

Attention-Deficit/Hyperactivity Disorder: Diagnosis, Lifespan, Comorbidities, and Neurobiology

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In this report, we provide an evidence-based overview of attention-deficit/hyperactivity disorder (ADHD), including diagnosis, prevalence, developmental expression of symptoms, persistence, the heterogeneity of functional outcome, impairment in afflicted adults, psychiatric comorbidity, pathophysiology, genetics, psychosocial and biologic risk factors, and neurobiology. Attention-deficit/hyperactivity disorder is an early-onset, highly prevalent neurobehavioral disorder, with genetic, environmental, and biologic etiologies, that persists into adolescence and adulthood in a sizable majority of afflicted children of both sexes. It is characterized by behavioral symptoms of inattention, hyperactivity, and impulsivity across the life cycle and is associated with considerable morbidity and disability. Comorbidity is a distinct clinical feature of both childhood and adult ADHD. Although its etiology remains unclear, emerging evidence documents its strong neurobiologic and genetic underpinnings. Despite the high diagnostic reliability and the robust evidence of the validity of ADHD, there are many underlying issues that remain to be resolved. These include establishing developmentally appropriate diagnostic criteria at older ages, further elaborating the impact of gender on symptom expression, and examining risk and protective factors in relationship to prevention or amelioration of ADHD as well as related functional impairments.

Key words attention-deficit/hyperactivity disorder; comorbidity; diagnosis; neurobiology.

Attention-deficit/hyperactivity disorder (ADHD) is the most common emotional, cognitive, and behavioral disorder treated in youth.^{1,2} Epidemiological studies indicate that ADHD is a prevalent disorder affecting from 4% to 7% of children worldwide, including the United States, New Zealand/Australia, Germany, and Brazil.³ Although previously thought to remit largely in adolescence, a growing literature supports the persistence of the disorder and/or associated impairment into adulthood in a majority of cases. It is a major clinical and public health problem because of its associated morbidity and disability in children, adolescents, and adults.² Data from cross-sectional, retrospective, and follow-up studies indicate that youth with ADHD are at risk for developing other psychiatric difficulties in childhood, adolescence, and adulthood, including delinquency as well as mood, anxiety, and substance use disorders.⁴

Early reports

The first coherent description of ADHD was by George Still⁵⁻⁷ in the Coombs lectures of 1902. He described an “abnormal defect in moral control in children.” Moral control was defined as “the control of action in conformity with the idea of the good of all ... (that) can only exist when there is a cognitive relationship to the environment.” Thus, moral control required a “consciousness” that informed the capacity of “inhibitory volition.”⁵⁻⁷ Other early observations on the relationship between behavioral disorders and cerebral trauma or encephalitis supported theories of a biologic etiology. For example, Strecker and Ebaugh⁸ and Ebaugh and Franklin⁹ noted behavior disorders, including hyperkinesis, explosive behavior, fatigability, and attention deficit, after acute epidemic encephalitis and cerebral trauma in children.

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Diagnostic Criteria

In the 1930s, hyperkinesis, impulsivity, learning disability, and short attention span were described as “minimal brain damage”—and later as “minimal brain dysfunction”—due to similarities to patients with frank central nervous system (CNS) injuries. In the 1950s, this label was modified to “hyperactive child syndrome” and then “hyperkinetic reaction of childhood” in Diagnostic and Statistical Manual of Mental Disorders (DSM)-II in 1968. Each of these labels and sets of criterion were focused exclusively on children and placed the greatest emphasis on motoric hyperactivity and overt impulsivity as hallmarks of the disorder.

The DSM-III represented a paradigm shift as it began to emphasize inattention as a significant component of the disorder. The DSM-III definition also recognized developmental variability presentation of the disorder at different ages. DSM-III introduced a residual type of ADHD if the remaining symptoms continued to cause significant levels of impairment. DSM-IV now defines 3 subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and a combined subtype. Criteria for each DSM-IV subtype require 6 or greater of 9 symptoms in each respective category. There are 4 additional criteria that include age of onset by 7, ADHD-specific adaptive impairments, pervasiveness, and separation from other existing conditions. The combined subtype is the most commonly represented subgroup accounting for from 50% to 75% of all ADHD individuals, followed by the inattentive subtype (20%–30%), and the hyperactive-impulsive subtype (less than 15%).^{10–13}

Factor analyses have revealed that ADHD is comprised of 2 separate dimensions of symptoms (hyperactive/impulsive and inattentive).¹⁴ Accordingly, DSM-IV moved away from the unitary model of DSM-III-R and returned to a model with separate dimensions. In addition, the 2 dimensions are associated with a different developmental course, comorbid disorders, sex ratios, and forms of functional impairment. In a multivariate analysis that included ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), anxiety and depressive symptoms, hyperactive/impulsive symptoms were strongly related to Children’s Global Assessment Scores and inattentive symptoms were related to academic impairment. Further analysis revealed that both combined and inattentive types of ADHD were associated with significant social impairment. Cluster analyses revealed the 3 subtypes now codified in DSM-IV.¹⁴

Children, adolescents, and adults with the inattentive subtype of ADHD are more likely to be female and have fewer other emotional or behavioral problems compared with the other subtypes. Youth with prominent inattentive problems as part of their ADHD (combined or inattentive subtype) have greater academic impairment compared with those with predominate hyperactivity/impulsivity. The combined-type ADHD individuals have more co-occurring psychiatric and substance abuse disorders and are the most impaired overall.

Diagnostic Considerations

The diagnosis of ADHD is made by careful clinical history.¹⁵ A child with ADHD is characterized by a considerable degree of inattentiveness, distractibility, impulsivity, and often hyperactivity that is inappropriate for the developmental stage of the child. Although ADHD is often first observed in early childhood, many overactive toddlers will not develop ADHD.¹⁶ Other common symptoms include low frustration tolerance, shifting activities frequently, difficulty organizing, and daydreaming. These symptoms are usually pervasive; however, they may not all occur in all settings. Children with predominately inattentive symptoms may have more difficulties in school and in completing homework, and somewhat fewer difficulties with peers or family. Conversely, children with excessive hyperactive or impulsive symptoms may do relatively well in school but have difficulties at home or in situations with less guidance and structure.

Adults must have childhood-onset, persistent, and current symptoms of ADHD to be diagnosed with the disorder. Adults with ADHD often present with marked inattention, distractibility, organization difficulties, and poor efficiency, which culminate in life histories of academic and occupational failure.^{4,13}

Rating scales are extremely helpful in documenting the individual profile of ADHD symptoms as well as assessing the response to treatments. It is important to emphasize that they should not be used for diagnosis without careful clinical confirmation and elicitation of the other criteria necessary for diagnosis. Although neuropsychological testing is not relied upon to diagnose ADHD, it may serve to identify particular weaknesses within ADHD¹⁷ or specific learning disabilities co-occurring with ADHD (for review see Barkley¹⁵).

A thorough review of rating scales for ADHD was recently published.¹⁸ Rating scales are available for all age groups and can be useful in assessing and monitoring home, academic, and occupational performance.

In general, ADHD rating scales have evolved over the last few decades in a manner consistent with the evolution of understanding and the general shift from hierarchal to nonhierarchal models of diagnosis in DSM. For example, there has been a growing appreciation of the relative independence of ADHD and aggression dimensions.¹⁹ Factor analyses, including the DSM field trials, have consistently found that these are separate dimensions.¹⁴

Increasingly, there has been a remarkable congruence of opinion in this area, with a number of the most widely used scales consisting of Likert ratings of the existing DSM-IV criteria.²⁰ There are 2 types of scales in wide use, the so-called “narrow” scales that are specific for ADHD and “broad” scales that measure additional dimensions, including comorbidity.²¹ The broad scales are useful for separating straightforward and complex cases, and the narrow scales are most useful for honing in on exclusively ADHD dimensions—for diagnosis and to monitor specific responses to treatment.

In looking to the future, there are proposals to expand the set of diagnostic symptoms to include executive functions (such as time management and multitasking), especially in older individuals.²² In fact, the symptom “often has difficulties organizing” is the most complex DSM item and appeared for the first time in DSM-IV. Field trials will have to clarify whether the executive function items identify a somewhat different population or are developmentally analogous to current criteria.

Prevalence of ADHD

Prevalence estimates of childhood ADHD in the USA are estimated to be 5% to 8%.²³ Estimates vary predictably depending on methodology. Definitions that require both symptom dimensions (hyperactivity/impulsivity and inattention) are more restrictive than those that require only one of these dimensions. Thus, estimates based on pre-DSM-III definitions or the International Classification of Diseases (ICD) codes of hyperkinetic disorder produce lower estimates. In addition, the surveys that estimate based on symptoms alone and do not include impairment yield higher estimates.¹² As recently reviewed by Faraone et al,²⁴ other factors that affect apparent prevalence estimates include pervasiveness criteria, informants (teacher, parent, and child), use of rating scales versus clinical interviews, and ascertainment issues. Community samples have higher rates than school samples.²⁵

Gender and age of the sample also affect estimates of prevalence. Girls more commonly have the inattentive type and also less commonly have accompanying

ODD/CD and disruptive disorders, factors leading to lower rates of diagnosis. The original descriptions were derived from a child-focused perspective and do not reflect what are thought to be more salient aspects of adult ADHD: the executive function disorders of poor organization, poor time management, and memory disturbance associated with academic and occupational failure. The lack of appropriate description of adult symptoms may reduce the true prevalence of ADHD in adulthood.

While there is a popular conception that ADHD is a cultural phenomenon, much of the cross-cultural disagreement has been due to criterion variance. In a scholarly review, Faraone et al²⁴ reviewed 20 US studies and 30 non-US studies. The results revealed that the prevalence in non-US studies was at least as high as that in US studies, especially when using DSM-IV criteria. In addition, studies of ADHD outside of the US have reported remarkable concordance with those of the US in external correlates of diagnosis, such as the pattern of adaptive impairments and neuropsychologic deficits; degree of familiarity; and estimation of the magnitude of genetic influence; association of specific candidate genes; structural, functional, and molecular imaging findings; and response to specific pharmacological treatment.²⁶

Despite the existence of studies from 5 continents, there is a paucity of studies in developing countries. Based on the higher prevalence of psychosocial risk factors in these countries, there may be a higher prevalence of ADHD and other disorders. Epidemiological studies in developing countries are needed to determine the nature of the condition in these countries.

Impact of Normal Development on ADHD Symptom Expression

We addressed the relative rate of decline of the core symptoms of ADHD from childhood into early adulthood to offer a developmental perspective on symptom decline.²⁷ As seen in Figure 1 we found a differential rate of symptomatic decline for inattention and hyperactivity/impulsivity. Although symptoms of inattention declined at a very modest rate, those of hyperactivity and impulsivity remitted much more abruptly. Hart et al²⁸ also documented a similar pattern of ADHD-subtype specific persistence: the mean number of hyperactive/impulsive symptoms declined with age, whereas the mean number of inattentive symptoms remained stable from age 8 to 15 years.

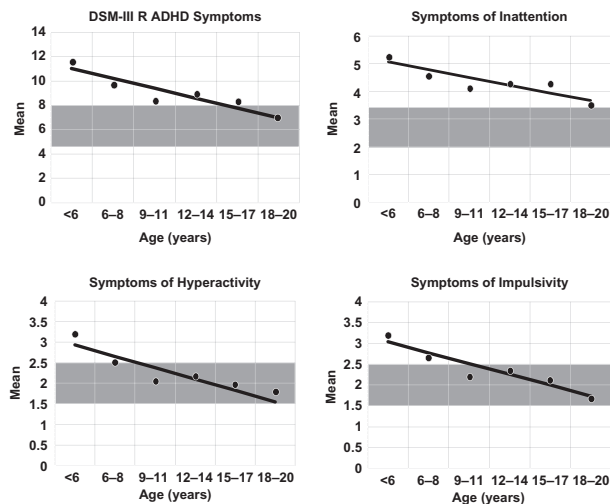


Figure 1. Age-dependent decline of symptoms of attention-deficit/hyperactivity disorder. Adapted from Biederman et al.²⁷

Follow-up Studies of ADHD

Samples ascertained before the publication of DSM-III relied on earlier definitions that highlighted hyperactivity as a hallmark of ADHD. Since it is hyperactivity that wanes earliest, it may be that older samples were enriched with subjects more likely to remit from ADHD than individuals identified today. There is evidence for this hypothesis in the data. A combined estimate of the persistence of ADHD is shown in the Table I. The persistence rate was lowest in studies ascertained according to DSM-II attention-deficit disorder and highest in those studies ascertained according to DSM-III-R ADHD.

Heterogeneous Outcome in Persistent ADHD

The adolescent and young adult with ADHD is at risk for school failure, emotional difficulties, poor peer relationships, and trouble with the law.^{29,30} Factors identifiable in younger youth that predict the persistence of ADHD into adulthood include familiarity with ADHD and psychiatric comorbidity—particularly aggression or delinquency problems.^{28,29,31,32}

Although the literature provides compelling evidence that the diagnosis of ADHD in childhood predicts persistent ADHD and poor outcome in adolescence, these findings also suggest that all children with ADHD do not share such a compromised outcome. The discussion thus far has not addressed a related clinical question: can the functioning of children with ADHD normalize in the context of persistent ADHD? We analyzed data from a 4-year-longitudinal study of referred children and adolescents with ADHD to assess

normalization of functioning and its predictors among boys with persistent ADHD.³³

Using indices of emotional, educational, and social adjustment, we found that 20% of children with persistent ADHD functioned poorly at follow-up in all 3 domains, 20% did well in all 3 domains, and 60% had intermediate outcomes.³³ These findings suggested that the syndromic persistence of ADHD is not associated with a uniform functional outcome but leads instead to a wide range of emotional, educational, and social adjustment outcomes that can be partially predicted by exposure to maternal psychopathology, larger family size, psychiatric comorbidity, and impulsive symptoms.³³

Related Impairment in Untreated Adults With Persistent ADHD

If adult ADHD is a clinically significant disorder, then ADHD adults should show functional impairments in multiple domains. Several studies suggest this to be true. In an early study, Borland and Heckman³⁴ compared ADHD adults with their non-ADHD siblings. The ADHD adults had lower socioeconomic status, more work difficulties, and more frequent job changes. Morrison^{35,36} compared ADHD adults with psychiatric controls matched for age and sex. The ADHD adults had fewer years of education and lower rates of professional employment. Similarly, others have shown that among patients with substance use disorders, ADHD predicts social maladjustment, immaturity, fewer social assets, lower occupational achievement, and high rates of separation and divorce.^{37,38}

Murphy and Barkley³⁹ compared 172 ADHD adults with 30 non-ADHD adults. The ADHD adults reported more psychological maladjustment, more speeding violations, and more frequent changes in employment. Compared with the non-ADHD adults, more ADHD adults had had their drivers license suspended, had performed poorly at work, and had quit or been fired from their job. Moreover, the ADHD adults were more likely to have had multiple marriages.

Given that academic underachievement is a well-known correlate of ADHD in childhood,⁴⁰ ADHD adults ought to have histories reflecting school problems. Our work^{41,42} demonstrated that compared with control adults, ADHD adults had significantly higher rates of repeated grades, tutoring, placement in special classes, and reading disability. Similarly, Murphy and Barkley³⁹ showed that ADHD adults had histories marked by poorer educational performance and more frequent school disciplinary actions against them.

Table I. Follow-Up Studies of ADHD

Study	Baseline Mean Age	Follow-Up Mean Age	Follow-Up Diagnostic Criteria	Persistence N%	
DSM-II Diagnosis at Baseline					
Mendelson ⁽⁸²⁾ a	9.9	13.4	DSM-II ^a	42	50
Borland ⁽³⁴⁾ a	7.5	30.4	DSM-II ^a	10	50*
Mannuzza ⁽⁸³⁾	7.9	17.4	DSM-III	12	33
Gittelman ⁽²⁹⁾	9.3	18.3	DSM-III	31	31
Mannuzza ⁽⁸⁴⁾	7.3	18.5	DSM-III	21	22
Mannuzza ⁽⁸⁵⁾	9.3	25.5	DSM-III, IIIR	7	8
Mannuzza ⁽⁸¹⁾	7.3	24.1	DSM-IIIR	3	4
Lambert ⁽⁷⁷⁾	7.7	14.3	DSM-III	25	43
Lambert ⁽⁸⁶⁾	9.3	18.3	DSM-III	47	80*
Feldman ⁽⁸⁷⁾ a	10.0	15.5	DSM-II ^a	35	43
August ⁽¹⁹⁾ a	10.7	14.2	DSM-III	19	86*
Weiss ⁽⁸⁸⁾ a	6–12	25.1	DSM-III	42	66*
Yan ⁽⁸⁹⁾ a	10.0	25.5	DSM-IIIR ^d	140	70*
Combined estimate; Rate (95%CI)				40 (36–45)	
DSM-III Diagnosis at Baseline					
Cantwell ⁽⁹⁰⁾	5.5	9.7	DSM-III	28	80
Offord ⁽⁹¹⁾	4–12	8–16	DSM-III	16	34
Claude ⁽⁹²⁾	7.3	19.7	DSM-IIIR	26	50
Rasmussen ⁽⁹³⁾ c	7	22	DSM-IV	28	56*
Rasmussen ⁽⁹³⁾ c	7	22	DSM-IV	24	48
Combined estimate; Rate (95%CI)				52 (39–67)	
DSM-IIIR Diagnosis at Baseline					
Barkley ⁽⁷⁹⁾ b	4–12	14.9	DSM-IIIR	88	72
Barkley ⁽⁷⁹⁾ b	4–12	14.9	DSM-IIIR	102	83*
Barkley ⁽⁸⁰⁾ b	4–12	21.1	DSM-IV	78	58
Barkley ⁽⁸⁰⁾ b	4–12	21.1	DSM-IV	89	66*
Hart ⁽²⁸⁾	9.4	10.4	DSM-IIIR	89	77
Hart ⁽²⁸⁾	9.4	11.4	DSM-IIIR	90	85
Hart ⁽²⁸⁾	9.4	12.4	DSM-IIIR	92	84
Biederman ⁽⁷⁸⁾	10.5	14.5	DSM-IIIR	109	85*
Biederman ⁽⁷⁸⁾	10.5	14.5	DSM-IIIR	78	61
Combined estimate; Rate (95%CI)				74 (69–79)	

*Residual ADHD diagnosis.

^aDiagnostic system not stated but completed in DSM-II era.

^bDiagnoses shown to be equivalent to DSM-IIIR.

^cDiagnoses shown to be equivalent to DSM-III.

^dDiagnostic system not stated but completed in DSM-IIIR era; adapted from Faraone S, Biederman J, Mick E: A Re-evaluation of the age dependent decline of attention deficit hyperactivity disorder. *American Journal of Psychiatry* 2003.

Psychiatric Comorbidity Oppositional Defiant Disorder and Conduct Disorder

There are important nosologic distinctions between attention and hyperactivity per se and that of associated symptoms common to the disruptive behavioral disorder category. Oppositional defiant disorder is characterized by a pattern of negativistic, hostile, and defiant behavior.¹⁶ Attention-deficit/hyperactivity disorder and ODD/CD have been found to co-occur in 30% to 50% of cases in both epidemiologic and clinical samples.⁴³ In contrast,

CD is a more severe disorder of habitual rule breaking defined by a pattern of aggression, destruction, lying, stealing, or truancy.

A recent follow-up study of children with ADHD confirmed that the overlap of CD and ODD was asymmetric.⁴⁴ While CD was almost always comorbid with and was preceded by ODD, ODD at baseline was a weak predictor of new onsets of CD at follow-up into midadolescence 4 years later. In addition, while CD was a strong predictor of substance abuse at follow-up, ODD without CD was not.

Mood Disorders

Major depression in a child may be apparent from a sad or irritable mood or a persistent loss of interest or pleasure in the child's favorite activities. Other signs and symptoms include physiologic disturbances, such as in changes in appetite and weight, abnormal sleep patterns, psychomotor abnormalities, fatigue, and diminished ability to think, as well as feelings of worthlessness or guilt and suicidal preoccupation. Associated features of depression in children include school difficulties, school refusal, withdrawal, somatic complaints, negativism, aggression, and antisocial behavior. Conduct disorder and substance abuse commonly co-occur with depression in older children and adolescents.

Classical mania in adults is characterized by euphoria, elation, grandiosity, and increased energy. However, in many adults and most children, mania is more commonly manifested by extreme irritability or explosive mood with associated poor psychosocial functioning that is often devastating to the patient and family. In milder conditions, additional symptoms include unmodulated high energy such as a decreased sleep, overtalkativeness, racing thoughts, or increased goal-directed activity (social, work, school, and sexual) or an associated manifestation of markedly poor judgment, such as thrill seeking or reckless activities. It is often difficult to differentiate juvenile mania from ADHD, CD, depression, and psychotic disorders because of overlapping developmental features. In adolescent-onset mania, one may obtain a clearer picture of childhood onset disorders such as ADHD, whose symptoms may precede the first manic episode by many years.

In several prospective studies, our group at Massachusetts General Hospital examined rates of depression in children with ADHD.⁴⁵ In a 4-year follow-up, lifetime rates of comorbid depression in children with ADHD increased from 29% at baseline to 45% at average age 15. A baseline diagnosis of major depression predicted lower psychosocial functioning, a higher rate of hospitalization, and impairments in interpersonal and family functioning. Similarly, mania was detected in 11% of children at baseline (mean age 11) and increased to 23% at 4-year follow-up. Children with ADHD with comorbid mania at either baseline or follow-up assessment had other correlates expected in mania, including additional psychopathology, psychiatric hospitalization, severely impaired psychosocial functioning, and a greater family history of mood disorders.

Childhood Anxiety Disorders

Anxiety symptoms are generally expressed in 4 domains: cognitive, affective, physical, and behavioral.⁴⁶ Cognitive elements may range from rumination and vigilant apprehension to catastrophic thinking, such as the anticipation of great embarrassment or threat to life. Behavioral features may include agitation, tantrums, attention seeking, overdependence, and rituals. Many of these symptoms may be misinterpreted because of overlap with ADHD. Childhood anxiety disorders are often not suspected in an overactive child, just as ADHD is often not assessed in inhibited children. When present, both contribute to social, behavioral, and academic dysfunction. In addition, anxiety may be associated with intense intrapsychic suffering. Thus, having both ADHD and anxiety disorders may substantially worsen the outcome of children with both disorders. In the Massachusetts General Hospital (MGH) follow-up study, children with ADHD with comorbid anxiety disorder had increased psychiatric treatment, more impaired psychosocial functioning, and a greater family history of anxiety disorders.⁴⁷

Cognitive Performance and Learning Disabilities

Children with ADHD perform more poorly than controls on standard measures of intelligence and achievement.⁴⁸ In addition, children with ADHD perform more poorly in school than do controls, as evidenced by more grade repetitions, poorer grades in academic subjects, more placement in special classes, and more tutoring.^{49–51} The reported degree of overlap ranges from as low^{52,53} as 10% to as high as 92%.⁵⁴ The prevalence varies by definition, the more restrictive definition has a rate of 20% to 25%.

ADHD Plus Tics

Children with ADHD have higher rates of tic disorders,⁵⁵ which may contribute additional dysfunction due to distractions and social impairments directly attributable to the movements or vocalizations themselves. A number of studies have noted that anti-ADHD treatment is highly effective for ADHD behaviors, aggression, and social skill deficits in children with Tourette's Syndrome (TS) or chronic tics.

Substance Use Disorders

Combined data from retrospective accounts of adults and prospective observations of youth indicates that juveniles with ADHD are at increased risk for cigarette smoking and substance abuse during adolescence. Recent work

suggests that ADHD youth disproportionately become involved with cigarettes, alcohol, and then drugs.^{56,57} Individuals with ADHD, independent of comorbidity, tend to maintain their addiction longer compared with their non-ADHD peers.⁵⁸

Pathophysiology and Genetics

Genetics and ADHD

Because ADHD is believed to be highly genetic, studies of twins have been used to establish its heritability, or the degree to which this disorder is influenced by genetic factors. Based on numerous studies of twins, which varied considerably in methodology and definitions of ADHD, the mean heritability for ADHD was shown to be 77% (Figure 2).

Molecular Genetics Studies

Two approaches are used to evaluate the genetic etiology of ADHD: 1) the genome scan, which examines all chromosomal locations without a priori guessing as to which genes underlie ADHD and 2) the candidate gene approach, which examines 1 or more genes based on theory and empirical evidence. A genome-wide linkage scan in 204 nuclear families (853 individuals and 270 affected sibling pairs) suggests that regions 16p13 and 17p11 likely harbor risk genes for ADHD.⁵⁹

Seven candidate genes show statistically significant evidence of association with ADHD on the basis of the

pooled odds ratio (1.18–1.46) across studies: DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B, and SNAP-25.⁶⁰

Other Etiologic Factors

Biologic Adversity

Several biologic factors have been proposed as contributors to ADHD, including food additives/diet, lead contamination, cigarette and alcohol exposure, maternal smoking during pregnancy, and low birth weight. Although the Feingold Diet for ADHD was popularized by the media and accepted by many parents, systematic studies showed that this diet was ineffective and that food additives do not cause this disorder.⁶¹ Several investigators have shown that lead contamination can cause symptoms of ADHD. However, lead does not account for the majority of ADHD cases, and many children with high lead exposure do not develop ADHD. An emerging literature documents that maternal smoking and alcohol exposure during pregnancy, low birth weight, and psychosocial adversity are additional independent risk factors for ADHD.^{62,63}

Pregnancy and delivery complications (i.e., toxemia, eclampsia, poor maternal health, maternal age, fetal postmaturity, duration of labor, fetal distress, low birth weight, and antepartum hemorrhage) appear to have a predisposition for ADHD.⁶⁴ Several studies documented that maternal smoking during pregnancy is an independent risk factor for ADHD.^{63,65,66}

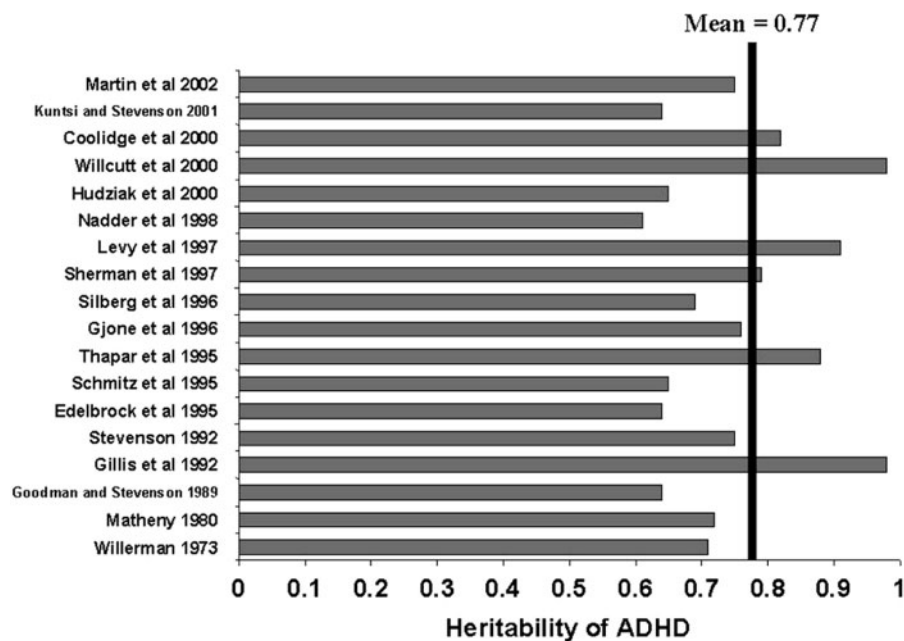


Figure 2. Heritability of attention-deficit/hyperactivity disorder. Adapted from Faraone et al.⁶⁰

Psychosocial Adversity

Compelling work by Rutter and colleagues⁶⁷ in the classic Isle of Wight studies revealed that the aggregate of adversity factors (i.e., severe marital discord, low social class, large family size, paternal criminality, maternal mental disorder, and foster care placement), rather than the presence of any single factor, led to psychopathology. Findings of more recent studies support the previous work of Rutter et al⁶⁷ and stress the importance of adverse family-environment variables as risk factors for ADHD.^{63,68} In one of these, chronic family conflict, decreased family cohesion, and exposure to parental psychopathology (particularly maternal) were more common in ADHD families compared with control families.⁶³ However, some of the findings are likely secondary to ADHD in the child and/or parent, rather than primary.

It remains unclear whether exposure to violence in childhood is a risk factor for ADHD. There are theoretic reasons to examine this potential association. Exposure to violence may act through psychosocial adversity but may also lead to permanent brain changes, based on the impact of prolonged exposure of the developing brain to steroid hormones.⁶⁹

It is important to note that, although many studies provide powerful evidence for the importance of psychosocial adversity in ADHD, such factors tend to emerge as universal predictors of children's adaptive functioning and emotional health, rather than specific predictors of ADHD. As such, they can be conceptualized as nonspecific triggers of an underlying predisposition or as modifiers of the course of illness.

Neurobiology of ADHD

The neurobiology of ADHD is not completely understood, although imbalances in dopaminergic and noradrenergic systems have been implicated in the core symptoms that characterize this disorder.^{70,71} As reviewed by Seidman et al,⁷² many brain regions are candidates for impaired functioning in ADHD. Prefrontal hypotheses in ADHD have primarily involved the dorsolateral prefrontal cortex, associated with organizational, planning, working memory, and attentional dysfunctions, and orbital lesions associated with social disinhibition and impulse control disorders.

While morphometric imaging studies cannot be used to make diagnoses, they are ideal for testing hypotheses about the locus of brain dysfunction in ADHD and provide direct assessments of brain structure and function. Structural imaging studies using computerized tomography or magnetic resonance imaging found evidence of structural brain abnormalities among ADHD patients, with the most

common findings being smaller volumes in frontal cortex, cerebellum, and subcortical structures. One of the most important neuroimaging studies of ADHD is that of Castellanos et al.⁷³ They found smaller total cerebral brain volumes from childhood through adolescence. This work suggested that genetic or early environmental influences on brain development in ADHD are fixed, nonprogressive, and unrelated to stimulant treatment. Limitations included the combining of both longitudinal and cross-sectional assessments. As reviewed by Bush et al,⁷⁴ numerous functional magnetic resonance imaging studies have reported dorsal anterior cingulate cortex hypofunction in ADHD on tasks of inhibitory control.

Brain imaging studies fit well with the concept that dysfunction in frontosubcortical pathways occurs in ADHD. Three subcortical structures implicated by the imaging studies (i.e., caudate, putamen, and globus pallidus) are part of the neural circuitry underlying motor control, executive functions, inhibition of behavior, and the modulation of reward pathways. These frontal-striatal-pallidal-thalamic circuits provide feedback to the cortex for the regulation of behavior.⁷⁵

The frontosubcortical systems pathways associated with ADHD are rich in catecholamines, which are involved in the mechanism of action of stimulant medications used to treat this disorder. A plausible model for the effects of medications in ADHD suggests that, through dopaminergic and/or noradrenergic pathways, these agents increase the inhibitory influences of frontal cortical activity on subcortical structures.⁷⁰

Imaging studies also implicate the cerebellum and corpus callosum in the pathophysiology of ADHD. The cerebellum contributes significantly to cognitive functioning, presumably through cerebellar-cortical pathways involving the pons and thalamus. The corpus callosum connects homotypic regions of the 2 cerebral hemispheres. Size variations in the callosum and volume differences in number of cortical neurons may degrade communication between these 2 hemispheres, which may account for some of the cognitive and behavioral symptoms of ADHD.^{73,76}

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