the genetic influences on the two traits are shared.

Genome-wide association study (GWAS): hypothesis-free approach to associate common genetic variations with particular diseases or traits. The method involves scanning the genomes from many different people and looking for genetic markers that are associated with the disease or trait.

Heritability: proportion of phenotypic variability that is attributable to genetic factors: higher estimates suggest that genetic variability has a large influence on the variability of a given trait in the population.

Horizontal (biological) pleiotropy: when genetic variants are associated independently (through different biological pathways) to two different traits.

Missing heritability: phenomenon in which the heritability estimated by single nucleotide polymorphisms (SNPs) do not account for much of the heritability of a disorder or phenotype that is estimated from familiar and twin data.

Next-generation sequencing (NGS): a high-throughput method used to determine a portion (or all) of the nucleotide sequence of an individual's genome or transcriptome. Since it is based on massively parallel sequencing it allows for sequencing of DNA and RNA much more quickly and cheaply than the previously used Sanger sequencing method.

Polygenic Risk Score (PRS): continuous score that uses the sum of all known common variants to quantify the aggregate effect of common variants for a given disorder or trait. PRS is calculated by multiplying the number of risk alleles a person carries at a particular SNP by the effect size of the risk allele and then, summing each of these products across the genome.

Reverse causality: when an association between an exposure and an outcome is due to the causal effect of the outcome on the exposure, rather than the exposure on the outcome.

Sanger sequencing: method of DNA sequencing based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication.

SNP-based heritability: proportion of phenotypic variability that is attributable to SNPs.

Vertical (mediated) pleiotropy: when genetic variants exert their effect on the outcome through the exposure, through a single biological pathway.

Whole-genome sequencing (WGS): genomic technique for determining the entirety, or nearly the entirety, of the DNA sequence of an organism's genome.

Whole-exome sequencing (WES): genomic technique for determining the DNA sequence of all the exonic (protein-coding) regions of an organism's genome.