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Insights into attention-deficit/hyperactivity disorder from recent genetic studies

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable neurodevelopmental disorder (NDD). In this narrative review, we summarize recent advances in quantitative and molecular genetic research from the past 5–10 years. Combined with large-scale international collaboration, these advances have resulted in fast-paced progress in understanding the etiology of ADHD and how genetic risk factors map on to clinical heterogeneity. Studies are converging on a number of key insights. First, ADHD is a highly polygenic NDD with a complex genetic architecture encompassing risk variants across the spectrum of allelic frequencies, which are implicated in neurobiological processes. Second, genetic studies strongly suggest that ADHD diagnosis shares a large proportion of genetic risks with continuously distributed traits of ADHD in the population, with shared genetic risks also seen across development and sex. Third, ADHD genetic risks are shared with those implicated in many other neurodevelopmental, psychiatric and somatic phenotypes. As sample sizes and the diversity of genetic studies continue to increase through international collaborative efforts, we anticipate further success with gene discovery, characterization of how the ADHD phenotype relates to other human traits and growing potential to use genomic risk factors for understanding clinical trajectories and for precision medicine approaches.

Invited Review

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder (NDD) (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007, 2014). Although the exact causes of ADHD remain unclear, advances in quantitative and molecular genetic methods demonstrate that genetic factors play a crucial role in its etiology. In this narrative review, we briefly outline the clinical presentation and epidemiology of ADHD and summarize insights from recent genetic research, focusing on studies from the past 5–10 years, and particularly genome-wide association studies (GWAS) and downstream analyses. By highlighting converging evidence from twin and family studies with recent molecular genetic approaches, we illustrate how genetic risks contribute to the development of ADHD across different definitions, ages, sex, and comorbidities. Finally, we discuss implications and future directions, highlighting areas where further genetic research is needed.

Clinical diagnosis

ADHD is characterized by developmentally inappropriate symptoms of inattention and/or hyperactivity/impulsivity. Based on current diagnostic criteria using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013), six inattention and/or six hyperactivity/impulsivity symptoms must be present for at least 6 months, before age 12, and impair function across multiple settings (e.g. home and school). The International Classification of Diseases (ICD-11) (WHO, 2018) includes the same symptoms and criteria, except that the number of symptoms and age-of-onset are not specified (Posner, Polanczyk, & Sonuga-Barke, 2020).

The first descriptions of clinically-significant attention deficits were published in the late 1700s (Martinez-Badía & Martinez-Raga, 2015). These early descriptions contain many features of ADHD (e.g. inattention and fidgeting), although hyperactivity was first formally described in 1932 (Faraone et al., 2015; Lange, Reichl, Lange, Tucha, & Tucha, 2010). ADHD first appeared in DSM-II and ICD-9. Currently, DSM-5 (APA, 2013) and ICD-11 (Posner et al., 2020) recognize three ADHD presentations: predominantly hyperactive/impulsive, predominantly inattentive, and a combined presentation.

Both pharmacological and non-pharmacological treatments are used to manage ADHD. Pharmacological treatments can be categorized into stimulant (methylphenidate and amphetamine-derivatives) and non-stimulant (atomoxetine, guanfacine, and clonidine) drugs, both of which increase extracellular levels of catecholamines (Golmirzaei et al.,

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2016). Stimulants are typically the first-line recommended drug treatment and have been shown to be effective in children and adults across several meta-analyses (Faraone & Buitelaar, 2010; Moriyama, Polanczyk, Terzi, Faria, & Rohde, 2013). Non-stimulants are typically used when stimulants are ineffective, contra-indicated, or have intolerable side-effects (Faraone, Biederman, & Mick, 2006b). Non-pharmacological treatments include behavioral management, psychoeducation, neurocognitive, and dietary interventions, which have all shown promise in individual studies, but only modest effects in meta-analyses (Thapar & Cooper, 2016). The multimodal treatment of ADHD study (MTA Cooperative Group, 1999) found that methylphenidate, alone or with psychosocial treatment, was the most effective at reducing ADHD symptoms. For more detailed information about treatments, see Faraone et al. (2015); Posner et al. (2020); and Thapar and Cooper (2016).

Epidemiology

ADHD is common worldwide, with meta-analyses reporting prevalence of 5–7% in children and adolescents (Polanczyk et al., 2007, 2014; Willcutt, 2012). Despite a public perception that ADHD is being increasingly diagnosed, a meta-analysis reported relatively stable prevalence estimates between 1985 and 2012 (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Although prevalence estimates vary by geographic location, with the highest prevalence observed in North America, followed by Europe, meta-analyses suggest that much of this variability is due to differences in study characteristics, assessment tools, diagnostic criteria, and availability of services (Polanczyk et al., 2007, 2014). The fact that ADHD is prevalent across the world reinforces why inclusion of genetic diversity, currently lacking in ADHD genetic research, is critical for equity in outcomes and progress.

ADHD is often persistent, with around 15% of affected children continuing to meet full diagnostic criteria by early adulthood and an additional 50–70% continuing to experience impairing symptoms (Caye et al., 2016; Faraone et al., 2006a). Remittance of symptoms with age, particularly hyperactivity/impulsivity, is one reason for the lower prevalence of ADHD in adults, which is estimated at 2.5% (Michielsen et al., 2012; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). However, current prevalence is likely underestimated (Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014), as ADHD in adults only recently became recognized (Asherson & Agnew-Blais, 2019; Franke et al., 2018). In childhood, ADHD is more common in males than in females, with a 4:1 ratio observed in clinical studies, whereas sex differences in adults are minor (Faraone et al., 2015).

Observational studies have linked several potential risk factors to ADHD, including pre- and peri-natal factors, exposure to toxins and pollutants, dietary factors, and psychosocial adversities (Faraone et al., 2021). However, it remains unclear whether these factors are causal or may in part, or fully, be confounded by genetic factors. For example, smoking during pregnancy was postulated to be a causal risk factor for offspring ADHD, but family-based studies strongly suggest that the association is better explained by unmeasured familial confounding, where shared genetic factors increase both the risk of maternal smoking during pregnancy and offspring ADHD (Langley, Heron, Smith, & Thapar, 2012; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014; Thapar et al., 2009). In contrast, putative risk factors such as low birth weight, low family income in early life, and severe psychosocial deprivation, show evidence of associations with ADHD even after accounting for shared familial factors (Hultman et al., 2007; Larsson, Sariaslan, Långström, D'Onofrio, & Lichtenstein, 2014; Stevens et al., 2008).

ADHD is frequently comorbid with other psychiatric and somatic disorders throughout the lifespan; however, the pattern of comorbidity changes across development (Franke et al., 2018). The most prevalent childhood-onset psychiatric comorbidities are other NDDs, such as autism spectrum disorders (ASDs) and learning disorders, as well as externalizing conditions including oppositional defiant disorder (ODD) and conduct disorder (CD) (Franke et al., 2018; Giacobini, Medin, Ahnemark, Russo, & Carlqvist, 2018; Taurines et al., 2010). Mood and anxiety disorders are common comorbidities across the lifespan, (Giacobini et al., 2018; Taurines et al., 2010) whereas substance use disorders (SUDs) and personality disorders become more prevalent during adulthood (Franke et al., 2018; Taurines et al., 2010). A recent systematic review concluded that obesity, sleep disorders, and asthma are well-documented somatic comorbidities of ADHD in adulthood (Instanes, Klungsøyr, Halmøy, Fasmer, & Haavik, 2018). Current research also supports an increased risk of diabetes, hypertension, certain autoimmune and inflammatory disorders, infections, migraine, and epilepsy in children, adolescents, and adults with ADHD (Akmatov, Ermakova, & Bätzing, 2019; Bertelsen, Larsen, Petersen, Christensen, & Dalsgaard, 2016; Chen et al., 2018; Cortese et al., 2018; Hegvik, Instanes, Haavik, Klungsøyr, & Engeland, 2018; Nielsen, Benros, & Dalsgaard, 2017; Salem et al., 2018). Increased mortality rates in ADHD have been reported in studies based on nation-wide register data in Denmark and Sweden. Although the observed absolute risk was small (0.3–0.5%), the relative risk of premature death in ADHD was found to be substantially higher than in the general population and appeared largely explained by unintentional injuries and suicide (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015; Sun et al., 2019). Notably, pharmacological treatment may reduce the risk of many negative outcomes associated with ADHD (Faraone et al., 2021).

Quantitative genetic studies of ADHD

Quantitative genetic research (e.g. family and twin studies) provides convincing evidence that genetic factors are important in ADHD (Faraone & Larsson, 2018). Early family studies found that first-degree relatives of children with ADHD had 4-to-5-fold higher risk of ADHD, compared to relatives of controls (Biederman et al., 1992; Faraone et al., 2000b). Such findings were recently extended in a large population-based register study ($N = 1\,656\,943$), showing that full siblings of individuals with clinically-diagnosed ADHD had an 8-fold increased risk of ADHD. Notably, the risk of ADHD in monozygotic (MZ) twins was increased 70-fold, whereas the risk in dizygotic (DZ) twins was no higher than that in full siblings (Chen et al., 2017). The greatly increased ADHD risk in MZ twins, who are genetically identical, compared to DZ twins, who share on average 50% of their segregating genes, is a well-replicated finding. Meta-analyses of twin studies (with the largest including 75 studies and 166 826 twin pairs) converge on heritability (h^2) estimates of 70–80% and provide limited evidence for shared family environmental contributions (Burt, 2009; Nikolas & Burt, 2010; Polderman et al., 2015). Meta-analyses also suggest that heritability is similar for inattentive and hyperactive/impulsive symptom dimensions, with 50–80% of genetic influences shared across

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dimensions (Nikolas & Burt, 2010). Although family studies have found ADHD risk to be somewhat higher in relatives of females with ADHD, compared to relatives of affected males (Faraone et al., 2000a; Martin, Taylor, & Lichtenstein, 2018b; Taylor et al., 2016), more than two decades of twin studies have provided limited support for differential heritability of ADHD by sex (Polderman et al., 2015).

It should be noted that the majority of twin studies rely on North American and European samples. In a meta-analysis spanning 50 years of twin research (2748 studies, 17 804 traits), less than 6% of studies were based on South American, African, or Asian samples (Polderman et al., 2015). Thus, many conclusions from twin research may not extend to other populations. For example, a recent study of ADHD traits in Chinese adolescent twins found smaller genetic and larger shared environmental influences compared to previously reported estimates in North American and European populations (Zheng, Pingault, Unger, & Rijsdijk, 2020), highlighting the necessity of collecting samples from diverse populations and suggesting that the contribution of environmental influences to ADHD may vary by societal and contextual factors.

Estimates from twin studies are also moderated by factors such as age and assessment method (Freitag, Rohde, Lempp, & Romanos, 2010). For example, in contrast to the stable and high heritability of ADHD found in meta-analyses of twin studies across childhood and early adolescence (Bergen, Gardner, & Kendler, 2007), considerably lower estimates (30–54%) have been reported in adults (Brikell, Kuja-Halkola, & Larsson, 2015; Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Ehringer, Rhee, Young, Corley, & Hewitt, 2006). Such differences appear to be partly driven by rater effects, with studies relying on self-ratings or different raters within a twin pair showing lower heritability (30–40%), compared to studies relying on a single rater (Kan et al., 2013, 2014; Merwood et al., 2013). When estimated from multiple informants or clinical diagnoses, the reported heritability of ADHD is high (70–80%), independent of age (Brikell et al., 2015). Measurement can also impact heritability estimates (Freitag et al., 2010). Most ADHD scales only assess the negative end of the ADHD symptom distribution, leading to potential contrast effects (i.e. exaggerated differences between twins) and skewed symptom distributions, which may artificially inflate heritability and hamper detection of shared environmental effects (Derks, Dolan, & Boomsma, 2004). Twin studies using scales that assess the full continuum of ADHD symptoms may be less affected by contrast effects, whereas the evidence for better capturing the shared environment is mixed (Ebejer et al., 2015; Hay, Bennett, Levy, Sergeant, & Swanson, 2007; Peng et al., 2016; Polderman et al., 2007).

Notwithstanding these methodological considerations, a large body of twin research has informed our conceptualization of ADHD in numerous ways. Several twin studies suggest that the development of ADHD is influenced by both stable genetic factors and the emergence of new genetic factors from childhood to adulthood (Chang, Lichtenstein, Asherson, & Larsson, 2013; Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005; Larsson, Lichtenstein, & Larsson, 2006; Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004). For example, a longitudinal assessment of 8395 8–16 year old twins showed that although both baseline symptoms and the change in hyperactive/impulsive symptoms over time were largely explained by genetic factors (90% and 81% h^2 respectively), only 40% of the genetic factors were shared between the two timepoints (Pingault et al., 2015). Twin studies also provided early evidence that ADHD is best viewed as the extreme end of a continuum of traits in the general population, by showing evidence for a strong genetic link between ADHD symptoms above a diagnostic threshold and subthreshold symptoms in the general population (Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997). Moreover, a recent study of nearly 28 000 twins estimated the genetic correlation (r_g) between clinically-diagnosed ADHD and parent-rated ADHD symptoms at 0.56 and reported that 89% of this association could be attributed to genetic factors (Taylor et al., 2019). Twin and family studies have also elucidated the etiology underlying several cognitive and neurobiological features associated with ADHD (for reviews on current understanding of the neurobiology of ADHD, see Faraone et al., 2021; Miranda, Cox, Alexander, Danev, & Lakey, 2020). ADHD or ADHD traits share genetic factors with various executive functions such as reaction time variability and response inhibition (Crosbie et al., 2013; Kuntsi et al., 2010, 2014; Michelini et al., 2021; Tye, McLoughlin, Kuntsi, & Asherson, 2011) as well as brain-based electroencephalographic (EEG) measures (McLoughlin, Palmer, Rijsdijk, & Makeig, 2014; Michelini et al., 2021; Tye et al., 2011, 2012, 2014). Also, there is some evidence that MZ twins discordant for ADHD show subtle differences in various brain metrics, including total caudate volume (Tistarelli, Fagnani, Troianiello, Stazi, & Adriani, 2020) and that unaffected siblings of ADHD cases show structural brain differences intermediate to those observed in cases and controls (Bralten et al., 2016; Greven et al., 2015). Together these studies support the brain-based, neurodevelopmental etiology of ADHD and that genetic factors which underpin clinically relevant ADHD are largely the same as those influencing variation in ADHD population traits.

Finally, twin and family studies strongly suggest that comorbidity in ADHD is partly explained by genetic factors shared with other disorders (see Table 1), as highlighted by recent reviews (Andersson et al., 2020; Tistarelli et al., 2020). Among childhood-onset disorders, most research has focused on ASD and ODD/CD, which both show considerable genetic overlap with ADHD (Andersson et al., 2020; Tistarelli et al., 2020). ODD/CD traits appear more strongly genetically correlated with hyperactivity/impulsivity (Hur, 2015; Wood, Rijsdijk, Asherson, & Kuntsi, 2009), whereas learning difficulties appear more closely genetically linked with inattentive symptoms (Greven, Harlaar, Dale, & Plomin, 2011, 2014; Liu, Li, Viding, Asherson, & Pingault, 2019; Wadsworth, DeFries, Willcutt, Pennington, & Olson, 2015). Twin studies on the associations of ADHD with anxiety and depression indicate moderate genetic correlations reported as early as preschool (Chen et al., 2016; Cole, Ball, Martin, Scourfield, & Mcguffin, 2009; Michelini, Eley, Gregory, & McAdams, 2015; Rydell, Taylor, & Larsson, 2017). Among later onset comorbidities, quantitative genetic research shows clear genetic links with substance misuse (Capusan, Bendtsen, Marteinsdottir, Kuja-Halkola, & Larsson, 2015; Derks, Vink, Willemsen, van den Brink, & Boomsma, 2014; Edwards & Kendler, 2012; Skoglund, Chen, Franck, Lichtenstein, & Larsson, 2015). Although there is less research for eating disorders, bipolar disorder, and schizophrenia, available evidence does support a genetic overlap with ADHD (Capusan et al., 2017; Larsson et al., 2013; Song et al., 2015; Yao et al., 2019). In a meta-analysis of 31 independent twin studies, genetic correlations between ADHD and externalizing (0.49 [0.37–0.61]), internalizing (0.50 [0.39–0.69]), and neurodevelopmental (0.56

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Table 1. Summary of the evidence for shared genetics risks between ADHD and common comorbid psychiatric and neurodevelopmental phenotypes

Phenotype	Twin and family genetic research[a]	Molecular genetic research[b]
Anxiety disorders	Twin r_g = 0.45 to 0.58[1]	LDSC r_g not significantly different from zero after multiple testing correction[14]
Autism spectrum disorder	Twin r_g = 0.59 (0.49–0.69)[c2]	LDSC r_g = 0.37 (0.05)[15]; overlap of rare CNVs and PTVs[16,17]
Bipolar disorder	Twin r_g = 0.33 (0.32–0.39)[3]	LDSC r_g = 0.14 (0.04)[15]
Depression, major depressive disorder	Twin r_g = 0.34 to 0.77[1]	LDSC r_g = 0.44 (0.03)[15]
Eating disorders (ED)	Twin r_g = 0.14 (0.0–0.22) with anorexia[4] Twin r_g = 0.28 (0.20–0.3) with bulimia[4] Twin r_g = 0.35 (0.25–0.46) with binge eating disorder[5]	LDSC r_g = −0.26 (0.06) with anorexia nervosa[15]; ADHD-PRS positively associated with ED symptoms in children in the general population[18]
Intellectual disability (ID)	91% of phenotypic correlation with ID due to shared genetic factors in quantitative genetic modeling of family data[6]	LDSC r_g = 0.73 (0.29)[19]; overlap of rare CNVs[17]
Language and learning difficulties	Twin r_g = 0.42 (0.35–0.49)[c] with reading difficulties[7] Twin r_g = −0.41 to −0.22 with maths ability[8]	ADHD-PRS associated with lower language grades, difficulties with reading and spelling, and dyslexia[20–23]
Motor difficulties, developmental coordination disorder (DCD), dyspraxia	Twin r_g = 0.99 (0.69–1.00) with DCD[9]	ADHD-PRS not associated with general neuromotor measures in infancy (except senses)[24]; studies of DCD are lacking
Obsessive compulsive disorder (OCD)	Twin r_g = 0.24[10] Sibling r_g = 0.63 (S.E. = 0.12)[11] Heritable latent factor underlying ADHD, OCD, and tics[10]	LDSC r_g not significantly different from zero after multiple testing correction[15]
Oppositional defiant disorder (ODD) and conduct disorder (CD), aggression	Twin r_g = 0.15 to 0.76 with ODD[2] Twin r_g = 0.17 to 0.70 with CD[2] Heritable latent factor underlying ADHD, ODD, and CD[12]	LDSC r_g = 0.74 (0.18) between ADHD and childhood aggression[25]
Schizophrenia	No twin studies: 1st degree relatives: OR = 1.17–2.22 2nd degree relatives: OR = 1.06–1.11[13]	LDSC r_g = 0.13 (0.03)[15]; overlap of rare CNVs[16,17]
Substance use disorders	Twin r_g = 0.33 to 0.44 with alcohol dependence[2]	LDSC r_g = 0.44 (0.10) with alcohol dependence[26]
Tic disorders, Tourette syndrome	Twin r_g = 1.00 (0.63–1.00)[9], 0.31[10] Sibling r_g = 0.26 (S.E. = 0.21)[11]	LDSC r_g = 0.27 (0.06)[15]

CNVs: copy number variants; LDSC: linkage disequilibrium score correlation; PRS: polygenic risk scores; r_g: twin or SNP-based genetic correlation; OR: odds ratio; S.E.: standard error; CIs: confidence intervals.

[a]A note about the evidence presented for twin/family genetic associations: results of genetic correlation are obtained from quantitative genetic modeling in twin- and/or extended family studies. Genetic correlations from published meta-analyses are presented preferentially, followed by ranges of estimates obtained from prior published reviews. Otherwise single study estimates are presented with 95% CIs/S.E., where available. When no twin studies are available, associations from large-scale family co-aggregation studies including multiple relative types are presented.

[b]A note about the evidence presented for common variant associations: results of the largest available genetic correlation analyses using LDSC are presented preferentially and where such analyses are not available, then available PRS results are summarized.

[c]Meta-analytic estimate (95% CI), estimated in the cited study.

References: [1](Martin et al., 2018a); [2](Andersson et al., 2020); [3](Song et al., 2015); [4](Yao et al., 2019); [5](Capusan et al., 2017); [6](Faraone, Ghirardi, Kuja-Halkola, Lichtenstein, & Larsson, 2017); [7](Daucourt, Erbeli, Little, Haughbrook, & Hart, 2020); [8]; (Greven, Kovas, Willcutt, Petrill, & Plomin, 2014); [9](Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010); [10](Pinto et al., 2016); [11](Mathews & Grados, 2011); [12](Tuvblad, Zheng, Raine, & Baker, 2009); [13](Larsson et al., 2013); [14]; (Purves et al., 2020); [15](Cross-Disorder Group of the PGC, 2019); [16](Williams et al., 2012); [17](Gudmundsson et al., 2019); [18](Yao et al., 2019); [19](Niemi et al., 2018); [20](Rajagopal et al., 2020); [21](Gialluisi et al., 2019); [22](Verhoef et al., 2019); [23](Gialluisi et al., 2020); [24](Serdarevic et al., 2020); [25](Demontis et al., 2021); [26](Walters et al., 2018).

[0.47–0.66]) traits were of similar magnitude and largely consistent across age, measurement scales, and raters (Andersson et al., 2020). Furthermore, emerging evidence from multivariate twin and family studies suggests that ADHD loads strongly onto a general genetic psychopathology factor. After accounting for this general factor, ADHD remains genetically associated with a specific neurodevelopmental factor, whereas genetic links to externalizing and internalizing psychopathology are considerably attenuated, supporting the neurodevelopmental etiology of ADHD (Du Rietz et al., 2020; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; Pettersson, Anckarsäter, Gillberg, & Lichtenstein, 2013, 2015). Although twin and family studies addressing non-psychiatric comorbidity in ADHD are sparse, genetic correlations with somatic and neurological conditions such as asthma, epilepsy, and obesity (twin r_g = 0.20–0.30) are weaker than those between ADHD and other psychiatric disorders (Brikell et al., 2018; Chen et al., 2019; Holmberg, Lundholm, Anckarsäter, Larsson, & Almqvist, 2015; Mogensen, Larsson, Lundholm, & Almqvist, 2011).

In summary, quantitative genetic studies have demonstrated that the heritability of ADHD is high and of similar magnitude across ADHD symptom dimensions, severity, sex, and development, and that genetic liability for ADHD is shared with neurodevelopmental, psychiatric, and somatic comorbidities.

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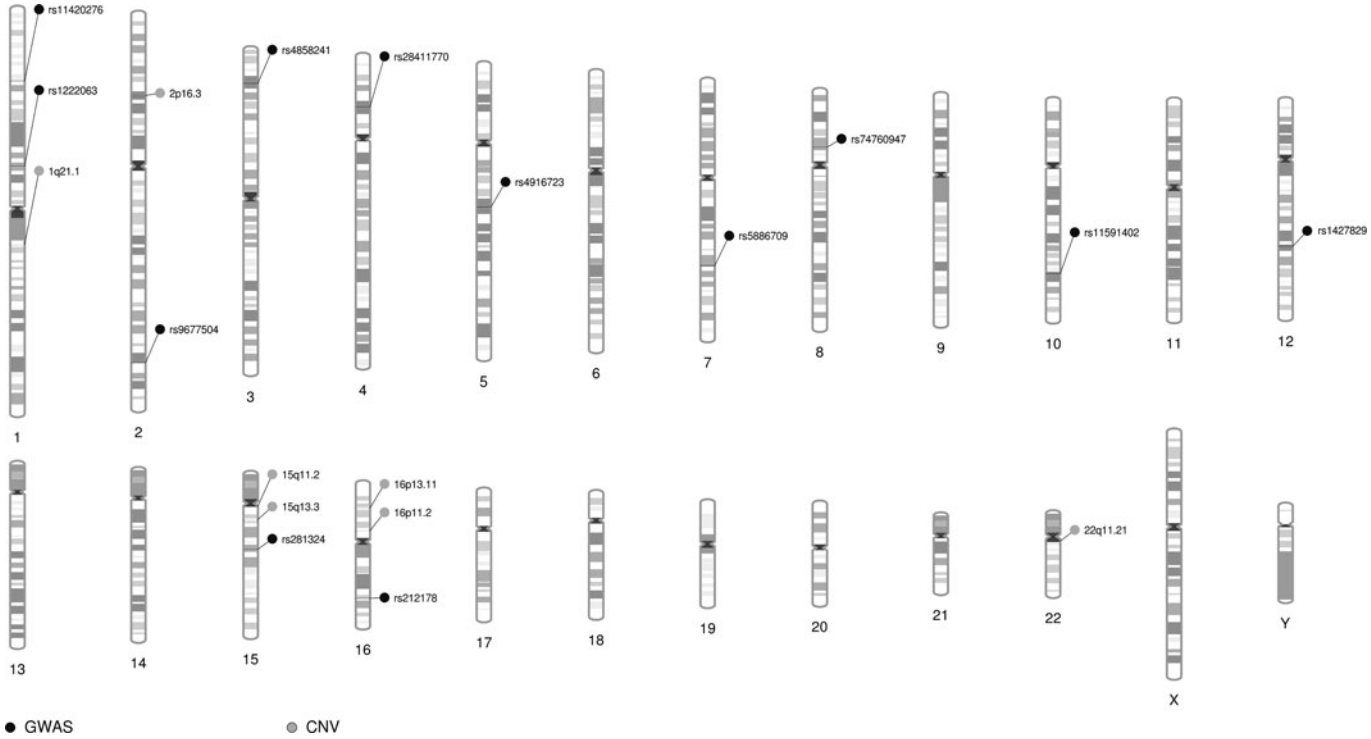


Fig. 1. Locations of genomic loci robustly-associated with risk of ADHD diagnosis. GWAS, genome-wide association study; top variants from the largest ADHD GWAS (index SNPs are shown) from Demontis et al. (2019). CNV, copy number variants implicated in ADHD, based on Gudmundsson et al. (2019). Visualization made using PhenoGram (Wolfe, Dudek, Ritchie, & Pendergrass, 2013).

Molecular genetic studies of ADHD

Advances in genotyping technology in the past two decades have greatly improved our understanding of the genetic architecture of ADHD (i.e. the number, allele frequencies, and locations of risk variants). Initial molecular genetic studies of ADHD focused on hypothesis-driven candidate gene and linkage approaches, with limited replication of results (Hawi et al., 2015), similarly to other psychiatric disorders (Sullivan, 2017). This literature and potential candidates that emerged (e.g. dopaminergic genes) has been extensively reviewed previously (e.g. Faraone & Larsson, 2018; Thapar, Langley, Owen, & O'Donovan, 2007) and this review focuses on more recent genome-wide studies. Initial ADHD GWAS (Neale et al., 2008, 2010; Stergiakouli et al., 2012) demonstrated important insights into the polygenic architecture of ADHD, but were under-powered to detect common risk variants at the established genome-wide significance level ($p < 5 \times 10^{-8}$). The first common genetic variants robustly associated with ADHD were recently identified through a large international collaborative effort led by the Psychiatric Genomics Consortium (PGC) and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) (Demontis et al., 2019). This GWAS of 20 183 individuals with ADHD and 35 191 controls implicated variants in 12 independent regions across the genome, many of which are located in/near genes involved in neurodevelopmental processes (e.g. *DUSP6* and *FOXP2*); see Fig. 1. There was little evidence to support a role for the most widely-studied candidate genes. These GWAS results showed partial replication (with significant sign concordance) using three different independent cohorts with self-reported ADHD or ADHD traits. Although the top loci each explained only a small proportion of phenotypic variance, the total estimated contribution from common risk alleles to variance in ADHD [i.e. the single-nucleotide polymorphism (SNP)-based heritability] was 21.6% (S.E. = 0.014), indicating that with growing GWAS sample sizes additional common risk variants will be identified. Efforts are ongoing to increase the sample size for the next international GWAS meta-analysis to confirm these findings and discover more loci. Characterization of the genomic signal revealed that ADHD risk variants impact regulatory elements specific to the central nervous system and located in evolutionarily-constrained genomic regions, i.e. genes that are particularly intolerant to loss-of-function mutations. Furthermore, ADHD genetic risk variants are shared with those implicated in lower total intracranial volume ($r_g = -0.23$, S.E. = 0.06) (Klein et al., 2019), further supporting its classification as a brain-based disorder. Although the latest GWAS represents a significant advance in our understanding of ADHD common variant genetics, one important limitation is that 96% of the individuals included are of European ancestry and data are lacking for individuals from other ancestries (Demontis et al., 2019). The genetic correlation between ADHD in individuals of Han Chinese and European ancestries was previously estimated as 0.39 (S.E. = 0.15) (Yang et al., 2013), suggesting that only a portion of common variants will extend to non-European ancestries.

Other recent GWAS, focusing on different definitions or groups of individuals with ADHD, demonstrate high genetic correlations between: (a) ADHD in childhood and persistent ADHD in adulthood ($r_g = 0.81$, S.E. = 0.11) (Rovira et al., 2020), (b) ADHD population traits and clinical diagnosis ($r_g = 0.97$, S.E. = 0.21) (Demontis et al., 2019), and (c) ADHD in males and females ($r_g = 1.22$, S.E. = 0.13) (Martin et al., 2018b). Notably,

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although very high, the genetic correlation between child and adult ADHD is not as high as across childhood ADHD cohorts (Rovira et al., 2020). Although the genetic correlation is also moderately high ($r_g = 0.65$, S.E. = 0.11) between clinically-diagnosed ADHD and self-reported ADHD in a population sample of adults taking part in personal genetic testing via 23andMe, there are also clearly phenotypic differences (e.g. in educational attainment) across these definitions of ADHD (Demontis et al., 2019).

Genetic correlations have also been seen with numerous additional phenotypes (see Table 1). Among psychiatric disorders, the strongest genetic correlations are with major depressive disorder and ASD, with more modest genetic correlations with other disorders (e.g. schizophrenia and bipolar disorder) (Cross-Disorder Group of the PGC, 2019). Genomic structural equation modeling shows that ADHD clusters with ASD, as well as Tourette syndrome and aggression (Cross-Disorder Group of the PGC, 2019; Waldman, Poore, Luningham, & Yang, 2020). ADHD is also strongly genetically correlated with lower age at birth of first child ($r_g = -0.61$, S.E. = 0.04), lower educational attainment ($r_g = -0.53$, S.E. = 0.03), smoking ($r_g = 0.48$, S.E. = 0.06), insomnia ($r_g = 0.42$, S.E. = 0.06), and higher body mass index ($r_g = 0.26$, S.E. = 0.03) (Demontis et al., 2019). Recent studies also suggest that the dopaminergic system may be a shared mechanism underlying ADHD and obesity, sleep problems, asthma, and migraine (Instanes et al., 2018; Mota et al., 2020).

Polygenic risk score (PRS) analyses have yielded significant insights into ADHD. Although PRS studies explain only a small proportion (~5.5%) of the phenotypic variance of ADHD case status (Demontis et al., 2019), they are a useful tool for hypothesis testing (e.g. testing for association between individual genetic risk burden and clinical features, comorbidity, and long-term outcomes, as well as mediation or gene-by-environment interaction). In general, PRS studies support twin and genome-wide correlation analyses, demonstrating shared genetic risks across ADHD diagnosis and population traits measured using different instruments, raters (parent- *v.* self-report), and at different ages (Burton et al., 2019; Groen-Blokhuis et al., 2014; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Riglin et al., 2020b; Ronald, de Bode, & Polderman, 2021), as well as many other psychiatric and brain-based traits, including autistic symptoms, cognitive difficulties, depression, anxiety, risk-taking, alcohol use, and smoking (Du Rietz et al., 2018; Martin et al., 2018a; Ronald et al., 2021). In the general population, ADHD-PRS captures a wide range of psychiatric outcomes, which can be partly summarized by a general factor of childhood psychopathology (Brikell et al., 2020; Riglin et al., 2020c).

Studies have also examined the impact of ADHD-PRS on outcomes in clinical ADHD samples. Collectively, they suggest that PRS do not just capture risk for ADHD diagnosis but may also be a marker of phenotypic severity in individuals with ADHD, showing association with a wide range of comorbid phenotypes, including CD (Demontis et al., 2021; Hamshere et al., 2013), irritability/emotional dysregulation (Nigg et al., 2020; Riglin et al., 2017), severity of clinical profile (Vuijk et al., 2020), executive function difficulties (working memory, inhibitory control, and response variability) (Chang, Yang, Wang, & Faraone, 2020; Nigg et al., 2018; Vainieri et al., 2021), and SUDs (i.e. alcohol and cannabis use disorders) (Wimberley et al., 2020). PRS studies also suggest that late-onset ADHD may differ in etiology from childhood-onset ADHD, but studies so far are inconclusive because of small sample sizes (Asherson & Agnew-Blais, 2019). The largest-to-date PRS study of sex differences found that males and females with ADHD do not differ significantly in terms of polygenic burden (Martin et al., 2018b).

In addition to the role of common (>1% minor allele frequency) genetic risk variants in ADHD described above, rare variants (<1% frequency) also contribute to ADHD. Studies of rare chromosomal alterations indicate that ADHD is frequently associated with known genetic syndromes (e.g. 22q11.2 deletion syndrome and Williams syndrome) (Scerif & Baker, 2015). ADHD is also associated more generally with large, rare deletions or duplications of DNA, known as copy number variants (CNVs) (Williams et al., 2010, 2012), particularly those that have previously been implicated in other NDDs (Gudmundsson et al., 2019); see Fig. 1. There is also preliminary evidence implicating *de novo* CNVs, i.e. variants not inherited from biological parents (Lionel et al., 2011; Martin et al., 2020). Evidence is currently mixed as to whether large, rare CNVs are associated with traits of ADHD in the general population (Guyatt et al., 2018; Martin et al., 2019). Results indicate that previously implicated neurodevelopmental CNVs are associated with diagnosed ADHD, whereas other large, rare CNV regions are implicated in more broadly-defined ADHD symptoms (Martin et al., 2019). Although the evidence collectively implicates these large structural variants in ADHD, further research is needed to uncover the specific genetic risks and biological mechanisms that are being disrupted. To this end, a recent paper integrated data from 11 published studies of CNVs in ADHD with existing biological databases and identified a credible list of 26 high confidence genes, enriched for expression in brain tissue and showing converging evidence from common variant analyses, which should be prioritized for further investigation (Harich et al., 2020).

A recent large exome sequencing study of 4378 individuals with ADHD implicated rare protein-truncating variants intolerant to mutation as being important for ADHD, but without identifying specific genes or mutations (Satterstrom et al., 2019). Interestingly, this group of very rare variants was indistinguishable from variants implicated in ASD. Thus, evidence from quantitative genetics, together with common and rare variant studies, demonstrates that genetic risks implicated in ADHD are also implicated in other neurodevelopmental and psychiatric phenotypes. Large whole-genome sequencing studies of ADHD are currently lacking, but as samples grow, sequencing will enable examination of the role of structural variants that are not captured by microarrays (Trost et al., 2020), such as variable number tandem repeats, which have shown promise in candidate gene work (e.g. the DRD4 7-repeat) (Faraone, Doyle, Mick, & Biederman, 2001; Li, Sham, Owen, & He, 2006; Nikolaidis & Gray, 2010).

Implications and future directions

There is a high degree of convergence from quantitative and molecular genetic approaches, yielding important insights into ADHD. Table 2 summarizes these robust findings based on large-scale studies, meta-analyses, and reviews. The successes of ADHD genome-wide approaches in the past few years have paved the way for further discovery and understanding of the genetic architecture of ADHD, while validating its categorization as a brain-based NDD.

Quantitative and molecular genetic research clearly demonstrates that ADHD diagnosis represents the extreme end of continuously distributed symptoms in the population. This poses a challenge for defining ADHD, with further research needed to determine how and when ADHD symptoms lead to impairment

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Table 2. Summary of robust converging findings from twin/family and molecular genetic ADHD research

Finding	Twin and family genetic evidence	Molecular genetic evidence
ADHD is highly heritable and polygenic	Twin-based h^2 = 70–80%[1,2,3]	Risk variants are distributed across the genome and across allelic frequency[17–19] Common variant SNP-based h^2 is 21.6% (S.E. = 0.014)[17] Rare variants (CNVs and protein-truncating variants) are implicated[18,19]
ADHD is a brain-based NDD	Strong twin/family r_g with other NDDs (e.g. ASD, ID, tics)[4] Twin r_g 0.30–0.80 with various EEG measures[5,6,7] Some evidence that ADHD discordant twins show differences in caudate, right striatum and thalamus volume, and frontoparietal network activation[8]	ADHD risk SNPs and high confidence CNVs are expressed in central nervous system tissue[17,20] Significant genetic correlation observed with intracranial volume (r_g = −0.23, S.E. = 0.06)[21]
Clinically diagnosed ADHD and population traits of ADHD share genetic risks	Strong genetic link between extreme and subthreshold variation in ADHD symptoms[9] Twin r_g = 0.56 (0.53–0.59) between ICD-based ADHD and ADHD symptoms in the population[10]	Very high genetic correlation (r_g = 0.97, S.E. = 0.21) between diagnosed ADHD and ADHD population traits[17] Rare CNVs are also associated with broadly-defined ADHD population traits[22]
ADHD and comorbid conditions share genetic risks (see Table 1 for details)	Twin and family studies show significant genetic correlations across ADHD and numerous comorbid conditions, and the cross-disorder co-variance is often primarily attributable to shared genetic factors[4,9]	Significant genetic correlations or associations with PRS and rare variants for numerous disorders[9,18]
Genetic factors are important for ADHD across development	h^2 of ADHD is high and stable across the lifespan when estimated from multple raters or clinical diagnosis[11] Age-to-age symptom stability is largely explained by genetic factors[12,13]	High genetic correlation between ADHD in childhood and persistent ADHD in adulthood (r_g = 0.81, S.E. = 0.11)[23]
ADHD genetic risks are shared between males and females	Most twin and family studies do not find evidence for sex-specific genetic effects[1,2,3]	Very high genetic correlation (r_g = 1.22, S.E. = 0.13) between male and female ADHD[24]
Many 'environmental' risk factors for ADHD share genetic risks with ADHD	E.g., the association between smoking during pregnancy and offspring ADHD is genetically confounded[14,15,16]	ADHD is genetically correlated with traits such as smoking (r_g = 0.48, S.E. = 0.06) and younger age at first birth of child (r_g = −0.61, S.E. = 0.04)[17]

Note: The studies highlighted in this table are based on large-scale data analyses, meta-analyses and other reviews, which collectively support this converging evidence from twin/family and molecular genetic studies. Although for some of these findings, individual studies may exist that do not support the finding, the majority of well-powered studies do converge to support the findings.

h^2, twin or single-nucleotide polymorphism (SNP)-based heritability; CNVs, copy number variants; PRS, polygenic risk scores; r_g, twin or SNP-based genetic correlation; ASD, autism spectrum disorder; EEG, electroencephalogram; ID, intellectual disability; NDDs, neurodevelopmental disorders.

References: [1](Faraone & Larsson, 2018); [2](Nikolas & Burt, 2010); [3](Polderman et al., 2015); [4](Andersson et al., 2020); [5](McLoughlin et al., 2014); [6](Tye et al., 2012); [7](Tye, Rijsdijk, & McLoughlin, 2014); [8](Tistarelli et al., 2020); [9](Martin et al., 2018a); [10](Taylor et al., 2019); [11](Brikell et al., 2015); [12](Bergen et al., 2007); [13](Chang et al., 2013); [14](Thapar et al., 2009); [15](Langley et al., 2012); [16](Skoglund et al., 2014); [17](Demontis et al., 2019); [18](Gudmundsson et al., 2019); [19](Satterstrom et al., 2019); [20](Harich et al., 2020); [21](Klein et al., 2019); [22](Martin et al., 2019); [23](Rovira et al., 2020); [24](Martin et al., 2018b).

and the need for clinical intervention. However, this finding also highlights an opportunity to leverage already existing studies of ADHD symptoms in large population samples to understand the genetics of ADHD, with ongoing research to this end [e.g. EAGLE consortium (Middeldorp et al., 2016), Spit for Science (Burton et al., 2019)].

There are many unresolved issues in ADHD genetics that will require larger sample sizes. For example, do shared genetic risks between ADHD and comorbid conditions (Table 1) (Anttila et al., 2017; Demontis et al., 2019) result from shared phenotypic factors (e.g. cognitive deficits) and/or is an additional trait contributing to both phenotypes? Which (if any) specific genetic risk factors are unique to ADHD? Analyses of secondary phenotypes such as dimensional behavioral and cognitive traits may help answer some of these questions. Other unresolved issues include determining why males are more likely than females to be diagnosed with ADHD during childhood/adolescence, understanding the influence of genetic risks on persistence and remittance patterns, and whether late-diagnosed ADHD is biologically the same condition as early-onset ADHD. Identifying causal risk factors for ADHD and establishing the mechanisms leading to negative outcomes has proven challenging and has primarily been done using twin and family data thus far. However, rapid advances in methods using measured genetic variants to evaluate causality (e.g. Mendelian randomization) (Davey Smith & Hemani, 2014) offer future research opportunities for ADHD. Mendelian randomization approaches have so far been used to study putative causal relationships between ADHD and phenotypes including SUD, depression, educational attainment, childhood obesity, and coronary artery disease, with results supporting a potentially causal effect of ADHD genetic risk on these outcomes, with limited evidence for the reverse relationship (Leppert et al., 2019; Riglin et al., 2020a; Treur et al., 2021). More research is also needed to clarify the role of environmental risk factors and gene-by-environment interactions in ADHD. This will be particularly important when genetic studies begin the much-needed inclusion of diverse ancestries in order to ensure equity of research outcomes and clinical benefit in ADHD, but also to improve prediction accuracy and understanding of biology (Peterson et al., 2019). Environmental variables will be particularly relevant in this context, given interplay of ethnocultural and environmental risk factors for mental health. Large-scale, well-powered gene-by-environment studies including genetically diverse samples will be an important step in identifying novel paths to prevention and treatment.

Emerging findings from studies of rare variants hold promise for future implementation of genetic testing for a subgroup of individuals with ADHD. Genetic testing is occasionally offered

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to families with children who have severe intellectual disability or ASD. Given that some of the same rare CNV loci and genetic mutations have been implicated in ADHD (Gudmundsson et al., 2019; Satterstrom et al., 2019), genetic testing could offer insights and helpful clinical information to families with children with ADHD, if appropriately combined with genetic counseling. However, the complexity of ADHD etiology warrants caution in the interpretation of genetic results. Also, given how common ADHD is, further research is needed to identify a subgroup of individuals who might benefit most from targeted genetic testing and counseling.

A major goal of genomic research is to understand the underlying biology of a disorder to develop new therapeutics and improve outcomes. Existing data point to possible biological mechanisms (Faraone et al., 2015) but large-scale GWAS and forthcoming whole-genome sequence data will undoubtedly aid in this endeavor. For example, the latest ADHD GWAS (Demontis et al., 2019) implicated *DUSP6*, a gene that may play a role in synaptic dopamine levels, which are targeted by stimulant medication; further investigation of this gene is therefore warranted. As more ADHD risk loci are discovered, methods will be required to parse out the functional variants in associated loci and functionally characterize their effects. Various types of quantitative trait loci (expression, protein, and methylation) as well as gene expression data will be essential to these efforts (Breen et al., 2016). Capitalizing on approaches that can mine possible therapeutic targets from genome-wide data has already proved promising for ADHD (Hegvik et al., 2019). In addition to identifying novel targets for therapeutics, understanding the role of genetic variation in treatment response to current medications is urgently needed (Jensen et al., 2007). Thus far, pharmacogenomic studies of treatment response in ADHD have had little success and progress has been hampered by limited sample sizes. Only two small ($n < 200$) GWAS of methylphenidate response have been published so far (Mick, Neale, Middleton, McGough, & Faraone, 2008; Pagerols et al., 2018). There is preliminary evidence that ADHD-PRS may be associated with response to stimulant treatment (Zhong et al., 2020), however this needs replication. Given that ADHD medication has been associated with positive effects across a range of outcomes (Chang et al., 2019), large-scale research efforts aimed at understanding the biological underpinnings of treatment efficacy and tolerance are urgently needed.

Conclusion

Following on from decades of quantitative and early molecular genetic (e.g. linkage) studies, recent advances in genotyping technology and bioinformatics methods have rapidly increased understanding of the genetic risk factors for ADHD in the past 5–10 years. In the near future, as larger and more diverse samples become available with the facilitation of large consortia such as the PGC and growing national biobanks linked to health records, an increasing number of loci associated with ADHD will undoubtedly be detected. Implementation of state-of-the-art bioinformatics will allow us to pinpoint causal variants and understand causal relationships between comorbid conditions and risk factors. These are necessary steps toward understanding the biology of ADHD and developing better interventions and treatments to improve the outcomes for individuals with ADHD and their families.

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References

Akmatov, M. K., Ermakova, T., & Bätzing, J. (2019). Psychiatric and nonpsychiatric comorbidities among children with ADHD: An exploratory analysis of nationwide claims data in Germany. *Journal of Attention Disorders*, *25* (6), 874–884. https://doi.org/10.1177/1087054719865779.

Andersson, A., Tuvblad, C., Chen, Q., Du Rietz, E., Cortese, S., Kuja-Halkola, R., … Larsson, H. (2020). Research review: The strength of the genetic overlap between ADHD and other psychiatric symptoms – a systematic review and meta-analysis. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *61*(11), 1173–1183. https://doi.org/10.1111/jcpp.13233.

Anttila, V., Bulik-Sullivan, B., Finucane, H., Walters, R., Bras, J., Duncan, L., … IGAP consortium, IHGC consortium, ILAE Consortium on Complex Epilepsies, … on behalf of the Brainstorm consortium. (2017). *Analysis of Shared Heritability in Common Disorders of the Brain* (p. 048991). https://doi.org/10.1101/048991.

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

Asherson, P., & Agnew-Blais, J. (2019). Annual research review: Does late-onset attention-deficit/hyperactivity disorder exist? *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *60*(4), 333–352.

Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: A meta-analysis. *Twin Research and Human Genetics*, *10*(3), 423–433.

Bertelsen, E. N., Larsen, J. T., Petersen, L., Christensen, J., & Dalsgaard, S. (2016). Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. *Pediatrics*, *138*(2), e20154654. https://doi.org/10.1542/peds.2015-4654.

Biederman, J., Faraone, S. V., Keenan, K., Benjamin, J., Krifcher, B., Moore, C., … Steingard, R. (1992). Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Archives of General Psychiatry*, *49*(9), 728–738.

Bralten, J., Greven, C. U., Franke, B., Mennes, M., Zwiers, M. P., Rommelse, N. N. J., … Buitelaar, J. K. (2016). Voxel-based morphometry analysis reveals frontal brain differences in participants with ADHD and their unaffected siblings. *Journal of Psychiatry & Neuroscience: JPN*, *41*(4), 272–279.

Breen, G., Li, Q., Roth, B. L., O'Donnell, P., Didriksen, M., Dolmetsch, R., … Edenberg, H. J. (2016). Translating genome-wide association findings into new therapeutics for psychiatry. *Nature Neuroscience*, *19*(11), 1392–1396.

Brikell, I., Ghirardi, L., D'Onofrio, B. M., Dunn, D. W., Almqvist, C., Dalsgaard, S., … Larsson, H. (2018). Familial liability to epilepsy and attention-deficit/hyperactivity disorder: A nationwide cohort study. *Biological Psychiatry*, *83*(2), 173–180.

Brikell, I., Kuja-Halkola, R., & Larsson, H. (2015). Heritability of attention-deficit hyperactivity disorder in adults. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *168*(6), 406–413.

Brikell, I., Larsson, H., Lu, Y., Pettersson, E., Chen, Q., Kuja-Halkola, R., … Martin, J. (2020). The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. *Molecular Psychiatry*, *25*(8), 1809–1821. https://doi.org/10.1038/s41380-018-0109-2.

https://doi.org/10.1017/S0033291721000982 Published online by Cambridge University Press

Burt, S. A. (2009). Rethinking environmental contributions to child and adolescent psychopathology: A meta-analysis of shared environmental influences. *Psychological Bulletin*, *135*(4), 608–637.

Burton, C. L., Wright, L., Shan, J., Xiao, B., Dupuis, A., Goodale, T., … Crosbie, J. (2019). SWAN Scale for ADHD trait-based genetic research: A validity and polygenic risk study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *60*(9), 988–997.

Capusan, A. J., Bendtsen, P., Marteinsdottir, I., Kuja-Halkola, R., & Larsson, H. (2015). Genetic and environmental contributions to the association between attention deficit hyperactivity disorder and alcohol dependence in adulthood: A large population-based twin study. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *168*(6), 414–422.

Capusan, A. J., Yao, S., Kuja-Halkola, R., Bulik, C. M., Thornton, L. M., Bendtsen, P., … Larsson, H. (2017). Genetic and environmental aspects in the association between attention-deficit hyperactivity disorder symptoms and binge-eating behavior in adults: A twin study. *Psychological Medicine*, *47*(16), 2866–2878.

Caye, A., Swanson, J., Thapar, A., Sibley, M., Arseneault, L., Hechtman, L., … Rohde, L. A. (2016). Life span studies of ADHD-conceptual challenges and predictors of persistence and outcome. *Current Psychiatry Reports*, *18*(12), 111.

Chang, Z., Ghirardi, L., Quinn, P. D., Asherson, P., D'Onofrio, B. M., & Larsson, H. (2019). Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: A qualitative review of pharmacoepidemiology studies using linked prescription databases. *Biological Psychiatry*, *86*(5), 335–343.

Chang, Z., Lichtenstein, P., Asherson, P. J., & Larsson, H. (2013). Developmental twin study of attention problems: High heritabilities throughout development. *JAMA Psychiatry*, *70*(3), 311–318.

Chang, S., Yang, L., Wang, Y., & Faraone, S. V. (2020). Shared polygenic risk for ADHD, executive dysfunction and other psychiatric disorders. *Translational Psychiatry*, *10*(1), 182.

Chen, Q., Brikell, I., Lichtenstein, P., Serlachius, E., Kuja-Halkola, R., Sandin, S., & Larsson, H. (2017). Familial aggregation of attention-deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *58*(3), 231–239.

Chen, Q., Hartman, C. A., Haavik, J., Harro, J., Klungsøyr, K., Hegvik, T.-A., … Larsson, H. (2018). Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. *PLoS One*, *13*(9), e0204516.

Chen, Q., Hartman, C. A., Kuja-Halkola, R., Faraone, S. V., Almqvist, C., & Larsson, H. (2019). Attention-deficit/hyperactivity disorder and clinically diagnosed obesity in adolescence and young adulthood: A register-based study in Sweden. *Psychological Medicine*, *49*(11), 1841–1849.

Chen, T.-J., Ji, C.-Y., Wang, S.-S., Lichtenstein, P., Larsson, H., & Chang, Z. (2016). Genetic and environmental influences on the relationship between ADHD symptoms and internalizing problems: A Chinese twin study. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *171*(7), 931–937.

Cole, J., Ball, H. A., Martin, N. C., Scourfield, J., & Mcguffin, P. (2009). Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(11), 1094–1101.

Cortese, S., Sun, S., Zhang, J., Sharma, E., Chang, Z., Kuja-Halkola, R., … Faraone, S. V. (2018). Association between attention deficit hyperactivity disorder and asthma: A systematic review and meta-analysis and a Swedish population-based study. *The Lancet. Psychiatry*, *5*(9), 717–726.

Crosbie, J., Arnold, P., Paterson, A., Swanson, J., Dupuis, A., Li, X., … Schachar, R. J. (2013). Response inhibition and ADHD traits: Correlates and heritability in a community sample. *Journal of Abnormal Child Psychology*, *41*(3), 497–507.

Cross-Disorder Group of the PGC (2019). Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell*, *179*(7), 1469–1482.e11.

Dalsgaard, S., Østergaard, S. D., Leckman, J. F., Mortensen, P. B., & Pedersen, M. G. (2015). Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: A nationwide cohort study. *The Lancet*, *385* (9983), 2190–2196.

Daucourt, M. C., Erbeli, F., Little, C. W., Haughbrook, R., & Hart, S. A. (2020). A meta-analytical review of the genetic and environmental correlations between reading and attention-deficit hyperactivity disorder symptoms and reading and math. *Scientific Studies of Reading*, *24*(1), 23–56.

Davey Smith, G., & Hemani, G. (2014). Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. *Human Molecular Genetics*, *23*(R1), R89–R98.

Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Als, T. D., Agerbo, E., … Neale, B. M. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*, *51* (1), 63–75.

Demontis, D., Walters, R. K., Rajagopal, V. M., Waldman, I. D., Grove, J., Als, T. D., … Børglum, A. D. (2021). Risk variants and polygenic architecture of disruptive behavior disorders in the context of attention-deficit/hyperactivity disorder. *Nature Communications*, *12*(1), 576.

Derks, E. M., Dolan, C. V., & Boomsma, D. I. (2004). Effects of censoring on parameter estimates and power in genetic modeling. *Twin Research*, *7*(6), 659–669.

Derks, E. M., Vink, J. M., Willemsen, G., van den Brink, W., & Boomsma, D. I. (2014). Genetic and environmental influences on the relationship between adult ADHD symptoms and self-reported problem drinking in 6024 Dutch twins. *Psychological Medicine*, *44*(12), 2673–2683.

Dick, D. M., Viken, R. J., Kaprio, J., Pulkkinen, L., & Rose, R. J. (2005). Understanding the covariation among childhood externalizing symptoms: Genetic and environmental influences on conduct disorder, attention deficit hyperactivity disorder, and oppositional defiant disorder symptoms. *Journal of Abnormal Child Psychology*, *33*(2), 219–229.

Du Rietz, E., Coleman, J., Glanville, K., Choi, S. W., O'Reilly, P. F., & Kuntsi, J. (2018). Association of polygenic risk for attention-deficit/hyperactivity disorder with co-occurring traits and disorders. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, *3*(7), 635–643.

Du Rietz, E., Pettersson, E., Brikell, I., Ghirardi, L., Chen, Q., Hartman, C., … Kuja-Halkola, R. (2020). ADHD is more closely linked to neurodevelopmental than externalizing and internalizing disorders: A genetically informed multivariate Swedish population study. *medRxiv*, 2020.02.26. 20028175.

Ebejer, J. L., Medland, S. E., van der Werf, J., Wright, M. J., Henders, A. K., Gillespie, N. A., … Duffy, D. L. (2015). Contrast effects and sex influence maternal and self-report dimensional measures of attention-deficit hyperactivity disorder. *Behavior Genetics*, *45*(1), 35–50.

Edwards, A. C., & Kendler, K. S. (2012). Twin study of the relationship between adolescent attention-deficit/hyperactivity disorder and adult alcohol dependence. *Journal of Studies on Alcohol and Drugs*, *73*(2), 185–194.

Ehringer, M. A., Rhee, S. H., Young, S., Corley, R., & Hewitt, J. K. (2006). Genetic and environmental contributions to common psychopathologies of childhood and adolescence: A study of twins and their siblings. *Journal of Abnormal Child Psychology*, *34*(1), 1–17.

Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., … Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews. Disease Primers*, *1*, 15020.

Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., … Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neuroscience and Biobehavioral Reviews*. Advance online publication https://doi.org/10.1016/j.neubiorev.2021.01.022.

Faraone, S. V., Biederman, J., & Mick, E. (2006a). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159–165.

Faraone, S. V., Biederman, J., Mick, E., Williamson, S., Wilens, T., Spencer, T., … Zallen, B. (2000a). Family study of girls with attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, *157*(7), 1077–1083.

Faraone, S. V., Biederman, J., & Monuteaux, M. C. (2000b). Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genetic Epidemiology*, *18*(1), 1–16.

Faraone, S. V., Biederman, J., Spencer, T. J., & Aleardi, M. (2006b). Comparing the efficacy of medications for ADHD using meta-analysis. *MedGenMed: Medscape General Medicine*, *8*(4), 4.

https://doi.org/10.1017/S0033291721000982 Published online by Cambridge University Press

Faraone, S. V., & Buitelaar, J. (2010). Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European Child & Adolescent Psychiatry*, *19*(4), 353–364.

Faraone, S. V., Doyle, A. E., Mick, E., & Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, *158*(7), 1052–1057.

Faraone, S. V., Ghirardi, L., Kuja-Halkola, R., Lichtenstein, P., & Larsson, H. (2017). The familial co-aggregation of attention-deficit/hyperactivity disorder and intellectual disability: A register-based family study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(2), 167–174.e1.

Faraone, S. V., & Larsson, H. (2018). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562–575.

Franke, B., Michelini, G., Asherson, P., Banaschewski, T., Bilbow, A., Buitelaar, J. K., … Reif, A. (2018). Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *28*(10), 1059–1088.

Freitag, C. M., Rohde, L. A., Lempp, T., & Romanos, M. (2010). Phenotypic and measurement influences on heritability estimates in childhood ADHD. *European Child & Adolescent Psychiatry*, *19*(3), 311–323.

Giacobini, M., Medin, E., Ahnemark, E., Russo, L. J., & Carlqvist, P. (2018). Prevalence, patient characteristics, and pharmacological treatment of children, adolescents, and adults diagnosed with ADHD in Sweden. *Journal of Attention Disorders*, *22*(1), 3–13.

Gialluisi, A., Andlauer, T. F. M., Mirza-Schreiber, N., Moll, K., Becker, J., Hoffmann, P., … Schulte-Körne, G. (2019). Genome-wide association scan identifies new variants associated with a cognitive predictor of dyslexia. *Translational Psychiatry*, *9*(1), 1–15.

Gialluisi, A., Andlauer, T. F. M., Mirza-Schreiber, N., Moll, K., Becker, J., Hoffmann, P., … Schulte-Körne, G. (2020). Genome-wide association study reveals new insights into the heritability and genetic correlates of developmental dyslexia. *Molecular Psychiatry*. Advance online publication. https://doi.org/10.1038/s41380-020-00898-x

Ginsberg, Y., Quintero, J., Anand, E., Casillas, M., & Upadhyaya, H. P. (2014). Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: A review of the literature. *The Primary Care Companion to CNS Disorders*, *16*(3), PCC.13r01600. https://doi.org/10.4088/PCC.13r01600.

Golmirzaei, J., Mahboobi, H., Yazdanparast, M., Mushtaq, G., Kamal, M. A., & Hamzei, E. (2016). Psychopharmacology of attention-deficit hyperactivity disorder: Effects and side effects. *Current Pharmaceutical Design*, *22*(5), 590–594.

Greven, C. U., Bralten, J., Mennes, M., O'Dwyer, L., van Hulzen, K. J. E., Rommelse, N., … Buitelaar, J. K. (2015). Developmentally stable whole-brain volume reductions and developmentally sensitive caudate and putamen volume alterations in those with attention-deficit/hyperactivity disorder and their unaffected siblings. *JAMA Psychiatry*, *72*(5), 490–499.

Greven, C. U., Harlaar, N., Dale, P. S., & Plomin, R. (2011). Genetic overlap between ADHD symptoms and reading is largely driven by inattentiveness rather than hyperactivity-impulsivity. *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie Canadienne de Psychiatrie de L'enfant et de L'adolescent*, *20*(1), 6–14.

Greven, C. U., Kovas, Y., Willcutt, E. G., Petrill, S. A., & Plomin, R. (2014). Evidence for shared genetic risk between ADHD symptoms and reduced mathematics ability: A twin study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *55*(1), 39–48.

Groen-Blokhuis, M. M., Middeldorp, C. M., Kan, K.-J., Abdellaoui, A., van Beijsterveldt, C. E. M., Ehli, E. A., … Boomsma, D. I. (2014). Attention-deficit/hyperactivity disorder polygenic risk scores predict attention problems in a population-based sample of children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(10), 1123–1129.e6.

Gudmundsson, O. O., Walters, G. B., Ingason, A., Johansson, S., Zayats, T., Athanasiu, L., … Stefansson, K. (2019). Attention-deficit hyperactivity disorder shares copy number variant risk with schizophrenia and autism spectrum disorder. *Translational Psychiatry*, *9*(1), 258.

Guyatt, A. L., Stergiakouli, E., Martin, J., Walters, J., O'Donovan, M., Owen, M., … Gaunt, T. R. (2018). Association of copy number variation across the genome with neuropsychiatric traits in the general population. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *177*(5), 489–502.

Hamshere, M. L., Langley, K., Martin, J., Agha, S. S., Stergiakouli, E., Anney, R. J. L., … Thapar, A. (2013). High loading of polygenic risk for ADHD in children with comorbid aggression. *The American Journal of Psychiatry*, *170*(8), 909–916.

Harich, B., van der Voet, M., Klein, M., Čížek, P., Fenckova, M., Schenck, A., … Franke, B. (2020). From rare copy number variants to biological processes in ADHD. *The American Journal of Psychiatry*, *177*(9), 855–866. https://doi.org/10.1176/appi.ajp.2020.19090923.

Hawi, Z., Cummins, T. D. R., Tong, J., Johnson, B., Lau, R., Samarrai, W., & Bellgrove, M. A. (2015). The molecular genetic architecture of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *20*(3), 289–297.

Hay, D. A., Bennett, K. S., Levy, F., Sergeant, J., & Swanson, J. (2007). A twin study of attention-deficit/hyperactivity disorder dimensions rated by the strengths and weaknesses of ADHD-symptoms and normal-behavior (SWAN) scale. *Biological Psychiatry*, *61*(5), 700–705.

Hegvik, T.-A., Instanes, J. T., Haavik, J., Klungsøyr, K., & Engeland, A. (2018). Associations between attention-deficit/hyperactivity disorder and autoimmune diseases are modified by sex: A population-based cross-sectional study. *European Child & Adolescent Psychiatry*, *27*(5), 663–675.

Hegvik, T.-A., Waløen, K., Pandey, S. K., Faraone, S. V., Haavik, J., & Zayats, T. (2019). Druggable genome in attention deficit/hyperactivity disorder and its co-morbid conditions. New avenues for treatment. *Molecular Psychiatry*. Advance online publication. https://doi.org/10.1038/s41380-019-0540-z

Holmberg, K., Lundholm, C., Anckarsäter, H., Larsson, H., & Almqvist, C. (2015). Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: A combined twin- and register-based study: Epidemiology of allergic disease. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, *45*(5), 964–973.

Hultman, C. M., Torrång, A., Tuvblad, C., Cnattingius, S., Larsson, J.-O., & Lichtenstein, P. (2007). Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: A prospective Swedish twin study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(3), 370–377.

Hur, Y.-M. (2015). Genetic and environmental etiology of the relationship between childhood hyperactivity/inattention and conduct problems in a south Korean twin sample. *Twin Research and Human Genetics*, *18*(3), 290–297.

Instanes, J. T., Klungsøyr, K., Halmøy, A., Fasmer, O. B., & Haavik, J. (2018). Adult ADHD and comorbid somatic disease: A systematic literature review. *Journal of Attention Disorders*, *22*(3), 203–228.

Jensen, P. S., Arnold, L. E., Swanson, J. M., Vitiello, B., Abikoff, H. B., Greenhill, L. L., … Hur, K. (2007). 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(8), 989–1002.

Kan, K.-J., Dolan, C. V., Nivard, M. G., Middeldorp, C. M., van Beijsterveldt, C. E. M., Willemsen, G., & Boomsma, D. I. (2013). Genetic and environmental stability in attention problems across the lifespan: Evidence from the Netherlands twin register. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(1), 12–25.

Kan, K.-J., van Beijsterveldt, C. E. M., Bartels, M., & Boomsma, D. I. (2014). Assessing genetic influences on behavior: Informant and context dependency as illustrated by the analysis of attention problems. *Behavior Genetics*, *44*(4), 326–336.

Klein, M., Walters, R. K., Demontis, D., Stein, J. L., Hibar, D. P., Adams, H. H., … Franke, B. (2019). Genetic markers of ADHD-related variations in intracranial volume. *The American Journal of Psychiatry*, *176*(3), 228–238.

Kuntsi, J., Pinto, R., Price, T. S., van der Meere, J. J., Frazier-Wood, A. C., & Asherson, P. (2014). The separation of ADHD inattention and hyperactivity-impulsivity symptoms: Pathways from genetic effects to cognitive impairments and symptoms. *Journal of Abnormal Child Psychology*, *42*(1), 127–136.

Kuntsi, J., Rijsdijk, F., Ronald, A., Asherson, P., & Plomin, R. (2005). Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. *Biological Psychiatry*, *57*(6), 647–654.

https://doi.org/10.1017/S0033291721000982 Published online by Cambridge University Press

Kuntsi, J., Wood, A. C., Rijsdijk, F., Johnson, K. A., Andreou, P., Albrecht, B., … Asherson, P. (2010). Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Archives of General Psychiatry*, *67*(11), 1159–1167.

Lahey, B. B., Van Hulle, C. A., Singh, A. L., Waldman, I. D., & Rathouz, P. J. (2011). Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Archives of General Psychiatry*, *68*(2), 181–189.

Lange, K. W., Reichl, S., Lange, K. M., Tucha, L., & Tucha, O. (2010). The history of attention deficit hyperactivity disorder. *Attention Deficit and Hyperactivity Disorders*, *2*(4), 241–255.

Langley, K., Heron, J., Smith, G. D., & Thapar, A. (2012). Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: Testing for intrauterine effects. *American Journal of Epidemiology*, *176*(3), 261–268.

Larsson, H., Anckarsater, H., Råstam, M., Chang, Z., & Lichtenstein, P. (2012). Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: A quantitative genetic study of 8500 twin pairs. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *53*(1), 73–80.

Larsson, H., Lichtenstein, P., & Larsson, J.-O. (2006). Genetic contributions to the development of ADHD subtypes from childhood to adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*(8), 973–981.

Larsson, H., Rydén, E., Boman, M., Långström, N., Lichtenstein, P., & Landén, M. (2013). Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. *The British Journal of Psychiatry: The Journal of Mental Science*, *203*(2), 103–106.

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, and Allied Disciplines*, *55*(5), 428–435.

Leppert, B., Riglin, L., Dardani, C., Thapar, A., Staley, J. R., Tilling, K., … Stergiakouli, E. (2019). ADHD genetic liability and physical health outcomes – A two-sample Mendelian randomization study. *bioRxiv*. https://doi.org/10.1101/630467.

Levy, F., Hay, D. A., McStephen, M., Wood, C., & Waldman, I. (1997). Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(6), 737–744.

Li, D., Sham, P. C., Owen, M. J., & He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics*, *15*(14), 2276–2284.

Lichtenstein, P., Carlström, E., Råstam, M., Gillberg, C., & Anckarsäter, H. (2010). The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *The American Journal of Psychiatry*, *167*(11), 1357–1363.

Lionel, A. C., Crosbie, J., Barbosa, N., Goodale, T., Thiruvahindrapuram, B., Rickaby, J., … Scherer, S. W. (2011). Rare copy number variation discovery and cross-disorder comparisons identify risk genes for ADHD. *Science Translational Medicine*, *3*(95), 95ra75.

Liu, C.-Y., Li, Y., Viding, E., Asherson, P., & Pingault, J.-B. (2019). The developmental course of inattention symptoms predicts academic achievement due to shared genetic aetiology: A longitudinal twin study. *European Child & Adolescent Psychiatry*, *28*(3), 367–375.

Martin, J., Hamshere, M. L., Stergiakouli, E., O'Donovan, M. C., & Thapar, A. (2014). Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population. *Biological Psychiatry*, *76*(8), 664–671.

Martin, J., Hosking, G., Wadon, M., Agha, S. S., Langley, K., Rees, E., … Thapar, A. (2020). A brief report: De novo copy number variants in children with attention deficit hyperactivity disorder. *Translational Psychiatry*, *10*(1), 135.

Martin, J., Tammimies, K., Karlsson, R., Lu, Y., Larsson, H., Lichtenstein, P., & Magnusson, P. K. E. (2019). Copy number variation and neuropsychiatric problems in females and males in the general population. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *180*(6), 341–350.

Martin, J., Taylor, M. J., & Lichtenstein, P. (2018a). Assessing the evidence for shared genetic risks across psychiatric disorders and traits. *Psychological Medicine*, *48*(11), 1759–1774.

Martin, J., Walters, R. K., Demontis, D., Mattheisen, M., Lee, S. H., Robinson, E., … Neale, B. M. (2018b). A genetic investigation of sex bias in the prevalence of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *83*(12), 1044–1053.

Martinez-Badía, J., & Martinez-Raga, J. (2015). Who says this is a modern disorder? The early history of attention deficit hyperactivity disorder. *World Journal of Psychiatry*, *5*(4), 379–386.

Mathews, C. A., & Grados, M. A. (2011). Familiality of Tourette syndrome, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder: Heritability analysis in a large sib-pair sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, *50*(1), 46–54.

McLoughlin, G., Palmer, J. A., Rijsdijk, F., & Makeig, S. (2014). Genetic overlap between evoked frontocentral theta-band phase variability, reaction time variability, and attention-deficit/hyperactivity disorder symptoms in a twin study. *Biological Psychiatry*, *75*(3), 238–247.

Merwood, A., Greven, C. U., Price, T. S., Rijsdijk, F., Kuntsi, J., McLoughlin, G., … Asherson, P. J. (2013). Different heritabilities but shared etiological influences for parent, teacher and self-ratings of ADHD symptoms: An adolescent twin study. *Psychological Medicine*, *43*(9), 1973–1984.

Michelini, G., Cheung, C. H. M., Kitsune, V., Brandeis, D., Banaschewski, T., McLoughlin, G., … Kuntsi, J. (2021). The etiological structure of cognitive-neurophysiological impairments in ADHD in adolescence and young adulthood. *Journal of Attention Disorders*, *25*(1), 91–104.

Michelini, G., Eley, T. C., Gregory, A. M., & McAdams, T. A. (2015). Aetiological overlap between anxiety and attention deficit hyperactivity symptom dimensions in adolescence. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *56*(4), 423–431.

Michielsen, M., Semeijn, E., Comijs, H. C., van de Ven, P., Beekman, A. T. F., Deeg, D. J. H., & Kooij, J. J. S. (2012). Prevalence of attention-deficit hyperactivity disorder in older adults in The Netherlands. *The British Journal of Psychiatry: The Journal of Mental Science*, *201*(4), 298–305.

Mick, E., Neale, B., Middleton, F. A., McGough, J. J., & Faraone, S. V. (2008). Genome-wide association study of response to methylphenidate in 187 children with attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *147B*(8), 1412–1418.

Middeldorp, C. M., Hammerschlag, A. R., Ouwens, K. G., Groen-Blokhuis, M. M., Pourcain, B. S., Greven, C. U., … Boomsma, D. I. (2016). A genome-wide association meta-analysis of attention-deficit/hyperactivity disorder symptoms in population-based pediatric cohorts. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(10), 896–905.e6.

Miranda, P., Cox, C. D., Alexander, M., Danev, S., & Lakey, J. R. T. (2020). In quest of pathognomonic/endophenotypic markers of attention deficit hyperactivity disorder (ADHD): Potential of EEG-based frequency analysis and ERPs to better detect, prevent and manage ADHD. *Medical Devices*, *13*, 115–137.

Mogensen, N., Larsson, H., Lundholm, C., & Almqvist, C. (2011). Association between childhood asthma and ADHD symptoms in adolescence – a prospective population-based twin study. *Allergy*, *66*(9), 1224–1230.

Moriyama, T. S., Polanczyk, G. V., Terzi, F. S., Faria, K. M., & Rohde, L. A. (2013). Psychopharmacology and psychotherapy for the treatment of adults with ADHD – a systematic review of available meta-analyses. *CNS Spectrums*, *18*(6), 296–306.

Mota, N. R., Poelmans, G., Klein, M., Torrico, B., Fernàndez-Castillo, N., Cormand, B., … Arias Vásquez, A. (2020). Cross-disorder genetic analyses implicate dopaminergic signaling as a biological link between attention-deficit/hyperactivity disorder and obesity measures. *Neuropsychopharmacology*, *45*(7), 1188–1195.

MTA Cooperative Group. (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *56*, 1073–1086. https://doi.org/10.1001/archpsyc.56.12.1073.

Neale, B. M., Lasky-Su, J., Anney, R., Franke, B., Zhou, K., Maller, J. B., … Faraone, S. V. (2008). Genome-wide association scan of attention deficit hyperactivity disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *147B*(8), 1337–1344.

https://doi.org/10.1017/S0033291721000982 Published online by Cambridge University Press

Neale, B. M., Medland, S. E., Ripke, S., Asherson, P., Franke, B., Lesch, K.-P., … Psychiatric GWAS Consortium: ADHD Subgroup. (2010). Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(9), 884–897.

Nielsen, P. R., Benros, M. E., & Dalsgaard, S. (2017). Associations between autoimmune diseases and attention-deficit/hyperactivity disorder: A nationwide study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(3), 234–240.e1.

Niemi, M. E. K., Martin, H. C., Rice, D. L., Gallone, G., Gordon, S., Kelemen, M., … Barrett, J. C. (2018). Common genetic variants contribute to risk of rare severe neurodevelopmental disorders. *Nature*, *562*(7726), 268–271.

Nigg, J. T., Gustafsson, H. C., Karalunas, S. L., Ryabinin, P., McWeeney, S. K., Faraone, S. V., … Wilmot, B. (2018). Working memory and vigilance as multivariate endophenotypes related to common genetic risk for attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *57*(3), 175–182.

Nigg, J. T., Karalunas, S. L., Gustafsson, H. C., Bhatt, P., Ryabinin, P., Mooney, M. A., … Wilmot, B. (2020). Evaluating chronic emotional dysregulation and irritability in relation to ADHD and depression genetic risk in children with ADHD. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *61*(2), 205–214.

Nikolaidis, A., & Gray, J. R. (2010). ADHD and the DRD4 exon III 7-repeat polymorphism: An international meta-analysis. *Social Cognitive and Affective Neuroscience*, *5*(2-3), 188–193.

Nikolas, M. A., & Burt, S. A. (2010). Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: A meta-analysis. *Journal of Abnormal Psychology*, *119*(1), 1–17.

Pagerols, M., Richarte, V., Sánchez-Mora, C., Rovira, P., Soler Artigas, M., Garcia-Martínez, I., … Ribasés, M. (2018). Integrative genomic analysis of methylphenidate response in attention-deficit/hyperactivity disorder. *Scientific Reports*, *8*(1), 1881.

Peng, C.-Z., Grant, J. D., Heath, A. C., Reiersen, A. M., Mulligan, R. C., & Anokhin, A. P. (2016). Familial influences on the full range of variability in attention and activity levels during adolescence: A longitudinal twin study. *Development and Psychopathology*, *28*(2), 517–526.

Peterson, R. E., Kuchenbaecker, K., Walters, R. K., Chen, C. Y., Popejoy, A. B., Periyasamy, S., … Duncan, L. E. (2019). Genome-wide association studies in ancestrally diverse populations: Opportunities, methods, pitfalls, and recommendations. *Cell*, *179*(3), 589–603.

Pettersson, E., Anckarsäter, H., Gillberg, C., & Lichtenstein, P. (2013). Different neurodevelopmental symptoms have a common genetic etiology. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *54*(12), 1356–1365.

Pettersson, E., Larsson, H., & Lichtenstein, P. (2015). Common psychiatric disorders share the same genetic origin: A multivariate sibling study of the Swedish population. *Molecular Psychiatry*, *21*(5), 717–721.

Pingault, J.-B., Viding, E., Galéra, C., Greven, C. U., Zheng, Y., Plomin, R., & Rijsdijk, F. (2015). Genetic and environmental influences on the developmental course of attention-deficit/hyperactivity disorder symptoms from childhood to adolescence. *JAMA Psychiatry*, *72*(7), 651–658.

Pinto, R., Monzani, B., Leckman, J. F., Rück, C., Serlachius, E., Lichtenstein, P., & Mataix-Cols, D. (2016). Understanding the covariation of tics, attention-deficit/hyperactivity, and obsessive-compulsive symptoms: A population-based adult twin study. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *171*(7), 938–947.

Polanczyk, G. V., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *The American Journal of Psychiatry*, *164*(6), 942–948.

Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *International Journal of Epidemiology*, *43*(2), 434–442.

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., 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.

Polderman, T. J. C., Derks, E. M., Hudziak, J. J., Verhulst, F. C., Posthuma, D., & Boomsma, D. I. (2007). Across the continuum of attention skills: A twin study of the SWAN ADHD rating scale. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *48*(11), 1080–1087.

Posner, J., Polanczyk, G. V., & Sonuga-Barke, E. (2020). Attention-deficit hyperactivity disorder. *The Lancet*, *395*(10222), 450–462.

Purves, K. L., Coleman, J. R. I., Meier, S. M., Rayner, C., Davis, K. A. S., Cheesman, R., … Eley, T. C. (2020). A major role for common genetic variation in anxiety disorders. *Molecular Psychiatry*, *25*(12), 3292–3303. https://doi.org/10.1038/s41380-019-0559-1.

Rajagopal, V. M., Ganna, A., Coleman, J. R. I., Allegrini, A. G., Voloudakis, G., Grove, J., … Demontis. (2020). Genome-wide association study of school grades identifies a genetic overlap between language ability, psychopathology and creativity. *bioRxiv* (p. 2020.05.09.075226). https://doi.org/10.1101/2020.05.09.075226.

Rietveld, M. J. H., Hudziak, J. J., Bartels, M., van Beijsterveldt, C. E. M., & Boomsma, D. I. (2004). Heritability of attention problems in children: Longitudinal results from a study of twins, age 3 to 12. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *45*(3), 577–588.

Riglin, L., Eyre, O., Cooper, M., Collishaw, S., Martin, J., Langley, K., … Thapar, A. (2017). Investigating the genetic underpinnings of early-life irritability. *Translational Psychiatry*, *7*(9), e1241.

Riglin, L., Leppert, B., Dardani, C., Thapar, A. K., Rice, F., O'Donovan, M. C., … Thapar, A. (2020a). ADHD and depression: Investigating a causal explanation. *Psychological Medicine*, 1–8.

Riglin, L., Leppert, B., Langley, K., Thapar, A. K., O'Donovan, M. C., Davey Smith, G., … Thapar, A. (2020b). Investigating attention-deficit hyperactivity disorder and autism spectrum disorder traits in the general population: What happens in adult life? *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. Advance online publication. https://doi.org/10.1111/jcpp.13297

Riglin, L., Thapar, A. K., Leppert, B., Martin, J., Richards, A., Anney, R., … Thapar, A. (2020c). Using genetics to examine a general liability to childhood psychopathology. *Behavior Genetics*, *50*(4), 213–220. https://doi.org/10.1007/s10519-019-09985-4.

Ronald, A., de Bode, N., & Polderman, T. J. C. (2021). Systematic review: How the attention-deficit/hyperactivity disorder polygenic risk score adds to our understanding of ADHD and associated traits. *Journal of the American Academy of Child and Adolescent Psychiatry*. Advance online publication. https://doi.org/10.1016/j.jaac.2021.01.019.

Rovira, P., Demontis, D., Sánchez-Mora, C., Zayats, T., Klein, M., Mota, N. R., … Ribasés, M. (2020). Shared genetic background between children and adults with attention deficit/hyperactivity disorder. *Neuropsychopharmacology*, *45*(10), 1617–1626. https://doi.org/10.1038/s41386-020-0664-5.

Rydell, M., Taylor, M. J., & Larsson, H. (2017). Genetic and environmental contributions to the association between ADHD and affective problems in early childhood - A Swedish population-based twin study. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *174*(5), 538–546.

Salem, H., Vivas, D., Cao, F., Kazimi, I. F., Teixeira, A. L., & Zeni, C. P. (2018). ADHD is associated with migraine: A systematic review and meta-analysis. *European Child & Adolescent Psychiatry*, *27*(3), 267–277.

Satterstrom, K. F., Walters, R. K., Singh, T., Wigdor, E. M., Lescai, F., Demontis, D., … Daly, M. J. (2019). Autism spectrum disorder and attention deficit hyperactivity disorder have a similar burden of rare protein-truncating variants. *Nature Neuroscience*, *22*(12), 1961–1965.

Scerif, G., & Baker, K. (2015). Annual research review: Rare genotypes and childhood psychopathology –Uncovering diverse developmental mechanisms of ADHD risk. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *56*(3), 251–273.

Serdarevic, F., Tiemeier, H., Jansen, P. R., Alemany, S., Xerxa, Y., Neumann, A., … Ghassabian, A. (2020). Polygenic risk scores for developmental disorders, neuromotor functioning during infancy, and autistic traits in childhood. *Biological Psychiatry*, *87*(2), 132–138.

Simon, V., Czobor, P., Bálint, S., Mészáros, A., & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. *The British Journal of Psychiatry: The Journal of Mental Science*, *194*(3), 204–211.

Skoglund, C., Chen, Q., D'Onofrio, B. M., Lichtenstein, P., & Larsson, H. (2014). Familial confounding of the association between maternal smoking

https://doi.org/10.1017/S0033291721000982 Published online by Cambridge University Press

during pregnancy and ADHD in offspring. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *55*(1), 61–68.
Skoglund, C., Chen, Q., Franck, J., Lichtenstein, P., & Larsson, H. (2015). Attention-deficit/hyperactivity disorder and risk for substance use disorders in relatives. *Biological Psychiatry*, *77*(10), 880–886.
Song, J., Bergen, S. E., Kuja-Halkola, R., Larsson, H., Landén, M., & Lichtenstein, P. (2015). Bipolar disorder and its relation to major psychiatric disorders: A family-based study in the Swedish population. *Bipolar Disorders*, *17*(2), 184–193.
Stergiakouli, E., Hamshere, M., Holmans, P., Langley, K., Zaharieva, I., deCODE Genetics, Psychiatric GWAS Consortium, Hawi, Z., … Thapar, A. (2012). Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. *The American Journal of Psychiatry*, *169*(2), 186–194.
Stevens, S. E., Sonuga-Barke, E. J. S., Kreppner, J. M., Beckett, C., Castle, J., Colvert, E., … Rutter, M. (2008). Inattention/overactivity following early severe institutional deprivation: Presentation and associations in early adolescence. *Journal of Abnormal Child Psychology*, *36*(3), 385–398.
Sullivan, P. F. (2017). How good were candidate gene guesses in schizophrenia genetics? [Review of *How Good Were Candidate Gene Guesses in Schizophrenia Genetics?*]. *Biological Psychiatry*, *82*(10), 696–697.
Sun, S., Kuja-Halkola, R., Faraone, S. V., D'Onofrio, B. M., Dalsgaard, S., Chang, Z., … Larsson, H. (2019). Association of psychiatric comorbidity with the risk of premature death among children and adults with attention-deficit/hyperactivity disorder. *JAMA Psychiatry*, *76*(11), 1141–1149. https://doi.org/10.1001/jamapsychiatry.2019.1944.
Taurines, R., Schmitt, J., Renner, T., Conner, A. C., Warnke, A., & Romanos, M. (2010). Developmental comorbidity in attention-deficit/hyperactivity disorder. *Attention Deficit and Hyperactivity Disorders*, *2*(4), 267–289.
Taylor, M. J., Lichtenstein, P., Larsson, H., Anckarsäter, H., Greven, C. U., & Ronald, A. (2016). Is there a female protective effect against attention-deficit/hyperactivity disorder? Evidence from two representative twin samples. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(6), 504–512.e2.
Taylor, M. J., Martin, J., Lu, Y., Brikell, I., Lundström, S., Larsson, H., & Lichtenstein, P. (2019). Association of genetic risk factors for psychiatric disorders and traits of these disorders in a Swedish population twin sample. *JAMA Psychiatry*, *76*(3), 280–289.
Thapar, A., & Cooper, M. (2016). Attention deficit hyperactivity disorder. *The Lancet*, *387*(10024), 1240–1250.
Thapar, A., Langley, K., Owen, M. J., & O'Donovan, M. C. (2007). Advances in genetic findings on attention deficit hyperactivity disorder. *Psychological Medicine*, *37*(12), 1681–1692.
Thapar, A., Rice, F., Hay, D., Boivin, J., Langley, K., van den Bree, M., … Harold, G. (2009). Prenatal smoking might not cause attention-deficit/hyperactivity disorder: Evidence from a novel design. *Biological Psychiatry*, *66*(8), 722–727.
Tistarelli, N., Fagnani, C., Troianiello, M., Stazi, M. A., & Adriani, W. (2020). The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies. *Neuroscience and Biobehavioral Reviews*, *109*, 63–77.
Treur, J. L., Demontis, D., Smith, G. D., Sallis, H., Richardson, T. G., Wiers, R. W., … Munafò, M. R. (2021). Investigating causality between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization. *Addiction Biology*, *26*(1), e12849.https://doi.org/10.1111/adb.12849.
Trost, B., Engchuan, W., Nguyen, C. M., Thiruvahindrapuram, B., Dolzhenko, E., Backstrom, I., … Yuen, R. K. C. (2020). Genome-wide detection of tandem DNA repeats that are expanded in autism. *Nature*, *586*(7827), 80–86.
Tuvblad, C., Zheng, M., Raine, A., & Baker, L. A. (2009). A common genetic factor explains the covariation among ADHD ODD and CD symptoms in 9–10 year old boys and girls. *Journal of Abnormal Child Psychology*, *37*(2), 153–167.
Tye, C., McLoughlin, G., Kuntsi, J., & Asherson, P. (2011). Electrophysiological markers of genetic risk for attention deficit hyperactivity disorder. *Expert Reviews in Molecular Medicine*, *13*, e9.
Tye, C., Rijsdijk, F., Greven, C. U., Kuntsi, J., Asherson, P., & McLoughlin, G. (2012). Shared genetic influences on ADHD symptoms and very low-frequency EEG activity: A twin study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *53*(6), 706–715.
Tye, C., Rijsdijk, F., & McLoughlin, G. (2014). Genetic overlap between ADHD symptoms and EEG theta power. *Brain and Cognition*, *87*, 168–172.
Vainieri, I., Martin, J., Rommel, A.-S., Asherson, P., Banaschewski, T., Buitelaar, J., … Kuntsi, J. (2021). Polygenic association between attention-deficit/hyperactivity disorder liability and cognitive impairments. *Psychological Medicine*, 1–9. Advance online publication. https://doi.org/10.1017/S0033291720005218.
Verhoef, E., Demontis, D., Burgess, S., Shapland, C. Y., Dale, P. S., Okbay, A., … St Pourcain, B. (2019). Disentangling polygenic associations between attention-deficit/hyperactivity disorder, educational attainment, literacy and language. *Translational Psychiatry*, *9*(1), 1–12.
Vuijk, P. J., Martin, J., Braaten, E. B., Genovese, G., Capawana, M. R., O'Keefe, S. M., … Doyle, A. E. (2020). Translating discoveries in attention-deficit/hyperactivity disorder genomics to an outpatient child and adolescent psychiatric cohort. *Journal of the American Academy of Child and Adolescent Psychiatry*, *59*(8), 964–977. https://doi.org/10.1016/j.jaac.2019.08.004.
Wadsworth, S. J., DeFries, J. C., Willcutt, E. G., Pennington, B. F., & Olson, R. K. (2015). The Colorado longitudinal twin study of reading difficulties and ADHD: Etiologies of comorbidity and stability. *Twin Research and Human Genetics*, *18*(6), 755–761.
Waldman, I. D., Poore, H. E., Luningham, J. M., & Yang, J. (2020). Testing structural models of psychopathology at the genomic level. *World Psychiatry*, *19*(3), 350–359.
Walters, R. K., Polimanti, R., Johnson, E. C., McClintick, J. N., Adams, M. J., Adkins, A. E., … Agrawal, A. (2018). Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nature Neuroscience*, *21*(12), 1656–1669.
WHO. (2018). *ICD-11 international classification of diseases for mortality and morbidity statistics* (11th revision). World Health Organization.
Willcutt, E. G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: A meta-analytic review. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *9*(3), 490–499.
Williams, N. M., Franke, B., Mick, E., Anney, R. J. L., Freitag, C. M., Gill, M., … Faraone, S. V. (2012). Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: The role of rare variants and duplications at 15q13.3. *The American Journal of Psychiatry*, *169*(2), 195–204.
Williams, N. M., Zaharieva, I., Martin, A., Langley, K., Mantripragada, K., Fossdal, R., … Thapar, A. (2010). Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: A genome-wide analysis. *The Lancet*, *376*(9750), 1401–1408.
Wimberley, T., Agerbo, E., Horsdal, H. T., Ottosen, C., Brikell, I., Als, T. D., … Dalsgaard, S. (2020). Genetic liability to ADHD and substance use disorders in individuals with ADHD. *Addiction*, *115*(7), 1368–1377.
Wolfe, D., Dudek, S., Ritchie, M. D., & Pendergrass, S. A. (2013). Visualizing genomic information across chromosomes with PhenoGram. *BioData Mining*, *6*(1), 18.
Wood, A. C., Rijsdijk, F., Asherson, P., & Kuntsi, J. (2009). Hyperactive-impulsive symptom scores and oppositional behaviours reflect alternate manifestations of a single liability. *Behavior Genetics*, *39*(5), 447–460.
Yang, L., Neale, B. M., Liu, L., Lee, S. H., Wray, N. R., Ji, N., … Wang, Y., & Psychiatric GWAS Consortium: ADHD Subgroup. (2013). Polygenic transmission and complex neuro developmental network for attention deficit hyperactivity disorder: Genome-wide association study of both common and rare variants. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *162B*(5), 419–430.
Yao, S., Kuja-Halkola, R., Martin, J., Lu, Y., Lichtenstein, P., Norring, C., … Larsson, H. (2019). Associations between attention-deficit/hyperactivity disorder and various eating disorders: A Swedish nationwide population study using multiple genetically informative approaches. *Biological Psychiatry*, *86*(8), 577–586.
Zheng, Y., Pingault, J.-B., Unger, J. B., & Rijsdijk, F. (2020). Genetic and environmental influences on attention-deficit/hyperactivity disorder symptoms in Chinese adolescents: A longitudinal twin study. *European Child & Adolescent Psychiatry*, *29*(2), 205–216.
Zhong, Y., Yang, B., Su, Y., Qian, Y., Cao, Q., Chang, S., … Yang, L. (2020). The association with quantitative response to attention-deficit/hyperactivity disorder medication of the previously identified neurodevelopmental network genes. *Journal of Child and Adolescent Psychopharmacology*, *30*(6), 348–354.

https://doi.org/10.1017/S0033291721000982 Published online by Cambridge University Press