REVIEW

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Systematic Review: Molecular Studies of Common Genetic Variation in Child and Adolescent Psychiatric Disorders

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Objective: A systematic review of studies using molecular genetics and statistical approaches to investigate the role of common genetic variation in the development, persistence, and comorbidity of childhood psychiatric traits was conducted.

Method: A literature review was performed using the PubMed database, following PRISMA guidelines. There were 131 studies meeting inclusion criteria, having investigated at least one type of childhood-onset or childhood-measured psychiatric disorder or trait with the aim of identifying trait-associated common genetic variants, estimating the contribution of single nucleotide polymorphisms (SNPs) to the amount of variance explained (SNP-based heritability), investigating genetic overlap between psychiatric traits, or investigating whether the stability in traits or the association with adult traits is explained by genetic factors.

Results: The first robustly associated genetic variants have started to be identified for childhood psychiatric traits. There were substantial contributions of common genetic variants to many traits, with variation in single nucleotide polymorphism heritability estimates depending on age and raters. Moreover, genetic variants also appeared to explain comorbidity as well as stability across a range of psychiatric traits in childhood and across the life span.

Conclusion: Common genetic variation plays a substantial role in childhood psychiatric traits. Increased sample sizes will lead to increased power to identify genetic variants and to understand genetic architecture, which will ultimately be beneficial to targeted and prevention strategies. This can be achieved by harmonizing phenotype measurements, as is already proposed by large international consortia and by including the collection of genetic material in every study.

Key words: child and adolescent genetics, child and adolescent psychiatry, genetic variation, molecular genetics, systematic review

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Over the past decade, the field of psychiatric genetics, including child and adolescent psychiatry, has made remarkable progress with many new discoveries. This has been facilitated by rapid progress in molecular genetic methods. That psychiatric disorders are heritable is well established via twin studies,[1] with estimates varying from 70%-80% for bipolar disorder and schizophrenia[2,3] to 40%-50% for anxiety and depression.[4] Estimates for childhood-onset and childhood-measured phenotypes are equally high. Both attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have heritability estimates ranging from 60% to 90%,[5] while estimates for parent-reported childhood anxiety and depressive symptoms average around 40%.[6,7] Further, twin studies have been used to show that stability and comorbidity among childhood and adolescent psychopathology traits are largely genetically mediated.[8,9]

The most widely applied method to investigate specific genetic variants contributing to heritability is a genome-wide association study (GWAS), where millions of common variants are tested for association with a complex trait.[10,11] Initial GWASs showed that large sample sizes are required to identify the typically small, polygenic effects of trait-associated genetic variants.[12,13] This gave rise to extensive collaborations that collated large amounts of data for genetic analyses in consortia within the field of genetics, such as the EArly Genetics and Lifecourse Epidemiology (EAGLE) consortium,[14] the Psychiatric Genomics Consortium (PGC),[15] and the Social Science Genetics Association Consortium (SSGAC). As a result, genetic variants have been identified for psychiatric disorders including ADHD, ASD, schizophrenia, bipolar disorder, and major depressive disorder (MDD).[16-21] Furthermore, there has been rapid development of polygenic techniques[22-24] that investigate the joint effect of genetic variants to assess the genetic architecture of traits.[9,13,25,26] These studies have provided insight into the contribution of common genetic variation to heritability estimates as well as the role of genetic factors in the

persistence of symptoms over time and in frequently occurring comorbidity.

With increasing sample sizes for childhood phenotypes, it is timely to provide an overview of findings on the contribution of common genetic variants to child and adolescent psychiatric traits. We were specifically interested in studies that investigated disorders/traits that typically have their onset in childhood, eg, neurodevelopmental disorders such as ASD and ADHD, as well as studies investigating traits that can be diagnosed across the life span but are measured in childhood samples. To this end, we systematically reviewed publications using genome-wide approaches to identify common genetic variants underlying vulnerability to these disorders and studies using polygenic analyses aiming to increase our understanding of factors influencing comorbidity and continuity in psychiatric disorders.

Methods in Studies Focusing on Common Genetic Variation

Before describing our search strategy and the results of the studies included in the review, we provide brief summaries of popular methods applied in molecular genetic studies focusing on common genetic variation. Extensive descriptions of these methods are provided in recently published reviews.[9,13,25,26]

Identification of Common Variants

Genome-wide Association Studies. GWASs test the associations between a trait and genetic markers across the genome, usually single base changes in the DNA sequence called single nucleotide polymorphisms (SNPs). If a SNP is significantly more common in cases or controls, this suggests that the SNP in question is associated with the trait and may play a role in its etiology, conferring risk or protective effects.[27,28] GWASs are not limited to dichotomous phenotypes, and quantitatively measured traits such as symptom counts can also be investigated using this method. GWASs typically use a significance threshold of 5×10^{-8}, based on an approximation of independent markers that are tested. This stringent threshold means that large samples are required to identify the typically small effects of genetic variants. To increase the statistical power to detect associated genetic variants for a given trait, multiple independent GWASs performed across distinct cohorts can be meta-analyzed.

Estimation of SNP Heritability

Linkage Disequilibrium Score Regression. SNP-based heritability indicates what proportion of the variance of a trait is explained by measured SNPs, in contrast to broad heritability estimates based on twin-family studies. Linkage disequilibrium score regression (LDSC) estimates SNP-based heritability using summary data from GWASs.[23] As a result of various evolutionary mechanisms, combinations of alleles/SNPs can occur. Linkage disequilibrium (LD) occurs when SNPs are nonrandomly correlated with other SNPs at different loci, ie, they are more or less frequently associated than would be expected at random.[29] LDSC uses a measure of LD, called LD score, that is estimated for each SNP by taking the sum of correlations between that SNP and all nearby SNPs and is calculated in an ancestrally similar reference sample when individual genotype data are unavailable for the GWAS sample. The slope from a regression of LD scores on GWAS test statistics is proportional to the SNP-based heritability of the trait examined in the GWAS.

Genetic Relationship Matrix Restricted Maximum Likelihood. Genetic relationship matrix restricted maximum likelihood (GREML), as implemented in Genome-wide Complex Trait Analysis (GCTA) software, estimates the phenotypic variance explained by all measured SNPs simultaneously.[24] First, a genetic relatedness matrix is built for a sample of unrelated people, indicating the genetic similarities between all people based on their genome-wide genotypes. Next, using a linear mixed model that includes the genetic relatedness matrix, the extent to which phenotypic similarity between unrelated people is due to their genetic similarity is calculated.[24,30]

Because LD structure differences between reference and sample data can bias LDSC estimates,[25,31] GREML is generally preferred where individual-level data are available. However, in the absence of individual-level data and with very large sample sizes, LDSC is more computationally efficient and provides a good alternative.[25,32]

Estimation of Shared Genetic Variance Explaining Comorbidity or Continuity of Symptoms Over Time

Genetic Relationship Matrix Restricted Maximum Likelihood and Linkage Disequilibrium Score Regression. Both GREML and LDSC can be extended to bivariate analyses that allow the estimation of the genetic coheritability, ie, the amount of variance shared between two traits as a result of genetics, also known as their genetic correlation.[33,34] These bivariate analyses can be performed both on nonoverlapping samples and on traits measured in the same people.

Polygenic Risk Score. To calculate a polygenic risk score (PRS), a GWAS is conducted in a discovery sample to define risk alleles of SNPs and their effect sizes. Next, in an independent target sample, a polygenic risk score is calculated for each person by totaling the number of risk alleles

the individual has (based on the discovery GWAS) and weighting the score by the effect sizes of each allele.[9] The proportion of risk alleles included in a score are generally selected based on thresholds depending on the exact methodology used. The PRS represents a person's genetic liability for a trait.

The method was initially developed to test the theory of polygenic inheritance when the first GWASs lacked significant effects. PRSs based on a GWAS without any or with a few significant hits were used to predict the same trait in another sample, in this way showing that there was an effect captured in these common variants that likely would become significant when sample sizes became large enough.[22] Presently, PRSs are generally used to assess genetic associations between different traits, or the same trait measured at different ages. Typically, an outcome measure of interest from a target sample (eg, depression) is regressed on the PRS for another trait (eg, ADHD) to test the association between them. A significant result suggests that genetic variants common to both traits underlie their association. While LDSC and GREML require tens of thousands of subjects for both sets of traits being investigated, PRSs work if the discovery sample is large but the target sample is small (approximately 2,000 subjects at least). This is particularly advantageous when a target trait is rare or expensive to measure.

METHOD

Search Strategy

The literature search was conducted on the PubMed database for studies published from 2008 up to August 9, 2020, as the most relevant/powerful molecular genetic studies are likely to have been published during the last decade. We included studies that investigated traits that have their onset in childhood or that investigated traits that can be diagnosed across the life span but were measured in childhood or adolescent samples. We followed PRISMA guidelines (Figure 1).[35] Search terms included psychiatry and psychopathology outcomes: autis*, depress*, mood, emotion*, affective disorder*, internali*, anxi*, worry, fear*, obses*, compul*, OCD, panic, phobi*, inhibit*, shy*, withdrawn, behav*, attenti*, inattenti* externalising, externalizing, conduct disorder*, ADHD*, hyperactiv*, impuls*, disruptive*, problem*, aggress*, violen*, oppositional, ODD, psychiatr*, and psychopatholog*. Additionally, each search included terms that were designed to produce studies using statistical methods to analyze molecular genetic data, including GWAS, genome-wide*, association stud*, polygenic*, polygenic scores, risk scores, PRS, summary statistics, LD score regress*, LD score, GCTA, GREML, LDSR, and LDSC. Finally, we included terms designed to limit results to childhood and adolescent samples as well as longitudinal genetic studies, as follows: child*, adolescen*, teen*, youth, develop*, continuity*, stab*, change*.

Study Inclusion Criteria

The studies included in this review met the following criteria: published in English in a peer-reviewed journal; investigated at least one type of childhood/adolescent-onset or childhood/adolescent-measured psychiatric disorder or trait; aimed to identify common trait-/disorder-associated genetic variants, estimate the contribution of SNPs to the amount of variance explained, investigate whether associations between psychiatric traits are explained by genetic factors, or investigate whether the stability in traits or the association with adult traits is explained by genetic factors. Finally, results published were based on analyses using one or more of the following methods: GWAS, LDSC, GREML, and PRS.

RESULTS

We identified 131 studies that addressed at least one aim of this review. See Table 1 for the proportion of studies that used each method, and assessed each relevant research question.

Identification of Common Variants

Of 50 relevant GWASs of childhood psychiatric traits, 15 reported significant genetic variants (Table S1, available online). The most commonly investigated phenotypes were ADHD and ASD and their related continuous measures. Early studies were family-based, primarily made up of probands/cases and their unaffected parents and/or siblings, with more recent studies additionally including unrelated cases and controls.

Significant genetic variants were detected for clinical measures of ADHD,[19,36-38] ASD,[20,39-41] anorexia nervosa,[42] and Tourette syndrome,[43] as well as continuous measures of ASD-related traits/symptoms such as social communication problems[44,45] and restrictive and repetitive behaviors,[46] for depressive symptoms,[47] and for the anhedonia domain of self-reported psychotic-like experiences.[48] Only results from the recent ASD[20] and ADHD[19] studies were replicated in independent samples. The ASD GWAS identified 3 loci, while the ADHD GWAS identified 12 loci. The direction of effect for the top loci from both GWASs were replicated in 5 cohorts for ASD and 3 cohorts for ADHD. Further, all 12 loci from the ADHD GWAS were significant in at least 1 of 3 replication meta-analyses. It is becoming common practice to perform functional

FIGURE 1 PRISMA Flowchart Showing Selection of Studies for Inclusion in Review

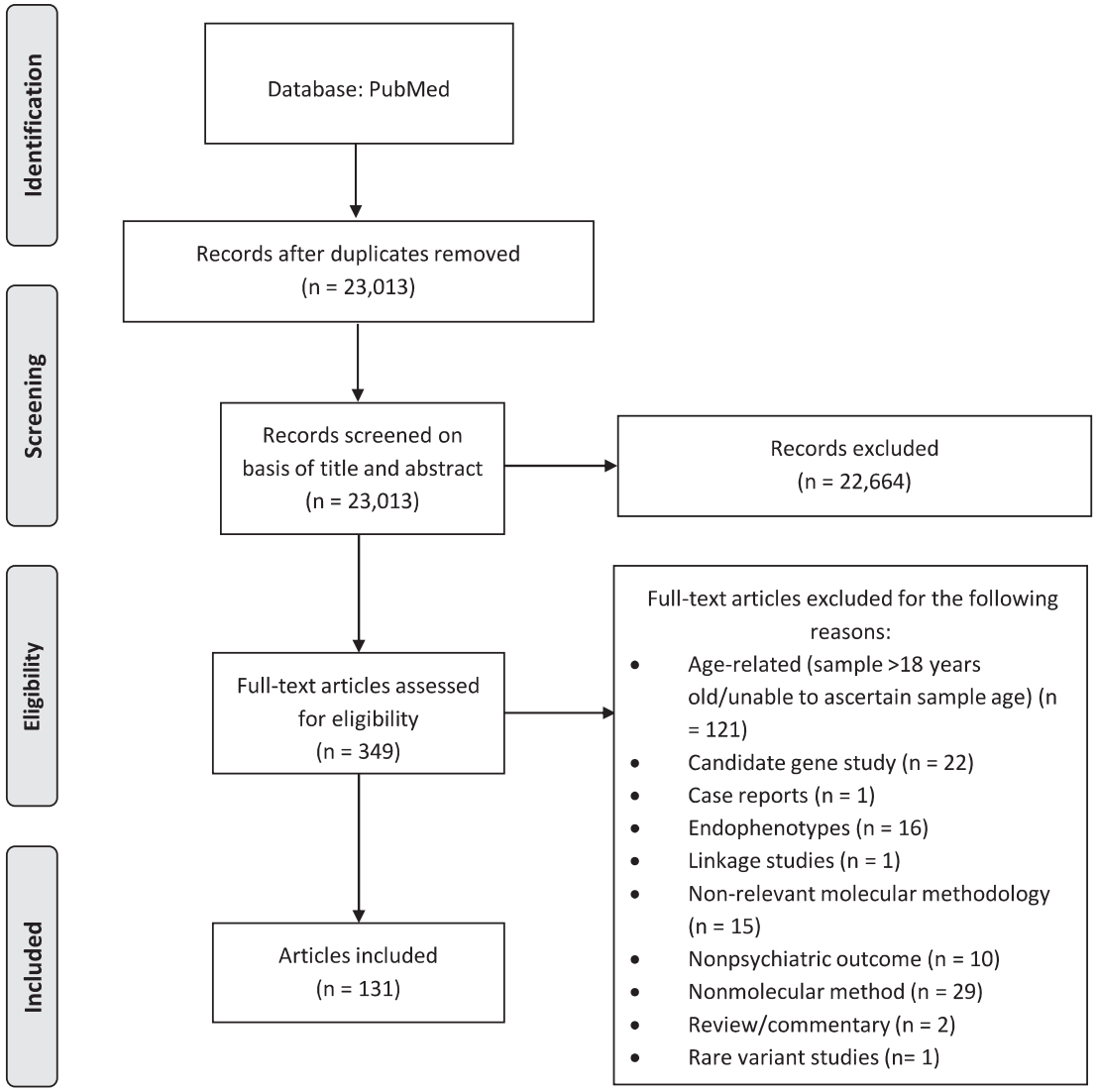


TABLE 1 Characteristics of Studies Included in Review

Research question addressed	Method	Number of studies
Variant identification	GWAS	50
SNP heritability estimation	GREML, LDSC	34
Genetic contributions to comorbidity	GREML, LDSC	5
	PRS	18
Genetic contributions to stability or associations with adult traits	GREML, LDSC	16
	PRS	63

Note: The sum of studies in this table is greater than the total number of studies included in this review owing to studies addressing multiple aims. This table does not account for studies investigating childhood within-trait analyses, as they do not strictly fit the aims of the review. GREML = genetic relationship matrix restricted maximum likelihood; GWAS = genome-wide association study; LDSC = linkage disequilibrium score regression; PRS = polygenic risk score; SNP = single nucleotide polymorphism.

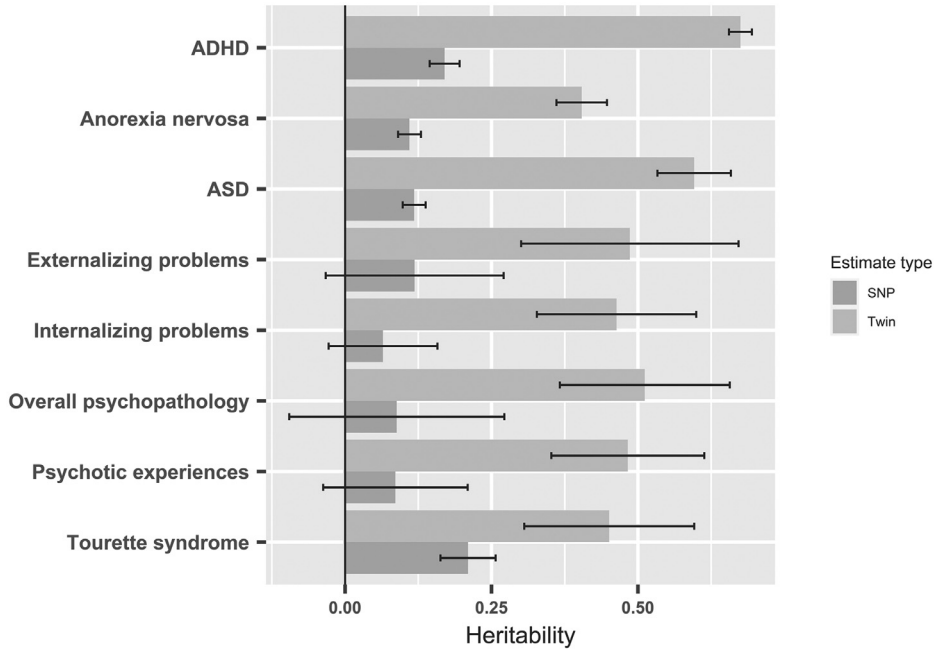
annotation analyses of GWAS results to further clarify the biological basis for genetic associations. Such analyses have implicated dopamine regulation and brain development in the etiology of ADHD and ASD, respectively.[19,20] It is important to note that the most recent findings from the case-control analyses were based on mixed adult and childhood samples, likely in a bid to maximize the power to detect significant variants.

SNP Heritability

We identified 34 studies that estimated the SNP heritability of childhood psychopathology traits using GREML or LDSC (Table S2, available online). Analyses of clinically diagnosed traits generally used the same samples in subsequent analyses. We thus report estimates from the most recent studies, with estimates from individual studies described in Table S2, available online. SNP-based heritability estimates for clinical disorders were based on mixed adult and childhood samples and were 17%, 11.8%, and 21% for ADHD,[38] ASD,[20] and Tourette syndrome,[43] respectively, while estimates ranged from 11% to 17% for anorexia nervosa depending on the assumed lifetime prevalence of the disorder (Figure 2).[42] Age-stratified analyses of childhood ADHD[38] and ASD[20] yielded heritability estimates of 19% and 4.9% respectively, while sex-stratified ADHD analyses found estimates to be significantly higher in male participants (24.7%) than female participants (12.3%).[37]

Estimates for continuous measures were mostly low and nonsignificant; this was likely due to a lack of power from individual studies. They also showed more variation across age, rater and methodology compared with clinically measured traits. We grouped results from relevant studies according to domains and meta-analyzed estimates from different traits across these domains, combining estimates across age, rater, and methods. We identified domains for ADHD symptoms, ASD symptoms, externalizing problems, internalizing problems, psychotic experiences, and general/overall psychopathology. Meta-analysis results as well as studies and traits included per domain are described in Figures S1-S6, available online. Heritability estimates from these meta-analyses ranged from 6.48% to 14.5% and

FIGURE 2 Comparison of Single Nucleotide Polymorphism (SNP)– and Twin-based Heritability Estimates of Childhood Psychiatric Traits



Note: *SNP-based estimates are those reported in the current review, while twin/family-based heritability estimates are of similar measures from other studies. Bars represent confidence intervals corresponding to α = .05 and are plotted for estimates for which they are provided. Twin-based heritability sources (specific trait names from publications in brackets): ADHD (hyperkinetic disorders),[1] ASD (pervasive developmental disorders),[1] anorexia (eating disorders),[1] externalizing problems (conduct disorder),[1] internalizing problems (depression + anxiety + emotional disorder),[1] overall psychopathology (mental and behavioral disorders),[1] psychotic experiences,[158] Tourette syndrome (tic disorders).[1] All twin-based estimates were obtained from Polderman et al.[1] using the MaTCH tool (https://match.ctglab.nl/#/home), apart from psychotic experiences, which was obtained from a recent publication that used similar measures and samples to the SNP-based estimates. ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder. Please note color figures are available online.*

are lower than relevant twin-based heritability estimates (Figure 2).

Aside from directly measured traits, the heritability of latent psychopathology factors was also investigated, with estimates of 38% for a general psychopathology factor, capturing the correlations between parent-, teacher-, and self-reported measures across multiple domains of internalizing and externalizing problems.[49] This indicates that it is possible to capture the genetic variation that is related to a person's broad risk of psychopathology. An estimate of 14% was also reported for stable genetic factors affecting emotional problems across childhood and adolescence,[50] suggesting that while genetic variants may have varying effects across development, it is also likely that a set of SNPs exist that have effects throughout development. Both estimates were meta-analyzed in the general psychopathology and internalizing problems domains respectively.

In summary, estimates for continuous measures showed variation across different population-based samples, while estimates for clinical measures were more stable. Differences between samples in age, rater, and instrument used to measure the continuous outcomes might contribute to the higher variation, although we did not detect overall trends of differences between these variables.

Genetic Factors Explaining Associations Between Childhood Traits

Polygenic Risk Scores. Childhood cross-trait analyses were mostly limited to ADHD and ASD (Table S3, available online), with studies showing associations between PRSs of ADHD and ASD, and childhood conduct disorder symptoms, irritability, ADHD symptoms, social communication problems/autistic traits, eating disorder symptoms, anxiety and depression as well as higher symptom levels in latent externalizing, internalizing, and general psychopathology factors (Table 2).[36,51-64] Further, female participants with clinical diagnoses of anxiety and depression were found to have higher ADHD PRSs than male participants,[52] while male, but not female, participants with higher ADHD PRSs had higher autistic trait scores.[56]

Genetic Relationship Matrix Restricted Maximum Likelihood and Linkage Disequilibrium Score Regression. As with the PRS analyses, childhood cross-trait analyses using GREML and LDSC generally focused on ADHD and ASD, with reported genetic correlations of up to 0.37 based on clinical samples (Figure 3, Table S4, available online).[20,87,88] Findings from childhood within-trait analyses do not strictly fit our aims but are described in Table S5, available online. Overall, they show associations between clinical measures of ADHD and ASD in one sample and clinical or continuous measures of the same trait in a different sample, suggesting the same underlying construct. Sex-stratified analyses of ADHD also reported a genetic correlation of almost 1 between male and female participants, suggesting that the same genetic variants underlie ADHD in both sexes,[37] while PRS analyses showed higher ADHD PRSs in female ADHD cases than male ADHD cases in some studies,[65,89] but not others.[52]

Genetic Factors Explaining Stability in Traits or Associations With Adult Traits

Polygenic Risk Scores. PRS analyses investigating the role of genetic factors in the continuity of symptoms across childhood were limited. Longitudinal analyses of aggression found that PRSs of aggression were not associated with aggression measured at different ages across childhood (Table S6, available online).[90] However, this may have been the result of a stringent threshold at which SNPs were included in the score, resulting in a lower number of SNPs included than usual. We further identified a subset of studies that used PRS to investigate developmental trajectories for childhood psychopathology (Table S7, available online). They showed that higher ADHD PRS was associated with a trajectory of persistent ADHD[91,92] as well as high-persistent and increasing trajectories for irritability.[93] In contrast, aggression PRS was not associated with any symptom-defined conduct disorder trajectories, although it moderated the effect of interventions on trajectory class membership.[94]

More studies have focused on the association between adult and childhood traits, investigating similar or different symptoms across development as well as disorder trajectories (Table 2, Tables S6 and S7, available online). Associations were reported between PRSs of adult traits including schizophrenia, MDD, obsessive-compulsive disorder (OCD), anxiety, and externalizing disorder and clinical and continuous measures of the same/similar trait in childhood and adolescence[48,50,64,66,67,69-74,95-98] or in those at high risk,[99,100] although this was not always the case.[60,68,73,75,95,101-105] An exception is bipolar disorder, for which no significant associations with similar childhood traits, such as mania, were identified.[66] Still, PRS analyses of bipolar disorder performed in relatives of people with bipolar disorder indicated that, as expected, children and siblings had higher PRSs for bipolar disorder compared with control participants.[106,107]

Similarly, myriad cross-trait associations were observed between PRSs of adult psychiatric traits and dissimilar childhood traits, including ADHD, depression, anxiety, OCD, conduct disorder, ASD, internalizing and externalizing problems, irritability, psychotic-like experiences, and binge eating as well as trajectories for

TABLE 2 Genetic Associations Between Childhood Psychiatric Traits and Other Psychiatric Traits Using Polygenic Risk Scores

Discovery trait (PRS)	Target trait	Target sample size	Variance explained (%)	Study references
Childhood cross-trait				
ADHD	ASD	1,238	0.80	61
	ASD symptoms	1,921-6,854	**0.40-3.00**	56,59
		5,653-6,854	0.00-0.10	59,65
	Eating disorder symptoms	5,674-5,680	**0.10-0.13**	55
		5,668	0.00	55
	Externalizing problems	394-6,854	**0.41-1.99**	59,60,62
		1,902-7,975	0.00-0.30	54,59,60
	Internalizing problems	6,603-7,975	**0.20-0.42**	54,59
		1,843-7,975	0.00-0.27	54,59,60
	Irritability	560-5,584	**0.40-1.70**	51
		4,023-4,960	0.01-0.20	51
	Neurodevelopmental problems	7,975	**0.90**	54
		7,975	0.10	54
	Overall psychopathology	6,603-7,975	**0.86-1.06**	54,59
ASD	ADHD	433-1,688	0.13-0.34	36,61,62
	ADHD symptoms	1,134	**0.77**	57
		394	0.19	62
	Childhood-onset schizophrenia	233	**6.48**	64
	Externalizing problems	1,902-7,975	0.00-0.13	54,60
	Internalizing problems	1,843-7,975	0.00-0.05	54,60
	Neurodevelopmental problems	7,975	0.00	54
	Overall psychopathology	7,975	0.00-0.10	54
Childhood-adult within				
Anxiety disorder	Internalizing problems	5,703-12,220	**0.09-0.41**	50,66
		3,755	0.07	66
Bipolar disorder	Bipolar disorder symptoms	3,808	0.023	66
Depression	Internalizing problems	7,975-42,998	**0.17-0.30**	54,67
		932-7,975	0.10-0.60	54,68
Depressive symptoms	Depressive symptoms	709	**1.50**	69
Externalizing disorder	Externalizing problems	246	**5.00**	70
MDD	Depression	466	**5.00**	71
	Depressive symptoms	1,450-6,826	**0.20-0.73**	66,71
	Internalizing problems	5,703-12,220	**0.44-0.48**	50,66
		1,843-2,202	0.004-0.02	60
OCD	OCD symptoms	650-3,982	**0.23-2.28**	66,72
		650-13,400	0.01-0.85	66,72
Schizophrenia	Childhood-onset schizophrenia	233	**18.52**	64
	Psychotic symptoms	2,096-10,098	**0.08-0.70**	48,66,73,74
		2,133-8,665	0.00-0.30	48,73,75
Tics/Tourette syndrome	Tics/Tourette symptoms	1,043-13,396	**0.12-0.46**	66,76
		4,813	0.16	76
Childhood-adult cross-trait				
ADHD	Anxiety disorder	120,362	**0.06**	77
	Bipolar disorder	120,019	0.04	77
	MDD	126,605	**0.11**	77
	Schizophrenia	118,075	0.05	77
ADHD (childhood)	ADHD (adult)	22,406	**0.41**	38
Anorexia nervosa	ADHD symptoms	13,451-13,455	0.02-0.03	55
Anxiety disorder	ADHD symptoms	5,154	0.02	78

(continued)

TABLE 2 Continued

Discovery trait (PRS)	Target trait	Target sample size	Variance explained (%)	Study references
ASD	Bipolar disorder	11,810	**0.08**	79
	MDD	16,610	**0.12**	79
	Schizophrenia	17,115	**0.04**	79
Bipolar disorder	ADHD	5,422-6,105	**0.18-0.88**	79,80
		727-6,102	0.11-0.99	36,80,81
	ADHD symptoms	1,134-42,998	0.00-0.16	57,67,80
	ASD	10,263	**0.08**	79
	ASD symptoms	6,128-42,998	0.002-0.2	67,80
	Borderline personality disorder traits	5,246	0.00	80
	Externalizing problems	1,843-6,133	0.02-4.00	60,80
	Internalizing problems	1,843-42,998	0.01-3.00	60,67,80
	Overall psychopathology	6,111-42,998	0.00-0.003	67,80
	Prosocial behavior	6,138	0.00	80
	Psychotic symptoms	8,665	**0.12**	48
		2,133-10,098	0.00-0.1	48,75
Depression	ADHD symptoms	42,998	**0.25**	67
	ASD symptoms	42,998	**0.16**	67
	Externalizing problems	932-7,975	0.00-0.40	54,68
	Neurodevelopmental problems	7,975	0.00	54
	Overall psychopathology	42,998	**0.17**	67
		7,975		54
Depressive symptoms	Externalizing problems	709	**1.40**	69
Externalizing disorder	ADHD symptoms	246	**7.00**	70
MDD	ADHD	1,688	0.25	36
	ADHD symptoms	1,134	0.19	57
	Externalizing problems	1,843-2,202	0.01-0.08	60
	Irritability	560-5,584	0.01-0.10	51
	Psychotic symptoms	6,579-10,098	**0.08-0.11**	48
		6,297-8,665	0.004-0.03	48
OCD	ADHD symptoms	5,154	0.02	78
	Tics/Tourette syndrome	461	−1.20	82
OCD + tics/Tourette syndrome	OCD	580	**1.70**	82
	Tics/Tourette syndrome	461	0.20	82
Polygenic *p* factor	Overall psychopathology	7,026	**0.64-0.76**	83
Schizophrenia	ADHD	727	**0.45**	81
		433-1,688	0.08-0.58	36,61,62
	ADHD symptoms	394-2,992	0.00-0.83	57,62,84
	ADHD/ASD	1,631	0.30	61
	Anxiety disorder	4,107	**0.50**	73
	ASD	10,263	**0.09**	79
		1,238	0.2	61
	ASD symptoms	3,978-5,137	0.10-0.43	85
	Externalizing problems	1,154-2,202	**0.10-1.10**	60,68,84
		545-7,975	0.00-0.15	54,60,68,84
	Internalizing problems	1,843-7,975	**0.20-0.77**	54,60,73
		932-7,975	0.00-0.40	54,68,84
	Irritability	1,358	**0.10**	84
			0.00	84
	MDD	4,106	0.005	73
	Neurodevelopmental problems	7,975	0.00	54

(continued)

TABLE 2 Continued

Discovery trait (PRS)	Target trait	Target sample size	Variance explained (%)	Study references
	OCD	813	**3.17**	86
	Overall psychopathology	7,975	**0.20-0.40**	54
Tics/Tourette syndrome	ADHD symptoms	6,046	0.10	76
	ASD symptoms	6,019	0.12	76
	OCD	580	0.04	82
	OCD symptoms	6,006	0.11	76

Note: Estimates are included for studies that reported them. Boldface type indicates estimates from significant association. Similar target traits were grouped by domain across different studies and ages (see Table S8, available online, for domain classifications). ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PRS = polygenic risk score.

increasing early- and adolescent-onset emotional problems,[20,54,60,68,79,81,84,86,98,102,105,108-110] though significant associations were not observed in all studies for all pairings (Table 2, Tables S6 and S7, available online).[36,51,57,61-63,67,68,76,78,80,82,84,91,95,111-113] Significant findings were generally more common in analyses with schizophrenia PRSs compared with other adult traits, including bipolar disorder, MDD, anxiety, and OCD. Given genetic correlations between schizophrenia and bipolar disorder, findings that bipolar disorder PRSs were not related to the measured childhood phenotypes while schizophrenia scores were, may be related to higher statistical power for schizophrenia GWASs compared with bipolar disorder GWASs. Schizophrenia was the first psychiatric disorder for which samples were large enough to obtain sufficient statistical power. Longitudinal analyses further showed associations between schizophrenia PRSs and internalizing and externalizing problems at different ages from age 3 to 16,[60,102,109] with one report of an increase in the strength of association with increasing age.[109] Similar longitudinal analyses of depression PRSs found that associations with childhood psychopathology were not moderated by age, rater, or type of childhood psychopathology, suggesting the existence of stable genetic factors that affect multiple traits across the life span.[67]

PRSs of ADHD and ASD were differentially associated with adult traits, including MDD, anxiety, adult ADHD, bipolar disorder, and schizophrenia as well as high decreasing trajectory for externalizing behaviors.[38,77,79,114] ADHD PRS was also found to distinguish bipolar disorder cases with childhood ADHD from controls without bipolar disorder.[115]

Genetic Relationship Matrix Restricted Maximum Likelihood and Linkage Disequilibrium Score Regression. Social communication problems, peer problems, and ADHD symptoms showed partly stable genetic effects across ages, with correlations between measures obtained from age 7 to 17 ranging from 0.1 to 1. Comparable estimates were also reported for cross-trait genetic correlations between traits. In all scenarios, correlations were highest at adjacent time points.[45,53,116]

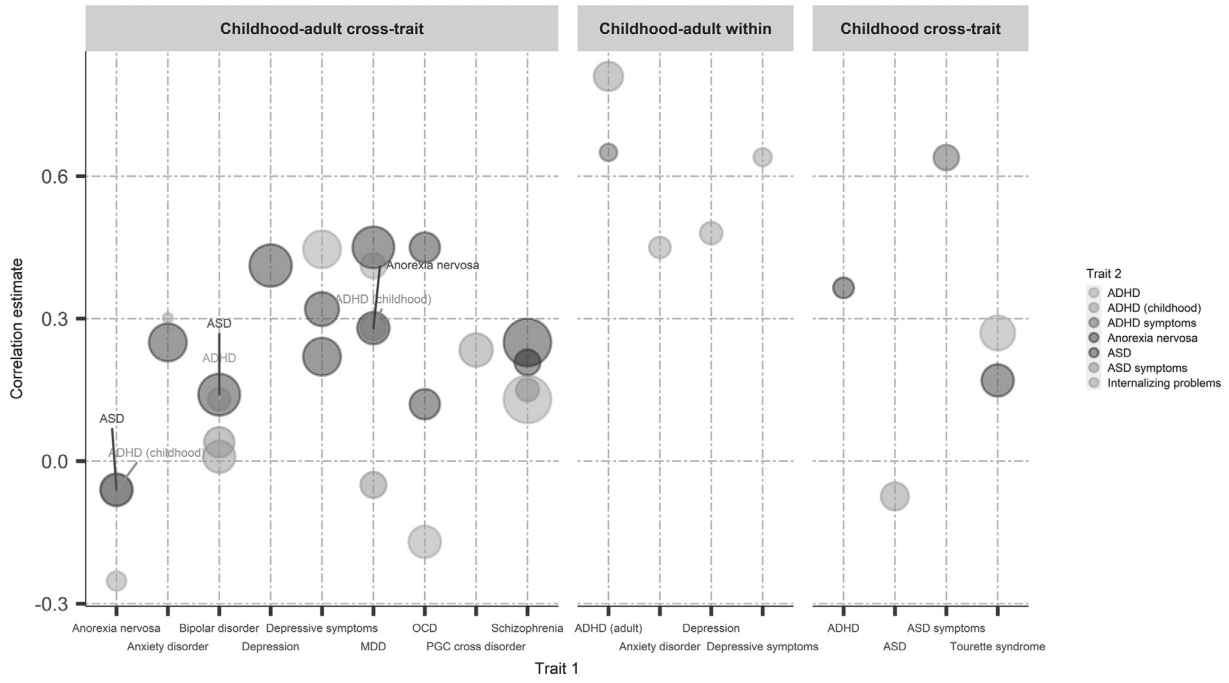
Studies also showed moderate to strong genetic correlations between ADHD, ASD, childhood emotional problems, anorexia nervosa, social communication problems, and symptoms of psychotic experiences including cognitive disorganization and anhedonia, and several adult psychiatric disorders.[19,20,42,50,85,87,88,117-121] The largest correlations were observed with depression, while correlations with bipolar disorder were lower (Figure 3, Table S9, available online).

In summary, although findings regarding genetic overlap were not always consistent, they provide evidence of pleiotropic effects in childhood psychopathology traits, ie, the existence of a set of genetic variants influencing multiple traits. They also suggest the existence of genetic variants that influence psychopathology across development and across multiple psychiatric traits. Nonsignificant findings may point to a lack of power in either discovery GWASs or target samples, or both, rather than an absence of pleiotropy. It is also important to highlight that effect sizes for PRS associations were generally low with variance by PRS ranging from 0 to 18%. This is largely a function of the methodology, and effect sizes are likely to increase with increasing GWAS sample sizes.

DISCUSSION

In this article, we review findings from molecular and statistical genetic approaches explaining the contribution of common genetic variants to childhood psychiatric traits. We highlight recent GWASs which have identified the first robustly associated genetic variants for childhood psychiatric traits. Further, we describe results based on genetic

FIGURE 3 Genetic Correlations Between Childhood Psychiatric Disorders/Traits and Other Psychiatric Traits



Note: *Correlation estimates are separated by analysis type. Included in this plot are associations between traits for which genetic correlation estimates are provided in their respective studies. Similar traits were grouped by domain (see Supplementary Material, available online, for domain classifications). Trait pairs for which there were multiple estimates were meta-analyzed to a single estimate. Point sizes correspond to the inverse of the estimate standard errors such that larger sizes represent estimates with smaller standard errors. Estimates with overlapping points are labeled for the sake of clarity. Relevant results from Barkhuizen* et al.[121] *are not plotted, as they were not reported with standard errors in the original study, while estimates from Anttila* et al.[88] *are excluded owing to negative standard errors being reported in the original study. A correlation matrix of all estimates is also provided in the Supplementary Material, available online. ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PGC = Psychiatric Genomics Consortium. Please note color figure is available online.*

techniques including GREML and LDSC, which have enabled estimations of heritability based on measured SNPs and have shown substantial contributions of common genetic variants to many childhood psychiatric traits. Along with PRS, these methods have been used to study genetic overlap across traits and/or across time, which has resulted in the discovery of abundant genetic associations between multiple childhood psychiatric traits as well as between childhood and adult traits, providing evidence for the presence of shared coheritability.

On the whole, the identification of trait-associated variants appears to be associated with increasing sample sizes (Table S1, available online). Many GWASs in this review that did not identify significant variants were likely underpowered. An increase in collaborative efforts and consortia-focused analyses have resulted in increasing sample sizes over the last few years, resulting in the identification of the first robust genetic risk variants for ASD and ADHD. This suggests similar outcomes for other childhood traits in the near future. It is important to highlight that large sample sizes for traits including ADHD and ASD were achieved by combining childhood and adult samples. This increases the power to detect trait-associated variants if these disorders are genetically similar/identical in childhood and later life. Studies have shown moderate to strong correlations between adult depression and anxiety and childhood emotional problems[50] as well as between adult ADHD and childhood ADHD, suggesting similar underlying architecture.[38] Further, GWASs of ADHD identified significant loci in combined analyses, but not in separate analyses, of adult and childhood ADHD. This was despite the fact that heritability estimates were slightly higher in the separate samples compared with the combined samples,[38] further highlighting the importance of statistical power to detect effects. Nevertheless, there is considerable need for well-powered GWASs with childhood samples and/or age-stratified analyses, as other traits may have different architecture across development. Other explanations for the lack of significant findings include heterogeneity and measurement error in phenotype definitions.[122] Heterogeneity may be introduced by the use of different raters and instruments to measure the same psychiatric traits. For example, varying degrees of concordance

have been reported for measures of aggression depending on rater and item content of available measures.[123,124] Rather than combining different measurements to achieve large sample sizes, more stringent phenotyping to obtain more homogeneous phenotypes may contribute to the identification of associated variants and SNP-based heritability.[122,123] Results from GWASs can also be informative in understanding the underlying genetic architecture and biological mechanisms of childhood psychiatric traits, and the identification of genome-wide significant hits is an important first step, as observed by the implication of dopamine regulation in ADHD.[19] Further, ADHD GWAS results have been used to investigate potential genes and pathways that can be targeted by existing drugs.[125] This study implicated signal transduction and cell adhesion as potential treatment targets, and future studies for other childhood psychiatric disorders may provide potential novel avenues for treatment as well.

For all traits considered in this review, SNP-based heritability estimates from LDSC and GREML are substantially lower than estimates from twin studies. This is in part because both methods are limited to additive effects of causal variants tagged by the common SNPs on current DNA genotyping arrays used in GWAS. Analyses of body mass index (BMI) and height suggest that the difference between family- and SNP-based heritability estimates may be explained by rare variants.[126] It is likely that this also holds for other complex traits such as childhood psychiatric traits. Indeed, increased burden of rare and de novo variants has been associated with disorders such as ASD, ADHD, and OCD,[127-129] and children carrying specific pathogenic-/disorder-associated copy number variations (CNVs) have increased frequency of psychiatric disorders, including ASD and ADHD as well as anxiety disorders and oppositional defiant disorders.[130,131] Sample sizes are still generally low for such analyses in childhood traits but may increase in the future as the cost of sequencing decreases, providing new opportunities to broaden our insight into the genetic architecture of these traits.

A major observation of the current review is a range of within- and cross-trait associations in childhood psychopathology using both PRS and GREML/LDSC. Childhood psychiatric traits were associated with other childhood traits as well as adult disorders, including MDD and schizophrenia. Further, modeling of genome-wide joint architecture of psychiatric disorders identified a factor composed of childhood-onset disorders, including ADHD, ASD, and Tourette syndrome, as well as MDD.[87] There was also evidence of a general psychopathology (p) factor,[83] which has been shown to explain a substantial amount of phenotypic and genetic variance across multiple childhood and adult psychiatric disorders.[132,133] Combined with the observed genetic overlap, these findings demonstrate a contribution of pleiotropic genetic effects to the development of psychopathology and may suggest shared biological pathways. The finding of cross-trait associations may be informative for the validity of current diagnostic practices, which define disorders in distinct categories based on the symptoms displayed.[134] Commonly occurring symptom overlap combined with substantial genetic overlap across disorders suggests a spectrum of psychopathology and thus the need for a re-evaluation of current diagnostic categories, as they may not be accurate.[135,136]

Along with pleiotropic effects, recent studies have also provided evidence of specific genetic effects contributing to psychopathology. A recent study has shown differential genetic and phenotypic associations between ADHD and neurodevelopmental disorders versus externalizing or internalizing disorders after accounting for the p factor in a large sample.[137] Another study showed that the p factor explained considerable variance in childhood psychopathology measures, but inclusion of more specific emotional, behavioral, and neurodevelopmental factors explained even more variance than just the p factor alone. The amount of (phenotypic) variance explained by the different factors differed depending on the childhood measure. For instance, for ADHD, most of the variance was explained by the p factor, while variance in anxiety/mood problems was explained more by the emotional factor. The strength of associations between PRSs of different psychiatric traits and these factors also varied depending on the PRS and whether the associations were tested in a univariate or a multivariate model that included PRSs of other traits. For example, depression PRSs were not independently associated with the p factor but were associated with the emotional problems factor, while schizophrenia and ADHD PRSs were associated with both the p factor and more specific neurodevelopmental and emotional problem factors.[54,59] Combined with the evidence of pleiotropy described above, these results suggest the existence of both general and specific genetic factors/variants that are involved in psychiatric etiologies. Future studies combining multivariate methodology with molecular data should focus on investigating and identifying both shared and specific genetic variants across childhood traits.

Some of the observed PRS associations are present at different ages across childhood and adolescence.[60,67,102,109] This suggests the presence of genetic variants affecting psychopathology across the lifetime, explaining not only homotypic continuity of the same disorder across time, but also

heterotypic continuity, where one disorder precedes or predicts another at a later time.[138] This may provide opportunities to identify children at risk for a chronic course early and provide targeted treatment. Although they currently explain too little variance to be clinically valid for individual risk prediction, there is potential for PRSs to be combined with other risk factors to build a more complete picture of risk profiles and eventually improve prediction of disorder risk. Schizophrenia PRS have shown improved predictive value of psychosis in people at high risk.[100] Predictive accuracy will likely increase with increasing sample sizes of genetic studies, and the inclusion of PRSs of correlated traits in multitrait analyses has been shown to improve predictive power for ASD and will likely show similar results for other traits.[20]

We conducted a further search on the bioRxiv and medRxiv servers for relevant studies that were not included with the main results, as they were yet to undergo peer review. We identified 17 additional studies initially published on either server from March 2019 to September 2020. In these studies, there were no genetic variants detected for aggression,[123] internalizing symptoms,[139] obsessive-compulsive traits,[140] and total childhood problem scores,[141] although 6 loci were identified in a cross-disorder meta-analysis of ADHD, ASD, OCD, and Tourette syndrome,[142] and 14 loci were identified in a cross-disorder analysis of MDD and ADHD.[143] Reported SNP heritabilities were similarly low to moderate, ranging from 2% to 21% for traits including ADHD, obsessive-compulsive traits, aggression, internalizing problems, and psychotic symptoms.[123,139-141,143-146] Again, there was evidence of both within- and cross-trait genetic associations.[123,140,142-153,159]

Overall, we identified numerous positive findings regarding the genetics of childhood psychopathology, particularly relating to cross-trait genetic overlap. However, we would be remiss not to address the important issue of publication bias in our reporting. Publication bias occurs when results from research influence whether or not it is published, such that published studies are skewed in favor of those with positive results. While not formally assessed in this review, we cannot rule out the possibility that our findings are affected by this phenomenon. In addition, while we did not filter on genetic ancestry, there was a clear Eurocentric focus on populations investigated, with a handful of studies also investigating East Asian populations. Future studies and data collection plans should include samples from more diverse ancestry. The accuracy of methods such as genetic risk prediction is reduced when discovery and target samples have divergent ancestry,[154,155] which may preclude the use of genomic medicine in people of other ancestries.

The results of this review show that understanding of the genetic architecture of childhood psychiatric traits is increasing. Common trait-associated variants are starting to be identified, and studies show abundant genetic overlap between multiple psychiatric traits. Many challenges remain to further increase our understanding of the genetic architecture of childhood psychiatric traits. Increasing sample sizes in diverse ancestries to identify more trait-associated variants is crucial and may be achieved in a variety of ways. For instance, genetic data can be collected in studies that do not have the identification of genetic variants as a primary aim, such as clinical trials and randomized controlled trials; this may also lead to better prediction of treatment outcomes. Moreover, the harmonization of data across studies and study types is crucial to maximize power to detect effects.[156,157] Continuation of efforts of large-scale collaborative consortia to collect longitudinal data beyond what are currently available is also important. Findings from genetic studies have the potential to impact disease prediction in children at risk, allowing for the possibility of earlier interventions, which may enable them to have a more favorable course.

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