Attention-deficit/hyperactivity disorder

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Abstract | Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide. Throughout an individual's lifetime, ADHD can increase the risk of other psychiatric disorders, educational and occupational failure, accidents, criminality, social disability and addictions. No single risk factor is necessary or sufficient to cause ADHD. In most cases ADHD arises from several genetic and environmental risk factors that each have a small individual effect and act together to increase susceptibility. The multifactorial causation of ADHD is consistent with the heterogeneity of the disorder, which is shown by its extensive psychiatric co-morbidity, its multiple domains of neurocognitive impairment and the wide range of structural and functional brain anomalies associated with it. The diagnosis of ADHD is reliable and valid when evaluated with standard criteria for psychiatric disorders. Rating scales and clinical interviews facilitate diagnosis and aid screening. The expression of symptoms varies as a function of patient developmental stage and social and academic contexts. Although there are no curative treatments for ADHD, evidenced-based treatments can markedly reduce its symptoms and associated impairments. For example, medications are efficacious and normally well tolerated, and various non-pharmacological approaches are also valuable. Ongoing clinical and neurobiological research holds the promise of advancing diagnostic and therapeutic approaches to ADHD. For an illustrated summary of this Primer, visit: http://go.nature.com/J6jiwl

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Attention-deficit/hyperactivity disorder (ADHD; also known as hyperkinetic disorder) is a common disorder characterized by inattention or hyperactivity–impulsivity, or both. The evidence base for the diagnosis and treatment of ADHD has been growing exponentially since the syndrome was first described by a German physician in 1775 (REF. 1) (FIG. 1). In 1937, the efficacy of amphetamine use to reduce symptom severity was serendipitously discovered. In the 1940s, the brain was implicated as the source of ADHD-like symptoms, which were described as minimal brain damage in the wake of an encephalitis epidemic. In 1980, the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) created the first reliable operational diagnostic criteria for the disorder. These criteria initiated many programmes of research that ultimately led the scientific community to view ADHD as a seriously impairing, often persistent neurobiological disorder of high prevalence that is caused by a complex interplay between genetic and environmental risk factors. These risk factors affect the structural and functional capacity of brain networks and lead to ADHD symptoms, neurocognitive deficits and a wide range of functional impairments.

We now have many large and well-designed epidemiological, clinical and longitudinal studies that have clarified the features, co-morbidities and impairments associated with ADHD. These studies have created reliable and valid measurement tools for screening, diagnosis and monitoring of treatment. Likewise, rigorous clinical trials have documented the safety and efficacy of ADHD treatment, and it is now clear which ADHD treatments work, which do not and which require further study. In this Primer, we discuss the evidence base that has created a firm foundation for future work to further clarify the aetiology and pathophysiology of ADHD and to advance diagnostic and therapeutic approaches to this disorder.

Epidemiology

Age-dependent prevalence of ADHD

ADHD is a common disorder among young people worldwide. In 2007, a meta-analysis of more than 100 studies estimated the worldwide prevalence of ADHD in children and adolescents to be 5.3% (95% CI: 5.01–5.56)[2]. Three methodological factors explained this variability among studies: the choice of diagnostic criteria, the source of information used and the inclusion of a requirement for functional impairment as well as symptoms for diagnosis. After adjusting for these factors, a subsequent meta-analysis concluded that the prevalence of ADHD does not significantly differ between countries in Europe, Asia, Africa and the Americas, as well as in Australia[3]. Although other meta-analyses have found either lower or

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higher prevalence rates, these presented important limitations, such as the exclusive use of DSM criteria to diagnose ADHD and the use of simulated prevalence rates[4,5]. In addition, there is no evidence, worldwide, of an increase in the real prevalence of ADHD over the past three decades[3]. Despite the fact that both overdiagnosis and underdiagnosis are common concerns in medicine, the common public perception that ADHD is overdiagnosed in the United States might not be warranted[6].

ADHD also affects adults. Although the majority of children with ADHD will not continue to meet the full set of criteria for ADHD as adults, the persistence of either functional impairment[7] or subthreshold (three or fewer) impairing symptoms into adulthood is high[8]. For instance, on the basis of a meta-analysis of six studies, Simon and colleagues[9] found the pooled prevalence of ADHD to be 2.5% (95% CI: 2.1–3.1) in adults. In addition, studies in older adults have found prevalence rates in the same range[10,11], and prospective longitudinal studies support the notion that approximately two-thirds of youths with ADHD retain impairing symptoms of the disorder in adulthood[7] (FIG. 2).

Recent alterations to diagnostic criteria have had an impact on ADHD prevalence measures in both young and adult populations. In 2013, DSM-5 (REF. 12) included three important changes: first, increasing the age of onset from 7 years to 12 years; second, decreasing the symptom threshold for patients ≥17 years of age from six to five symptoms; and third, enabling ADHD to be diagnosed in the presence of an autism spectrum disorder. The third change is consistent with the reconceptualization of ADHD in DSM-5 as a neurodevelopmental disorder rather than a disruptive behavioural disorder. Overall, these new criteria have yielded an increase in ADHD prevalence, which is insubstantial for children but is likely to have had a more considerable effect on diagnosis rates in adults[13,14].

Sociodemographic factors

Alongside age, other factors such as sex, ethnicity and socioeconomic status are also important when considering the prevalence of ADHD. In children and adolescents, ADHD predominantly affects males and exhibits a male-to-female sex ratio of 4:1 in clinical studies and 2.4:1 in population studies[2]. In adulthood, this sex discrepancy almost disappears[14], possibly owing to referral biases among treatment-seeking patients or to sex-specific effects of ADHD over the course of the disorder.

Larsson and colleagues[15] found that low family income predicted an increased likelihood of ADHD in a Swedish population-based cohort study of 811,803 individuals. However, this finding does not necessarily support the conclusion that socioeconomic status increases the risk of ADHD because the disorder runs in families and leads to educational and occupational underattainment. Underemployment could in turn lead to the over-representation of socioeconomic disadvantage among families affected by ADHD[16].

Finally, although the true prevalence of ADHD does not vary with ethnicity, some studies have inconsistently associated ethnicity with ADHD owing to referral patterns and barriers to care that disproportionately affect particular ethnic groups[17–19].

Mechanisms/pathophysiology

Genes and environment

Genetic epidemiology. ADHD runs in families, with parents and siblings of patients with ADHD showing between a fivefold and tenfold increased risk of developing the disorder compared with the general population[20,21]. Twin studies show that ADHD has a heritability of 70–80% in both children and adults[22–25], with little or no evidence that the effects of environmental risk factors shared by siblings substantially influence aetiology[26]. Environmental risk factors play their greatest part in the non-shared familial environment and/or act through interactions with genes and DNA variants that regulate gene expression — such as those in promoters, untranslated regions of genes or loci that encode microRNAs.

Although ADHD is a categorical diagnosis, results from twin studies suggest that it is the extreme and impairing tail of one or more heritable quantitative traits[27]. The disorder is influenced by both stable genetic factors and those that emerge at different developmental stages from childhood through to adulthood[28]. Thus, genes contribute to the onset, persistence and remission of ADHD, presumably through stable neurobiological deficits as well as maturational or compensatory processes that

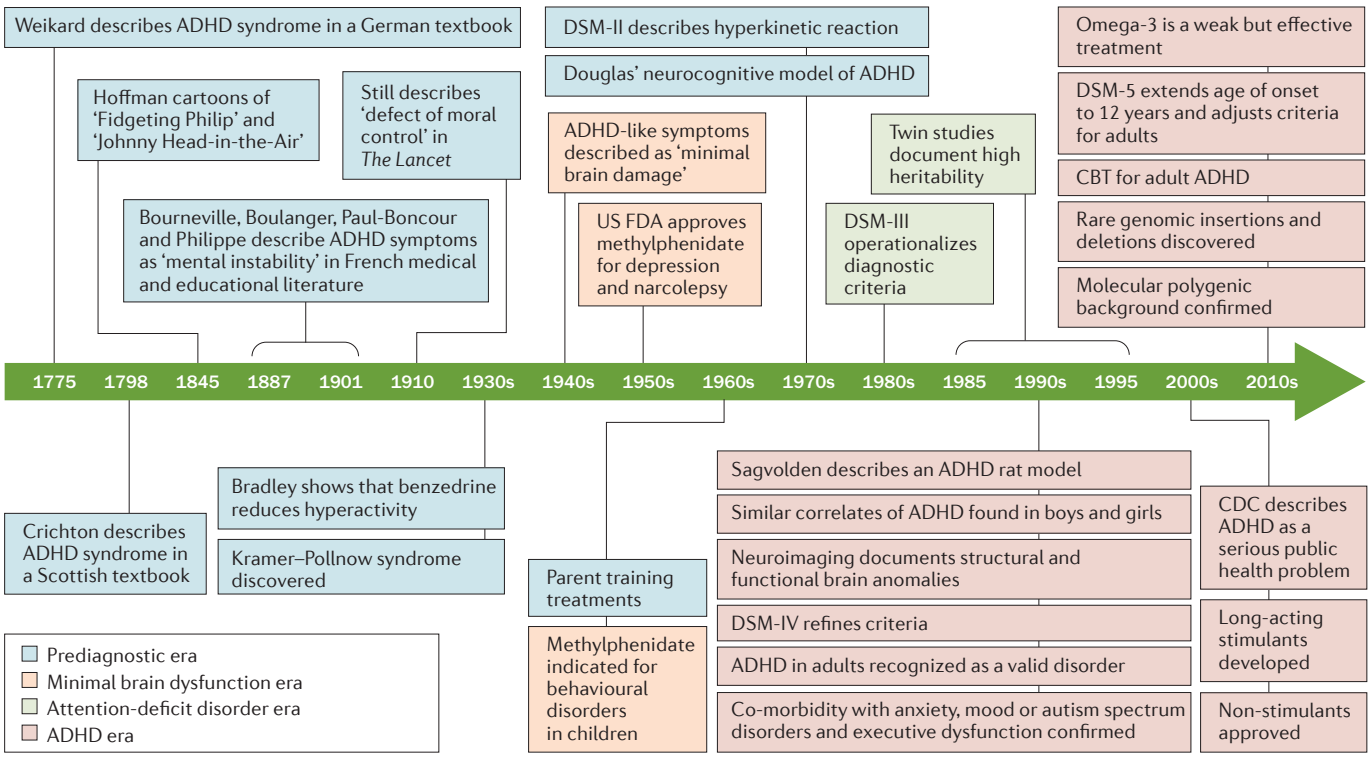

Figure 1 | **The history of attention-deficit/hyperactivity disorder.** Attention-deficit/hyperactivity disorder (ADHD) 'syndromes' have been described in the medical literature since the eighteenth century, but the growth of systematic research required the development of operational diagnostic criteria in the late twentieth century. This schematic outlines selected important developments in the history of ADHD research. CBT, cognitive–behavioural therapy; CDC, Centers for Disease Control and Prevention; DSM, *Diagnostic and Statistical Manual of Mental Disorders*.

influence development. The inattention and hyperactivity or impulsivity that characterize ADHD are separate domains of psychopathology, with a genetic correlation of around 0.6, reflecting substantial genetic overlap but also genetic influences that are domain specific[29]. Shared genetic factors also account for the co-occurrence of ADHD with emotional dysregulation — an independent source of impairment in ADHD[30,31]. Family and twin studies have also demonstrated that genetic influences are shared between ADHD and a wide range of other neurodevelopmental and psychopathological traits and disorders, including conduct disorder and problems[32], cognitive performance[33], autism spectrum disorders[34] and mood disorders[35,36].

Molecular genetics. On the basis of data from genome-wide association studies (GWAS), approximately 40% of the heritability of ADHD can be attributed to numerous common genetic variants[37]. In polygenic risk score analysis, the genetic signals attributed to common variants derived from a discovery sample are used to predict phenotypic effects in a second sample. The polygenic risk for clinically diagnosed ADHD predicts ADHD symptoms in the population more broadly[38], confirming the conclusion from twin studies that the genes determining the diagnosis of ADHD also regulate the expression of subclinical levels of ADHD symptoms. In addition, these analyses have confirmed earlier evidence from family and twin studies that found significant co-aggregation of ADHD with depression[37], conduct problems[39] and schizophrenia[40]. Furthermore, combined GWAS of ADHD, autism spectrum disorders, depression, bipolar disorder and schizophrenia identified four genome-wide significant loci shared by these disorders[37].

In addition to the common-variant studies, rare (prevalence of <1%) genomic insertions and deletions known as copy number variants (CNVs) have a role in ADHD[41,42]. One study found that 15.6% of patients with ADHD carry large CNVs of >500,000 base pairs in length compared with 7.5% of individuals without the disorder. The rate of large CNV carriage was even higher (42.4%) in those with both ADHD and an IQ below 70 ± 5 (which, along with poor adaptive functioning, defines intellectual disability)[42]. These findings have been replicated[43], and together these studies implicate genes at 16p13.11 along with the 15q11–15q13 region in ADHD. The 15q11–15q13 region contains the gene that encodes the nicotinic α7 acetylcholine receptor subunit, which participates in neuronal and nicotinic signalling pathways. Finally, ADHD-associated CNVs also span several glutamate receptor genes, which are essential for neuronal glutamatergic transmission[44], and the gene encoding neuropeptide Y, which is involved in signalling in the brain and autonomic nervous system[45]. CNVs associated with ADHD also occur in schizophrenia and autism[42].

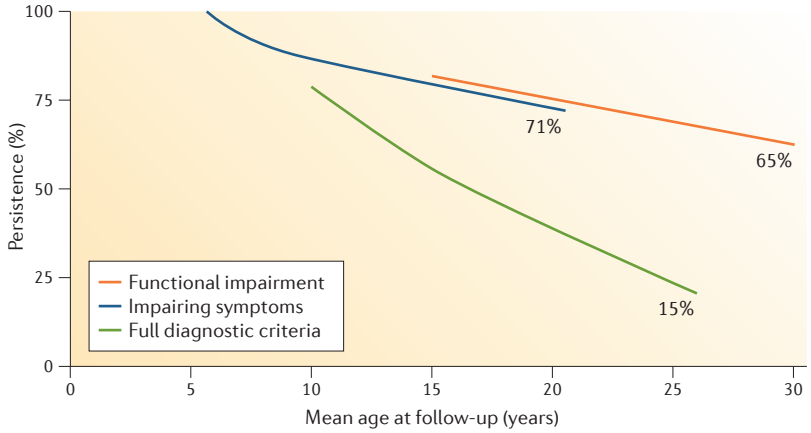

Figure 2 | **The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime.** Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an age-dependent decline in ADHD symptoms, ADHD is also a highly persistent disorder when defined by the persistence of functional impairment[7] or the persistence of subthreshold (three or fewer) impairing symptoms[8]. By contrast, many patients remit full diagnostic criteria[7].

Although GWAS that investigated common genetic variants (FIG. 3) have not identified specific ADHD genes at genome-wide levels of significance[46], intriguing results have emerged from meta-analyses of studies of candidate genes involved in the monoamine neurotransmitter systems[47]. These systems had been implicated in the pathophysiology of ADHD by the mechanisms of action of drugs used in clinical management. Methylphenidate and amphetamine target the sodium-dependent dopamine transporter (encoded by *SLC6A3*), atomoxetine targets the sodium-dependent noradrenaline transporter, and both extended-release guanfacine and extended-release clonidine target the α2A-adrenergic receptor. Within the monoamine systems, the strongest evidence of ADHD association is for variants in the genes encoding the D4 and D1B dopamine receptors[47]. The association of the *SLC6A3* gene variant is equivocal[47], possibly owing to age-related effects[48]. Other genes that show possible associations with ADHD include *SLC6A4* (which encodes the sodium-dependent serotonin transporter), *HTR1B* (which encodes 5-hydroxytryptamine receptor 1B (also known as serotonin receptor 1B)) and *SNAP25* (which encodes synaptosomal-associated protein 25)[47]. Owing to methodological issues, a cautious approach must be taken to the interpretation of candidate gene studies. Nevertheless, the role of the dopamine, noradrenaline, serotonin and neurite outgrowth systems is supported by genome-wide association study-based gene-set analyses reporting that, as a group, genes regulating these systems were associated with ADHD and hyperactivity or impulsivity[46,49,50].

Environmental risk factors. Identifying environmental causes of ADHD is difficult because environmental associations might arise from other sources, such as from child or parental behaviours that shape the environment, or they might reflect unmeasured third variables. For example, children with ADHD might evoke 'hostile' styles of parenting, and genes linked to ADHD might explain the association of parental variables, such as maternal smoking during pregnancy, with offspring who have ADHD[51,52]. One notable study investigated maternal hostility while controlling for genetic effects by studying children adopted at birth and children conceived through *in vitro* fertilization and their genetically unrelated rearing mothers[53]. The study found a role for genetically influenced early child behaviour on the hostility of biologically unrelated mothers, which in turn was a predictor of subsequent ADHD symptoms developed by the children. Another study followed Romanian adoptees who had experienced severe early maternal deprivation in orphanages before adoption. It showed a dose-dependent relationship between length of deprivation and risk of developing ADHD-like symptoms[54]. Other environmental risk factors that have been associated with ADHD include prenatal and perinatal factors, such as maternal smoking and alcohol use, low birth weight, premature birth and exposure to environmental toxins, such as organophosphate pesticides, polychlorinated biphenyls, zinc and lead[55,56]. Animal models have also contributed much to the study of environmental risk factors[57–59]. Similar to genetic risk factors, the effects of any one environmental risk factor are small and could reflect either small effects in many cases or larger effects in a few cases. Furthermore, rather than being specific to ADHD, these environmental risk factors are associated with several psychiatric disorders[29].

In addition to the main effects of the environment, the high heritability of ADHD suggests that gene–environment (G × E) interactions might be the main mechanism by which environmental risk factors increase the risk of ADHD. For example, a variant of *5-HTTLPR* — a polymorphic region located in the promoter of *SLC6A4* — is involved in the hyperactivity and impulsivity dimensions of ADHD in interaction with stress[60]. Although some early studies identified other G × E effects, none has been reliably reproduced. Future success in this area requires the use of large data sets, such as those emerging from the use of national databases in Denmark and Sweden, which can combine large-scale genetic studies with recorded data on exposure to environmental risks.

Another approach to identify environmental risk factors in ADHD is to focus on the detection of epigenetic changes, such as DNA methylation, which are reversible changes in genomic function that are independent of DNA sequence. Epigenetics provides a mechanism by which environmental risk factors alter gene function. However, as epigenetic changes are highly tissue specific, they are difficult to study in ADHD because of limited access to brain tissue. Studies must, therefore, rely on peripheral tissues such as blood, the epigenetic profile of which partly overlaps with that of brain tissue. Environmental toxins and stress can all induce epigenetic changes, thus the identification of genes that show epigenetic changes linked to ADHD, or in response to environmental risk factors, might in the future provide new insights into the mechanisms involved in the pathogenesis of ADHD[61].

Brain mechanisms

Cognition. ADHD is characterized by deficits in multiple, relatively independent, cognitive domains. Executive functioning deficits are seen in visuospatial and verbal working memory, inhibitory control, vigilance and planning[62,63]. Studies of reward dysregulation show that patients with ADHD make suboptimal decisions[64], prefer immediate rather than delayed rewards[65] and overestimate the magnitude of proximal relative to distal rewards[66]. Other domains impaired in ADHD include temporal information processing and timing[67]; speech and language[68]; memory span, processing speed and response time variability[69]; arousal and activation[70]; and motor control[71]. Although most patients with ADHD show deficits in one or two cognitive domains, some have no deficits and very few show deficits in all domains[72]. In addition, across the lifespan of patients with ADHD, deficits in cognitive control, reward sensitivity and timing have been shown to be independent of one another[73], and it is currently unclear whether cognitive deficits cause ADHD symptoms and drive the development of the clinical phenotype[72] or reflect the pleiotropic outcomes of risk factors.

Structural and functional brain imaging. Several brain regions and neural pathways have been implicated in ADHD (FIG. 4). Functional MRI studies in patients with ADHD that used inhibitory control, working memory and attentional tasks have shown underactivation of frontostriatal, frontoparietal and ventral attention networks[74]. The frontoparietal network mediates goal-directed executive processes, whereas the ventral attention network facilitates reorientation of attention towards salient and behaviourally relevant external stimuli. In reward-processing paradigms, most studies report lower activation of the ventral striatum of patients with ADHD in anticipation of reward than in controls[75]. ADHD is also associated with hyperactivation in somatomotor and visual systems[74], which possibly compensates for impaired functioning of the prefrontal and anterior cingulate cortices[76]. A single dose of methylphenidate (a stimulant) markedly enhances activation in the inferior frontal cortex and insula bilaterally — which are key areas of cognitive control — during inhibition and time discrimination but does not affect working memory networks[77]. By contrast, long-term treatment with stimulants is associated with normal activation in the right caudate nucleus during the performance of attention tasks[78]. Resting-state MRI studies have shown that ADHD is associated with less-pronounced or absent anti-correlations between the default-mode network (DMN) and the cognitive control network, lower connectivity within the DMN itself and lower connectivity within the cognitive and motivational loops of the frontostriatal circuits[79].

Along with functional changes, a range of structural brain alterations are also associated with ADHD. For example, ADHD is associated with a 3–5% smaller total brain size than unaffected controls[80,81] that can be attributed to a reduction of grey matter[82]. Consistent with genetic data that support a model of ADHD as the extreme of a population trait, total brain volume correlates negatively with ADHD symptoms in the general population[83]. In patients with ADHD, meta-analyses have documented smaller volumes across several brain regions, most consistently in the right globus pallidus, right putamen, caudate nucleus and cerebellum[84,85]. In addition, a meta-analysis of diffusion tensor imaging studies showed widespread alterations in white matter integrity, especially in the right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellum[86]. Both structural and functional imaging findings are very variable across studies, suggesting that the neural underpinnings of ADHD are heterogeneous, which is consistent with studies of cognition.

Just as the prevalence of ADHD is associated with age (FIG. 2), so too are many changes in the brains of patients with ADHD[7]. Some brain volumetric alterations observed in childhood normalize with age[82,85], whereas other measures remain fixed. For example, a longitudinal MRI study found lower basal ganglion volumes and reduced dorsal surface area in adolescents with ADHD compared with controls, and this difference did not change as patients aged[87]. Furthermore, for ventral striatal surfaces, control individuals showed surface area expansion with age, whereas patients with ADHD experienced a progressive contraction of the surface area. The as-yet-unknown process underlying this contraction might explain abnormal processing of reward in ADHD[87]. ADHD is also associated with delayed maturation of the cerebral cortex. In one study, the age of attaining peak cortical thickness was 10.5 years for patients with ADHD and 7.5 years for unaffected individuals; this delay was most prominent in the prefrontal regions that are important for executive functioning, attention and motor planning[88]. The development of cortical surface area was also shown to be delayed in patients with ADHD, but ADHD was not associated with altered developmental

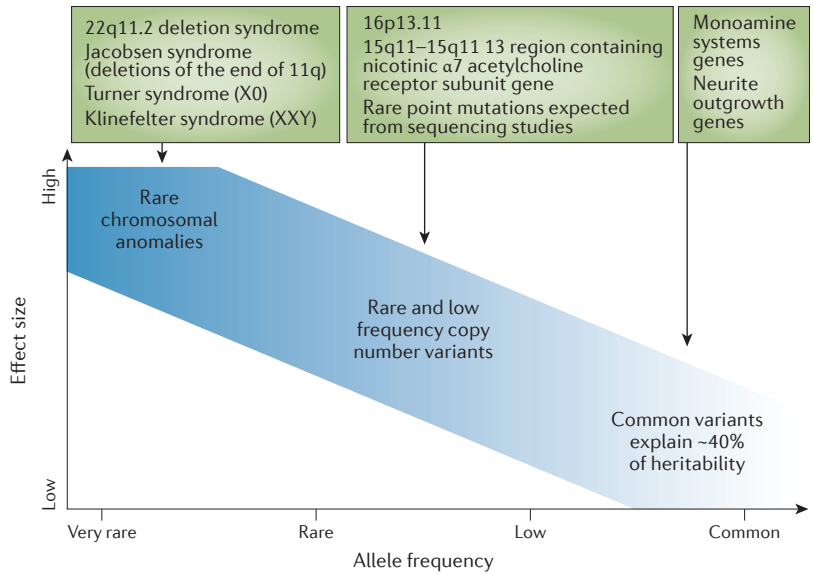

Figure 3 | **Genetics of attention-deficit/hyperactivity disorder.** Common variants explain approximately 40% of the heritability of attention-deficit/hyperactivity disorder but, compared with rarer causes, individual common variants have much smaller effects on the expression of the disorder.

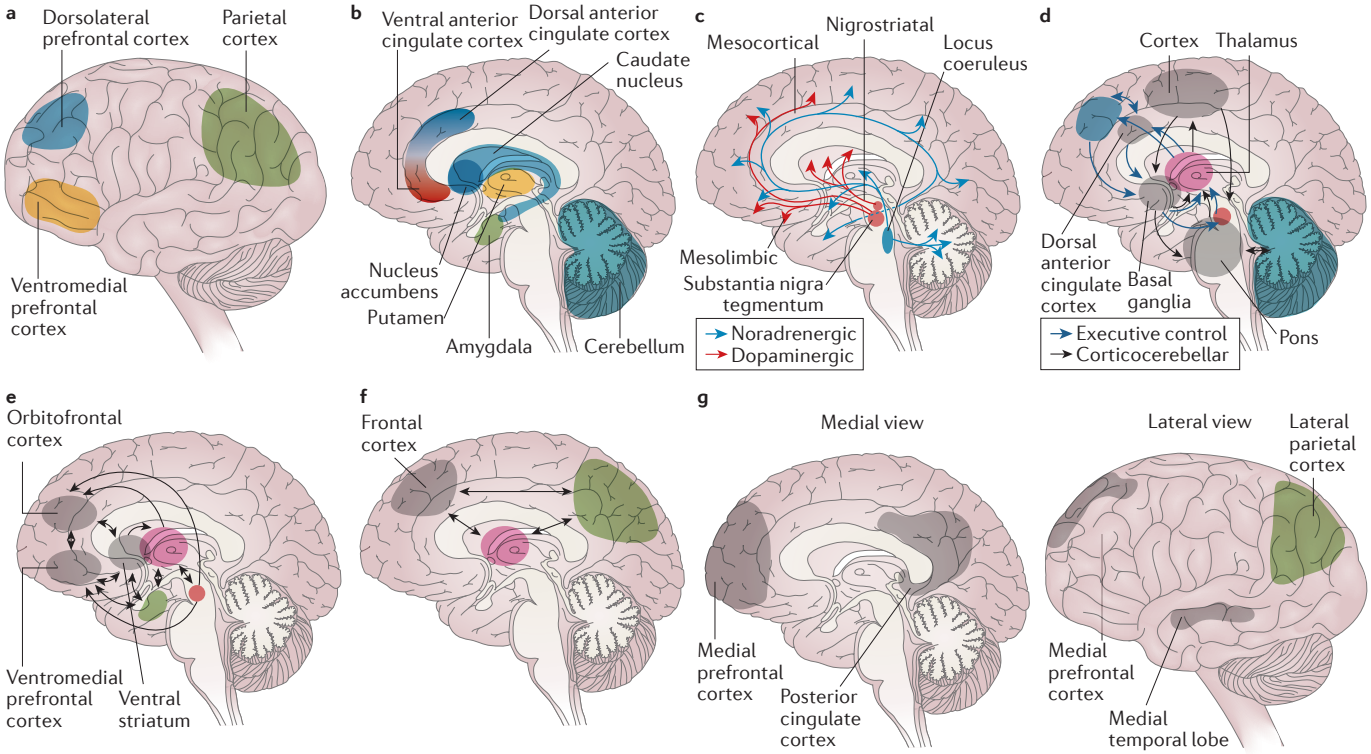

Figure 4 | **Brain mechanisms in attention-deficit/hyperactivity disorder.** **a** | The cortical regions (lateral view) of the brain have a role in attention-deficit/hyperactivity disorder (ADHD). The dorsolateral prefrontal cortex is linked to working memory, the ventromedial prefrontal cortex to complex decision making and strategic planning, and the parietal cortex to orientation of attention. **b** | ADHD involves the subcortical structures (medial view) of the brain. The ventral anterior cingulate cortex and the dorsal anterior cingulate cortex subserve affective and cognitive components of executive control. Together with the basal ganglia (comprising the nucleus accumbens, caudate nucleus and putamen), they form the frontostriatal circuit. Neuroimaging studies show structural and functional abnormalities in all of these structures in patients with ADHD, extending into the amygdala and cerebellum. **c** | Neurotransmitter circuits in the brain are involved in ADHD. The dopamine system plays an important part in planning and initiation of motor responses, activation, switching, reaction to novelty and processing of reward. The noradrenergic system influences arousal modulation, signal-to-noise ratios in cortical areas, state-dependent cognitive processes and cognitive preparation of urgent stimuli. **d** | Executive control networks are affected in patients with ADHD. The executive control and corticocerebellar networks coordinate executive functioning, that is, planning, goal-directed behaviour, inhibition, working memory and the flexible adaptation to context. These networks are underactivated and have lower internal functional connectivity in individuals with ADHD compared with individuals without the disorder. **e** | ADHD involves the reward network. The ventromedial prefrontal cortex, orbitofrontal cortex and ventral striatum are at the centre of the brain network that responds to anticipation and receipt of reward. Other structures involved are the thalamus, the amygdala and the cell bodies of dopaminergic neurons in the substantia nigra, which, as indicated by the arrows, interact in a complex manner. Behavioural and neural responses to reward are abnormal in ADHD. **f** | The alerting network is impaired in ADHD. The frontal and parietal cortical areas and the thalamus intensively interact in the alerting network (indicated by the arrows), which supports attentional functioning and is weaker in individuals with ADHD than in controls. **g** | ADHD involves the default-mode network (DMN). The DMN consists of the medial prefrontal cortex and the posterior cingulate cortex (medial view) as well as the lateral parietal cortex and the medial temporal lobe (lateral view). DMN fluctuations are 180 degrees out of phase with fluctuations in networks that become activated during externally oriented tasks, presumably reflecting competition between opposing processes for processing resources. Negative correlations between the DMN and the frontoparietal control network are weaker in patients with ADHD than in people who do not have the disorder.

trajectories of cortical gyrification[89]. Remission of ADHD has been associated with normalization of abnormalities as measured by activation during functional imaging tasks[90], cortical thinning[91] and structural and functional brain connectivity[92–95].

Although these data could be taken to suggest that the age-dependent decline in the prevalence of ADHD might be due to the late development of ADHD-associated brain structures and functions, most patients with ADHD do not show complete developmental 'catch up'. Indeed, widespread deviations in cortical thickness persist in many adults with ADHD. Findings include both cortical thinning (in the superior frontal cortex, precentral cortex, inferior and superior parietal cortex, temporal pole and medial temporal cortex)[89,96] and cortical thickening (in the pre-supplementary motor area, somatosensory cortex and occipital cortex)[97]. More work is needed to determine how developmental changes in patterns of cortical thickness predict developmental changes in ADHD symptom expression.

Summary

Neurocognitive, neuroimaging and genetic theories of ADHD have shifted from single-cause or single-pathway models to models that delineate causes that lead to ADHD through several molecular, neural and neurocognitive pathways[33,98–102]. These approaches have received clear support from aetiological studies indicating that most cases of ADHD arise from a 'pool' of genetic and environmental risk factors. Most of these risk factors have only a small effect on causal pathways. Cumulative vulnerability increases ADHD trait scores, and our current model suggests that ADHD emerges when these exceed a certain threshold. In most cases, no single factor is necessary or sufficient to cause ADHD. However, in some patients, rare genetic variants[41,42] or environmental risk factors — for example, psychosocial deprivation[54] — might have a major influence.

The multifactorial causation of ADHD leads to a heterogeneous profile of psychopathology, neurocognitive deficits and abnormalities in the structure and function of the brain. Many cases probably involve dysregulation of the structure and function of the frontal–subcortical–cerebellar pathways that control attention, response to reward, salience thresholds, inhibitory control and motor behaviour. A meta-analysis of peripheral biomarkers in the blood and urine of drug-naive or drug-free patients with ADHD and unaffected individuals found several measures — specifically, noradrenaline, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), monoamine oxidase (MAO) and cortisol — to be significantly associated with ADHD[56]. Several of these metabolites were also related to response to ADHD medication and symptom severity of ADHD. These results support the idea that catecholaminergic neurotransmitter systems (discussed in further detail in the following section) and the hypothalamic–pituitary–adrenal axis are dysregulated in ADHD. Finally, genetic and clinical studies also implicate other systems, including the serotonergic, nicotinic, glutamatergic and neurite outgrowth systems.

Diagnosis, screening and prevention

The diagnostic process for ADHD assesses the inattentive and hyperactive–impulsive symptom criteria for ADHD, evidence that symptoms cause functional impairments and age of onset before 12 years. Although ADHD is associated with other features such as executive dysfunction[62] and emotional dysregulation[31,103], these are commonly observed in other disorders and are not core diagnostic criteria for ADHD[12]. To assist diagnosis, several open access assessment tools have been created for use in both children (TABLE 1) and adults (TABLE 2), and excellent, well-normed (standardized) commercial scales are available[104]. Importantly, patient age is relevant when assessing standard diagnostic criteria, such as those of the DSM or the *International Statistical Classification of Diseases and Related Health Problems* (ICD), owing to changes in the expression of ADHD symptoms and impairments throughout an individual's lifetime (FIGS 2,5).

Children and adolescents

The diagnosis of ADHD relies on clinical symptoms reported by patients or informants (including relatives and teachers), which is standard for all psychiatric disorders[12]. National clinical guidelines and practice parameters for ADHD, developed over the past decade, show good consensus and the potential to enhance evidence-based clinical practice[105]. Diagnosis is based on information from a detailed clinical interview, which remains the 'gold standard'. Diagnosticians ask about each ADHD symptom, the age of onset and resultant functional impairments. A clinical interview aims to establish whether symptoms are more extreme, persistent and impairing than expected for the developmental level of the patient. Validated rating scales (TABLE 1) help with such decisions, as they enable informants to quantitatively rate the behaviour of the patient at home, at school and in the community.

Several factors present challenges to clinicians aiming to determine whether a diagnosis of ADHD is appropriate. For instance, cultural and ethnic differences can hinder diagnosis owing to variability in attitudes towards ADHD, willingness to report symptoms or the acceptance of the diagnosis. For example, a literature review suggested that African-American youths had more ADHD symptoms than Caucasian youths but were diagnosed with ADHD only two-thirds as often, possibly owing to parent beliefs about ADHD and the lack of treatment access and use[106]. In addition, patient age can be an issue. Developmental changes can internalize or modify some symptoms. For example, the hyperactivity of childhood might be experienced as inner restlessness in adolescence, and distractibility could manifest as distracting thoughts. Accordingly, self-reports from adolescents are useful, but patients can sometimes lack insight into their own difficulties. Furthermore, although younger children can provide useful information, especially about internalizing symptoms[107], parents remain the main source of information for this group of patients. Parents can report on symptoms during school recesses and vacations when teacher reports are not available. Although parent reports show good concurrent and predictive validity[108,109], information from other informants such as teachers, when available, is valuable for documenting ADHD in other settings, for predicting prognosis and for increasing the confidence of diagnoses[110–112]. Finally, diagnosticians can also inquire about other medical conditions associated with symptoms of ADHD, such as seizure disorders, sleep disorders, hyperthyroidism, physical or sexual abuse and sensory impairments[113], as these can confound diagnosis.

Although screening for ADHD is theoretically feasible given the availability of parent and self-reported scales (TABLE 1), the few studies that have investigated the use of early screening for ADHD have yielded inconsistent findings. For example, a 6-year longitudinal study suggested that a parent-rated questionnaire might help with early detection, prediction and treatment planning[114]. However, owing to a lack of accurate predictors of onset, attempts at early prevention of ADHD currently rely on population-level efforts to mitigate

the effects of environmental risk factors for the disorder. Primary prevention strategies optimize maternal health during pregnancy by reducing extreme stress and psychosocial adversity, eliminating smoking, alcohol and drug use and reducing risk factors for preterm birth and low birth weight. Secondary prevention approaches that detect symptoms of ADHD at an early stage — for example at infancy or preschool age — include screening programmes in primary care, parent training programmes, and specific games and play-based programmes to enhance self-regulation when symptoms are identified[115,116].

Adults

Over the past 40 years, clinical, family, treatment, longitudinal and population studies have generated

Table 1 | **A selection of open access resources for assessing attention-deficit/hyperactivity disorder in childhood**

Approach	Comments	Websites
Interviews		
Schedule for Affective Disorders and Schizophrenia in School Age Children (K-SADS)	• A semi-structured diagnostic interview • Evaluates past and current psychopathology in children and adolescents, according to DSM-IV and DSM-III criteria • Translations in many languages • A DSM-5 version is imminent	http://www.psychiatry.pitt.edu/node/8233
Diagnostic Interview Schedule for Children (DISC)	• A structured diagnostic that uses DSM-IV to assess psychopathology in children and adolescents • Translations in many languages	http://www.cdc.gov/nchs/data/nhanes/limited_access/interviewer_manual.pdf
Child and Adolescent Psychiatric Assessment (CAPA)	• A semi-structured interview that evaluates current psychopathology in children and adolescents • Based on DSM-IV criteria • Versions for youths and preschool-aged children • Spanish and Portuguese translations	https://devepi.duhs.duke.edu/capa.html https://devepi.duhs.duke.edu/pubs/papachapter.pdf
Development and Well-Being Assessment (DAWBA)	• For clinicians and trained non-clinicians • Uses a prespecified set of questions and probes for impairment • Generally used together with the SDQ • Translations in many languages	http://www.dawba.com/b0.html
Parent Interview for Child Symptoms (PICS)	• A semi-structured interview focused on diagnostic criteria for ADHD, ODD and CD in children and adolescents • Addresses symptoms of other psychiatric disorders • Has been updated for DSM-5 criteria • Includes the TTI, which assesses symptoms of ADHD, ODD and CD in school, with screening questions for other psychopathology • Dutch translation	http://www.sickkids.ca/MS-Office-Files/Psychiatry/17145-Administration_Guidelines_PICS6.pdf http://www.sickkids.ca/pdfs/Research/Tannock/6013-TTI-IVManual.pdf
Child ADHD TTI (CHATTI)	• A structured telephone interview for teachers • Focuses on DSM-IV criteria for ADHD in school • Only available in English	Available from the authors[254]
Scales		
Vanderbilt ADHD Diagnostic Rating Scales (VARS)	• Versions for a parent or caregiver and teacher • Part of the American Academy of Pediatrics ADHD Toolkit • Spanish translation	http://www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales
Swanson, Nolan and Pelham (SNAP)-IV Rating Scale	• A rating scale for symptoms of ADHD and ODD • Can be completed by a teacher, parent or caregiver • Sensitive to changes related to treatment • Portuguese, Spanish and French translations	Short scale (26-item) available from: http://www.caddra.ca/pdfs/caddraGuidelines2011SNAP.pdf Scoring guidelines available from: http://www.caddra.ca/pdfs/caddraGuidelines2011SNAPInstructions.pdf Full scale (90-item) available from: http://www.adhd.net/snap-iv-form.pdf Scoring guidelines available from: http://www.adhd.net/snap-iv-instructions.pdf
Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (SWAN)	• Versions for a teacher, parent or caregiver • Based on DSM-IV criteria • Unusual in that the items are positively worded and it covers both strengths as well as weaknesses in ADHD and ODD symptoms • Spanish and French translations	http://www.adhd.net/SWAN_SCALE.pdf
SDQ	• Brief measure of emotional, ADHD, conduct and relationship problems • Versions for a parent, caregiver or teacher and a self-report • Translations in many languages	http://sdqinfo.org

ADHD, attention-deficit/hypersensitivity disorder; CD, conduct disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ODD, oppositional defiant disorder; SDQ, Strengths and Difficulties Questionnaire; TTI, Teacher Telephone Interview.

Table 2 | **A selection of open access resources for assessing attention-deficit/hyperactivity disorder in adulthood**

Approach	Comments	Websites
Interviews		
Diagnostic Interview for Adult ADHD, second edition (DIVA 2.0)	• A structured diagnostic interview for ADHD in adults according to DSM-IV • A new version based on DSM-5 criteria is in press	http://www.divacenter.eu/DIVA.aspx
Adult (ACDS) v1.2	• A semi-structured interview of current symptoms of ADHD in adults • Provides age-specific prompts for rating both childhood and adulthood symptoms	Available from the author (Lenard Adler) at: http://www.med.nyu.edu/biosketch/adlerl01
Scales		
Adult ADHD Self-Report Scale (ASRS)	• Developed by WHO to measure ADHD symptoms in individuals >18 years of age • An 18-item version covers all DSM-IV symptoms of ADHD • A 6-item version is a screening tool validated for adolescents and adults • The 6-item version (ASRS-Telephone Interview Probes for Symptoms; ASRS-TIPS) uses semi-structured interview probes for examples of ADHD symptoms • Both versions have been translated into many languages	http://www.hcp.med.harvard.edu/ncs/asrs.php
Adult ADHD Investigator Symptom Rating Scale (AISRS)	• Incorporates suggested prompts for each ADHD item • Descriptors for each ADHD item are explicitly defined • Takes context into account	Available from Lenard Adler at: http://www.med.nyu.edu/biosketch/adlerl01
Wender Utah Rating Scale (WURS)	• Developed to retrospectively diagnose childhood ADHD in adults	Available from the authors[255]

ADHD, attention-deficit/hypersensitivity disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders*.

very strong evidence that ADHD frequently persists into adulthood, although its presentation changes with age[23,117–119] (FIG. 5). Nevertheless, ADHD in adults is still undertreated[120], leading to international efforts to educate clinicians (TABLE 3) and to drive changes to DSM. DSM-5 provides guidance about the differential expression of ADHD symptoms throughout the patient's lifetime. For instance, in contrast to young children, adults with many impairing ADHD symptoms do not typically climb on tables, have boundless energy or run around in a place where one should remain still. Hyperactivity in adulthood is often experienced as a feeling of inner restlessness — an internal 'motor' that never stops — which makes it difficult for the individual to relax[121]. By adopting symptom descriptors of this sort, DSM-5 is easier to apply to adults compared with its predecessors.

Despite these differences in symptom presentation, the diagnostic process for adults parallels the process for youths in regards to documenting symptoms, impairment and onset of the disorder on the basis of a clinical interview with the patient and, when available, reports from informants. This process is aided by the availability of structured diagnostic interviews, such as the Conners' Adult ADHD Diagnostic Interview[122], along with rating scales for patients and informants, including the Adult Self-Report Scale (TABLE 2)[123].

In adulthood, additional domains of impairment emerge and can include difficulties related to occupation, marriage and parenting. Patients with high intelligence also present with a unique set of challenges. In these individuals, impairment can be assessed relative to their aptitude. Some of these patients go to great lengths to accommodate their symptoms, which itself indicates impairment to the degree that it causes distress or displaces other activities. For example, to achieve satisfactory grades, a university student with ADHD might need to work twice as hard as peers with the same aptitude to focus attention or to organize school work. If that restricts the student's social life or causes other problems, it might be viewed as impairing. Nonetheless, ADHD can be reliably diagnosed in these patients[124]. Finally, in adults with ADHD, hyperactive–impulsive symptoms usually become internalized, such as feeling restless, and deficient emotional self-regulation[125] and executive dysfunction[126] become increasingly prominent. Although deficient emotional regulation and executive dysfunction are not diagnostic for ADHD, they are highly characteristic of the disorder in adults and could indicate the need for specific treatments, such as cognitive–behavioural therapy, to improve organizational or emotional self-regulation skills.

Heterogeneity of ADHD

Patients with ADHD show marked variation in profiles of symptoms, impairments, complicating factors, neuropsychological weaknesses and underlying causes[127]. Accordingly, effective partitioning of this heterogeneity to refine diagnostic approaches and to provide tailored and targeted treatments remains an important research goal. To address this aim, DSM-5 recognizes three presentations: predominantly inattentive, predominantly hyperactive–impulsive and combined. These presentations are no longer deemed 'subtypes', as in prior versions, because they can change over time[128]. Moreover, even within presentations, patients greatly differ in symptom profiles. For instance, the predominantly inattentive presentation applies to individuals with a wide range of inattention and can include subthreshold hyperactive–impulsive symptoms. Although common in population samples, inattentive ADHD is less common in the clinic, which suggests that

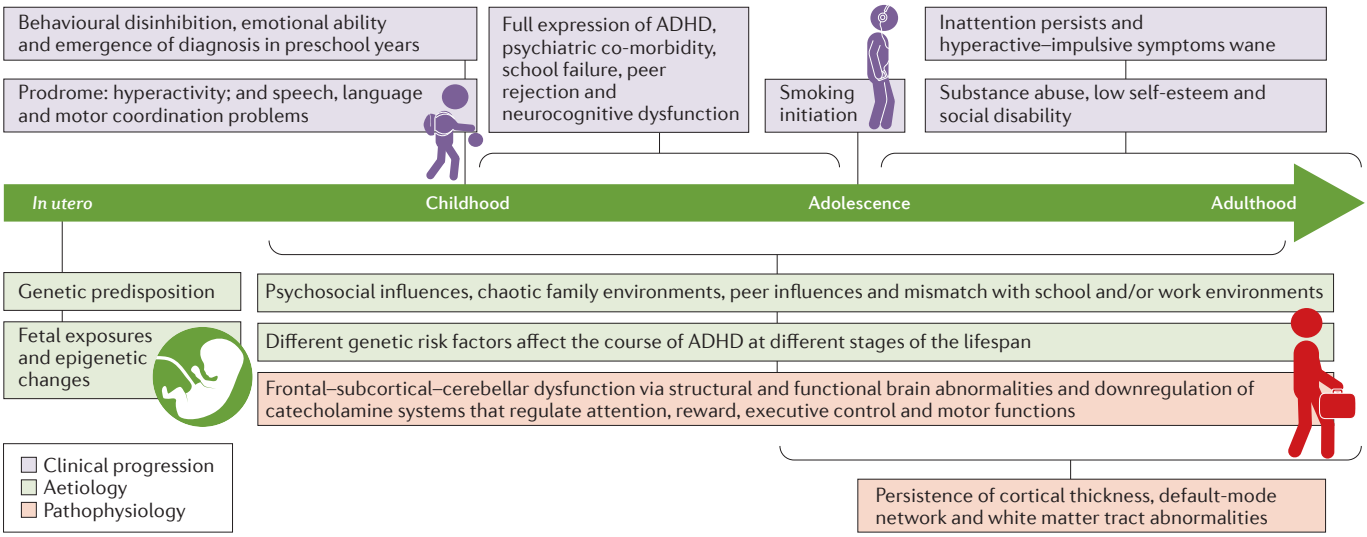

Figure 5 | **Developmental course of attention-deficit/hyperactivity disorder in persistent cases.** Although no single sequence of events describes the pathway from *in utero* to adulthood, this figure describes key developmental events, with boxes spanning their approximate onset along with hypotheses about the timing of the biological underpinnings of aetiological events and pathophysiological expression. ADHD, attention-deficit/hyperactivity disorder.

population screening for marked inattention should be considered, especially in female children and adults, in which this pattern might be particularly impairing[129]. Persistent inattention — even at subthreshold levels — is a key predictor of poor academic outcomes[130].

Psychiatric co-morbidity is another clinically important dimension of ADHD heterogeneity. At one extreme, a small proportion of clinic-referred individuals are free of co-morbidity; at the other end, some patients have a complex pattern of multiple problems, including communication disorders, intellectual disabilities[131], sleep disorders[132], specific learning disabilities[131], mood disorders[131], disruptive behaviour[131], anxiety disorders[131], tic disorders[131], autism spectrum disorders[131,133] and substance use disorders[131,134,135]. Consideration of a patient's co-morbidity profile is important, as it will influence treatment planning.

Pathophysiological heterogeneity might be important clinically — although new research is required to determine whether subtyping on the basis of genetic, environmental, neurobiological or neuropsychological factors will improve diagnostic and treatment approaches. In this regard, the largest body of evidence relates to cognition. Objective tests indicate that several distinct deficit profiles exist. For example, only a minority of patients show a deficit in executive function[136], which was once thought to be the core deficit in ADHD. Other patients, who are clear of such deficits, have problems in non-executive cognitive processes, which include those involved in basic memory and temporal processing, motivational processing (delay tolerance or reinforcement processing) and cognitive energetic regulation[72,73,137]. Four cognitive ADHD subtypes were revealed in a study based on a community of children with or without ADHD[70]; however, whether these subtypes predict treatment response or course remains unclear.

The heterogeneity of ADHD has implications for both research and practice. In research, the diluting effect of heterogeneity reduces effect sizes in ADHD case–control comparisons and renders biomarkers that are identified on the assumption that ADHD is pathophysiologically homogeneous obsolete. Clinically, heterogeneity means that tests — either neuropsychological or tests of other underlying processes — that focus on only one domain will be of very limited diagnostic value. However, such assessments could help to identify specific targets for therapeutic and educational interventions that are aimed at remediating particular areas of impairment and weakness. For instance, individuals with working memory deficits might respond favourably to working memory training[138].

Management

By educating patients and families, clinicians can create a framework that increases treatment adherence, proactively plans for continuity of treatment throughout the lifetime of the patient and effectively integrates pharmacological and non-pharmacological approaches. Education includes information about the causes of ADHD, its associated morbidity, the potential for a compromised course, the rationale for treatments and plans for key life transitions[139]. This education sets the stage for managing ADHD within a chronic care paradigm that uses shared decision making to bolster treatment adherence and prepare patients for developmental challenges[140].

There are geographic variations in the sequencing of pharmacological and non-pharmacological treatments. For example, in the United States pharmacological treatment is typically the first approach, whereas in Europe medication is usually reserved for severe cases or for milder cases that do not respond to non-pharmacological treatments[141].

Pharmacological treatments

Before choosing a treatment, clinical experience advises several common-sense precautions. Appropriate attention needs to be given to the psychosocial environment. In children, particular attention needs to be paid as to whether the family is intact or separated, whether both parents are supportive of the child's treatment and whether there are any concerns about abuse or maltreatment. In addition, legal concerns, psychopathology and substance use in the parents, psychosocial stressors (such as financial and medical distress), access to firearms and the intellectual abilities of the parents are assessed because treatments might not be effective in 'chaotic' or potentially dangerous environments. Access to medications can also be an issue, owing to a lack of health insurance or restrictive policies by some governments or managed care formularies. Pharmacotherapy for ADHD will not address these issues, but appropriate social services or non-pharmacological interventions can mitigate their effects. It is important to educate parents and patients about ADHD and its treatments to help them to understand the value of treatment options.

The choice of medication is guided by assessing the severity of the symptoms, the presence of co-morbidities (FIG. 6) and what periods of the day symptom relief is needed — for example, during school hours only, during an extended school day, during a work day or during the evening. With few exceptions, medications to treat ADHD help patients 7 days a week throughout the year because the condition affects aspects of life outside the school or work day, such as socializing, driving, doing homework and functioning in the family environment.

The pharmacological decision-making approach starts with whether the patient will benefit from a stimulant or non-stimulant treatment. Meta-analyses have demonstrated that stimulant and non-stimulant medications for ADHD effectively reduce ADHD symptoms in children and adults[142,143]. By contrast, in preschool-aged children, evidenced-based non-pharmacological treatments are recommended as the first approach, when available, but medication is indicated when symptoms are severe[144]. On average, stimulants (amphetamine and methylphenidate) are more efficacious than non-stimulants (atomoxetine, guanfacine and clonidine)[145]. Accordingly, stimulants continue to be the first-line psychopharmacological treatment for patients of all ages with ADHD[120].

Pharmacological treatments are typically long term, except for those patients who do not have a persistent course of ADHD. These treatments are generally associated with improved outcomes in children and adults, as have been demonstrated by systematic reviews that considered a range of different criteria to measure long-term outcomes. For instance, a systematic review examined five randomized controlled trials (RCTs) and ten open-label extension studies of adults with ADHD that had been conducted for at least 2 years[146]. The authors concluded that stimulant therapy for ADHD has long-term beneficial effects and is well tolerated. In addition, a systematic review of adult and child studies that had been carried out over at least 2 years concluded that treating

Table 3 | **Selected resources for clinicians, parents and patients**

Organization	Content	Websites
US NIMH	Information for patients and families	http://www.nimh.nih.gov
American Professional Society for ADHD and Related Disorders	Meetings for health professionals and researchers	http://www.apsard.org
ADHD World Federation	Meetings for health professionals and researchers	http://www.adhd-federation.org
Children and Adults with ADHD	Information for patients and families	http://www.chadd.org
ADHD in Adults	Continuing education for health professionals	http://www.adhdinadults.com
Canadian ADHD Resource Alliance	Continuing education and meetings for health professionals and researchers; National Clinical Guidelines for ADHD; and policy work with the government	http://www.caddra.ca
Australian NHMRC	Information for health professionals, patients and families	http://www.nhmrc.gov.au/guidelines-publications/mh26
ADHD Europe	Information for patients and families	http://www.adhdeurope.eu
European Network on Adult ADHD	Meetings for health professionals and researchers	http://www.eunetworkadultadhd.com/
International Collaboration on ADHD and Substance Abuse	Meetings for health professionals and researchers	http://www.adhdandsubstanceabuse.org
UK Adult ADHD Network	Meetings for health professionals and researchers	http://www.ukaan.org
ADHD India	Information for patients and families	http://www.adhdindia.com
China ADHD Alliance	Information for patients and families	http://www.adhd-china.org/en-index.htm
Zentrales adhs-netz (German Central ADHD Network)	Information for patients and families	http://www.zentrales-adhs-netz.de
American Academy of Pediatrics ADHD Toolkit	Information for health professionals	http://www2.aap.org/pubserv/adhd2/1sted.html

ADHD, attention-deficit/hyperactivity disorder; NHMRC, National Health and Medical Research Council; NIMH, National Institute of Mental Health.

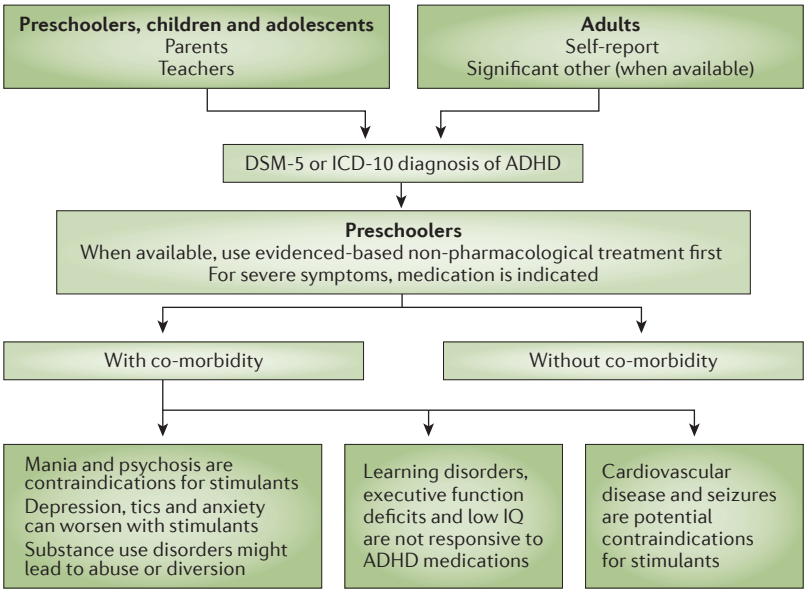

Figure 6 | **Assessment guides management.** The management of attention-deficit/hyperactivity disorder (ADHD) considers psychiatric, psychological and medical co-morbidity. DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, tenth edition; IQ, intelligence quotient.

ADHD improved long-term outcomes but generally not to normal levels[147]. Another study found that long-term medication use was associated with improved achievement test scores[148]. Furthermore, a systematic review of placebo-controlled discontinuation studies and prospective long-term observational studies concluded that medication reduced ADHD symptoms and impairments, but that there was limited and inconsistent evidence for long-term medication effects on improved social functioning, academic achievement, employment status and psychiatric co-morbidity[149]. Finally, although pharmacological approaches are generally efficacious, an important source of treatment failure is non-adherence to medication. For example, this was demonstrated in the 2-year follow-up of the Multimodal Treatment of ADHD (MTA) study of children with ADHD, which reported that continuing medication use partly mediated improved long-term outcomes[150].

Stimulants. When choosing a stimulant, the first decision is whether to use a methylphenidate product or an amphetamine product, both of which modulate the action of dopamine. Methylphenidate and amphetamine block the dopamine transporter and amphetamine also promotes the release and reverse transport of dopamine. Although the efficacy of both classes of stimulants is similar, some patients preferentially respond to and tolerate one or the other[143]. There are no reliable predictors of individual patient responses. Both families of stimulants have short-acting (2–4 hours), intermediate-acting (6–8 hours) and long-acting (10–12 hours) formulations that enable clinicians to tailor duration of coverage for each patient. Starting the patient on a low dose and titrating at weekly intervals depending on response and adverse effects is prudent — the goal being to provide the optimal duration of coverage throughout the day according to the needs of the patient[151]. For all stimulant formulations, the duration of effect varies from patient to patient[152]. Thus, the titration of stimulants addresses the onset and duration of effect as well as overall efficacy and adverse events. For example, long-acting stimulants take 1–2 hours to begin working; thus, patients are told when to take the medication to secure benefit at the beginning of the school or work day. For some patients, the effects of long-acting stimulants can wear off by mid-to-late afternoon, and they might, therefore, need additional pharmacological coverage to help to control symptoms later in the day. In such cases, the prescription of a short-acting formulation of the same drug can be used to extend its coverage.

Common adverse effects of stimulants are initial insomnia, decreased appetite, dysphoria and irritability. Sleep disturbances are very common in patients with ADHD, independent of stimulant use[132], but those related to stimulant use require parents to be instructed on how to improve sleep hygiene or pharmacological management. For example, a long-acting stimulant can be replaced with an intermediate-acting formulation, or sleep onset can be improved with sleep aids such as melatonin[153]. As appetite suppression usually occurs in the middle of the day, its effects can usually be mitigated by taking the medication after breakfast. In addition, a substantial breakfast and dinner as well as snacking during the day will manage energy levels and safeguard nutrition. If these measures are not sufficient, nutritional supplementation can be useful[154]. In severe cases of weight loss or growth delays, reducing the dose or discontinuing it over the weekend may be appropriate. Management of dysphoria and irritability depends on whether these symptoms occur during the peak or trough of the bioavailability of the medication, as indicated by its pharmacokinetic curve[155,156]. If these symptoms occur during the peaks of drug bioavailability, switching to another stimulant is an option. If they occur during the troughs, they might be attributable to withdrawal or rebound effects, which can be mitigated by adding a small dose of a short-acting stimulant 1 hour before the symptoms occur. For patients that are sensitive to peaks and troughs of bioavailability, single-peak formulations can be considered.

Although serious adverse effects are rare, they do occur. The onset of tics, acute anxiety states, depression, psychosis and mania requires both the prompt discontinuation of treatment and the search for alternative approaches consistent with emergent symptoms and diagnoses[157]. Stimulants can be associated with small delays in growth in height, but these tend to attenuate with time and seem not to affect ultimate height and weight in adulthood[158]. Nevertheless, abnormal growth parameters can indicate the need to change treatments. Evidence for the association of other serious adverse events with stimulant use for ADHD is less robust. For example, some studies have raised concerns that stimulants cause sudden cardiac death, and one Danish study ($n = 714{,}258$) found that stimulant use was associated with an increased risk of any adverse cardiovascular event (adjusted hazard ratio of 1.83). These data from the Danish study are difficult

to interpret because the category of 'any' included hypertension, rheumatic fever and cardiovascular disease not otherwise specified; this final category accounted for 40% of cases[159]. Moreover, a study from the United States (n = 1,200,438) reported that ADHD drugs (methylphenidate, amphetamine and atomoxetine) did not increase the risk of serious cardiovascular events in children and young adults[160]. The same was true for a subanalysis limited to methylphenidate, which was the only drug with sufficient data. In addition, a meta-analysis of observational studies concluded that ADHD drugs (mostly methylphenidate and amphetamine) did not increase the risk of sudden death in children[161]. Thus, for patients with pre-existing cardiac conditions, stimulants should be used cautiously and only after consultation with a cardiologist[162,163], and in all patients treated with stimulants, blood pressure should be monitored during treatment. Stimulants can be used cautiously — or not at all — in the presence of tic, bipolar, anxiety, and substance use disorders and seizures.

Non-stimulants. Two classes of non-stimulants have been approved by regulatory agencies for the treatment of ADHD. These include the selective noradrenaline reuptake inhibitor atomoxetine[164] and long-acting formulations of two α2-adrenergic agonist drugs — clonidine[165] and guanfacine[166]. These drugs are effective in the management of ADHD, but the sedative effects of α2-adrenergic agonists limit their use in some patients[165,167].

Similar to stimulants, these medications require slow titration to avoid adverse effects by starting with a low dose and adjusting it based on outcomes. Atomoxetine can be administered once or twice daily. Long-acting guanfacine was tested in children and found to be more effective at higher doses, but these doses were associated with more adverse effects. α2-adrenergic agonists can also be administered once or twice daily. Their efficacy has been documented for young children but not for adolescents and adults.

Combined therapy with stimulants and atomoxetine or a long-acting α2-adrenergic agonist might be effective for patients who have been unresponsive to monotherapy[168], but the implications of these combined therapies for cardiovascular safety have not been adequately studied. Patients who do not respond to stimulants, atomoxetine or α2-adrenergic agonists might respond to other medications that have been used off-label in the management of ADHD, such as tricyclic antidepressants, bupropion (an antidepressant) or modafinil (a wakefulness-promoting agent that is commonly used to treat narcolepsy). Although some data support the efficacy of these off-label medications for the treatment of ADHD[169], regulatory agencies in the United States and the European Union have not approved their use in this context.

Psychiatric co-morbidity. The co-morbidities of ADHD affect the clinical picture of this disorder and its management. The rule of thumb is to address the most serious disorder first. For example, it would be almost impossible to manage ADHD in the presence of a serious, active mood or substance use disorder; these conditions need to be addressed first. However, when the other disorder is appropriately managed, ADHD can then be treated effectively[170]. As a result, combined treatments are frequently used for the management of ADHD in individuals with co-morbidity.

For patients with active substance use disorders, stimulants are contraindicated or are used cautiously, owing to concerns about the potential for abuse, misuse or diversion by the patient or caregiver. Such concerns contrast with substantial literature that indicates stimulant use in childhood has a protective effect on subsequent smoking[171] and neutral or protective effects on subsequent drug and alcohol use disorders[172–175]. However, substantial data indicate that a minority of patients with ADHD divert their stimulant medication for misuse by others[176].

Atomoxetine has been tested successfully in the management of ADHD in the context of co-morbidity with tics, anxiety and depression[177,178], and one review suggested that α2-adrenergic agonists yield the best combined improvement for ADHD that is co-morbid with tic disorders[179]. Bupropion is approved for use in depression in adults, and its efficacy in ADHD has been confirmed in a meta-analysis[180]. Some reports have documented the efficacy of stimulants[181], extended-release guanfacine[182] and atomoxetine[183] for the treatment of co-morbid oppositional defiant disorder symptoms.

When treated with ADHD medications, patients with intellectual disabilities[184] or traumatic brain injury[185] show a reduction in ADHD symptoms. General cognitive ability is not responsive to ADHD pharmacotherapy; however, some data suggest that atomoxetine can modestly improve dyslexia[186] and that stimulants[187] and atomoxetine[188] yield modest improvements in behavioural measures of executive functioning as well as performance on executive memory, reaction time and inhibitory control tasks[72]. Although some academic performance problems associated with symptoms of ADHD (for example, homework completion) can improve with treatment, medication cannot replace missing skills, improve academic achievement scores or ameliorate specific learning disabilities[189].

Taken together, it is clear that finding an effective formulation, daily dose and dosing schedule for an ADHD medication is crucial for successful treatment. The use of tools such as management decision trees that summarize recommendations about pharmacotherapy and the integration of non-pharmacological treatments can be useful in guiding ADHD management (FIG. 7). The efficacy of these treatments will be augmented by monitoring both symptomatic and functional outcomes and promoting adherence[151].

Non-pharmacological treatments

Non-pharmacological approaches for the treatment of ADHD might be required for several reasons. First, some patients do not respond positively to medication and might experience, for example, poor symptom control, unmanageable adverse events or both. Second, medication alone might not produce optimal results across all domains of ADHD-related impairment. Third, patients might not have access to medication because of either

parent or clinician concern or restrictive government policies that limit access. Even in jurisdictions where medications are licensed and available, there are variations in expert recommendations. Last, patients might be considered too young or to have an insufficiently severe presentation to warrant medication[190].

A range of dietary, behavioural and neurocognitive therapies are used as either precursors to, instead of, or as a complement to medication to target co-morbid conditions and broader patterns of psychosocial impairment. The strength and quality of supporting evidence vary widely from treatment to treatment; in general, even when efficacy is shown, effect sizes are substantially smaller than for optimized medication[191,192]. In addition, adverse events are typically not reported in non-pharmacological trials — whether the lack of reporting is because adverse events do not occur or are not measured remains unclear. Data on the cost effectiveness of treatment are also scant. No simple algorithm can choose among these treatments, and treatment use should be determined by the individual needs and circumstances of patients and their families.

Dietary interventions. Dietary interventions are of two general types: supplements and exclusions. A meta-analysis concluded that dietary treatments can play a potentially positive but limited therapeutic part in managing ADHD[193]. The clearest evidence has supported supplementation with free fatty acids, but the clinical effects were small[193]. Insufficient evidence supports other supplement types, for example, vitamins or herbs, or homeopathic approaches. Finally, exclusion diets — those generally targeting artificial additives and those addressing idiosyncratic intolerances — also demonstrated positive effects, but these were, on average, very small (when blinded measures were used) or predominantly in a subgroup of patients with known food intolerances[193,194].

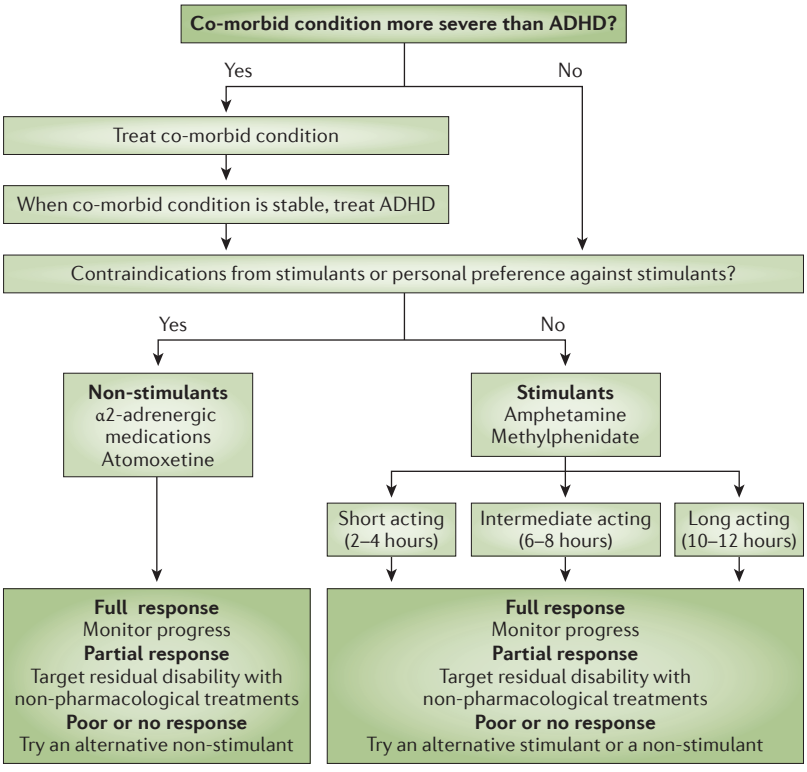

Figure 7 | **Management decision tree.** The choice of medication for treating attention-deficit/hyperactivity disorder (ADHD) considers contraindications, personal preferences, psychiatric co-morbidity and the duration of coverage required. Non-pharmacological treatments target residual disability and are used initially for preschool-aged children or when medication is declined by the patient or parent.

Behavioural interventions. Behavioural interventions are the best-established, most positively recommended and most widely used form of psychological treatment[195]. The well-tested principles of positive and negative reinforcement and social learning provide the foundation for a range of techniques that are often modified to increase their value for patients with ADHD, to reduce inappropriate and promote appropriate behaviour and to improve parent–child relationships[195,196]. In early and middle childhood, this practice typically takes the form of parent training. In addition, behaviourally based, school-focused interventions combined with approaches aimed at adapting classroom structure to aid concentration and deportment also have value[197]. Group and individually administered interventions are also available[198], and game-like elements designed to increase the child's core regulatory abilities are being introduced. Parent training is positively received by families, especially when child compliance is the primary problem[140]. However, on the basis of a recent meta-analysis of RCTs restricted to blinded outcomes, behavioural interventions are probably best used to complement — not replace — ADHD medication[199]. Although behavioural interventions have minimal effects on symptoms of ADHD, they have a considerable influence on the quality of parenting and co-occurring conduct problems in children with ADHD[199].

More-focused approaches improve specific areas of daily functioning, such as social[200] or organizational skills[201]. Although perhaps most beneficial for children who have co-occurring difficulties, behavioural approaches might also be valuable for children without these difficulties. Indeed, improving the quality of parenting has longer-term protective effects and thereby reduces the chance that ADHD will escalate to more-complex and severe forms. School-based approaches that focus on broad-based skills training and academic achievement are also of value in the long term[197,202]. In addition to approaches for children with ADHD, cognitive–behavioural therapy and life-management skills coaching are recommended for adolescent[203] and adult[204] patients. These skills include self-instructional self-control training, problem solving, use of compensatory strategies, diaries or time schedules and social communication coaching[205]. Individual RCTs provide support for these approaches based on patient-reported ratings, but corroboration through meta-analyses is required. Individual trials also suggest that psychotherapy[206], family therapy[207] and lifestyle interventions[115] might improve specific areas of functioning in some patients.

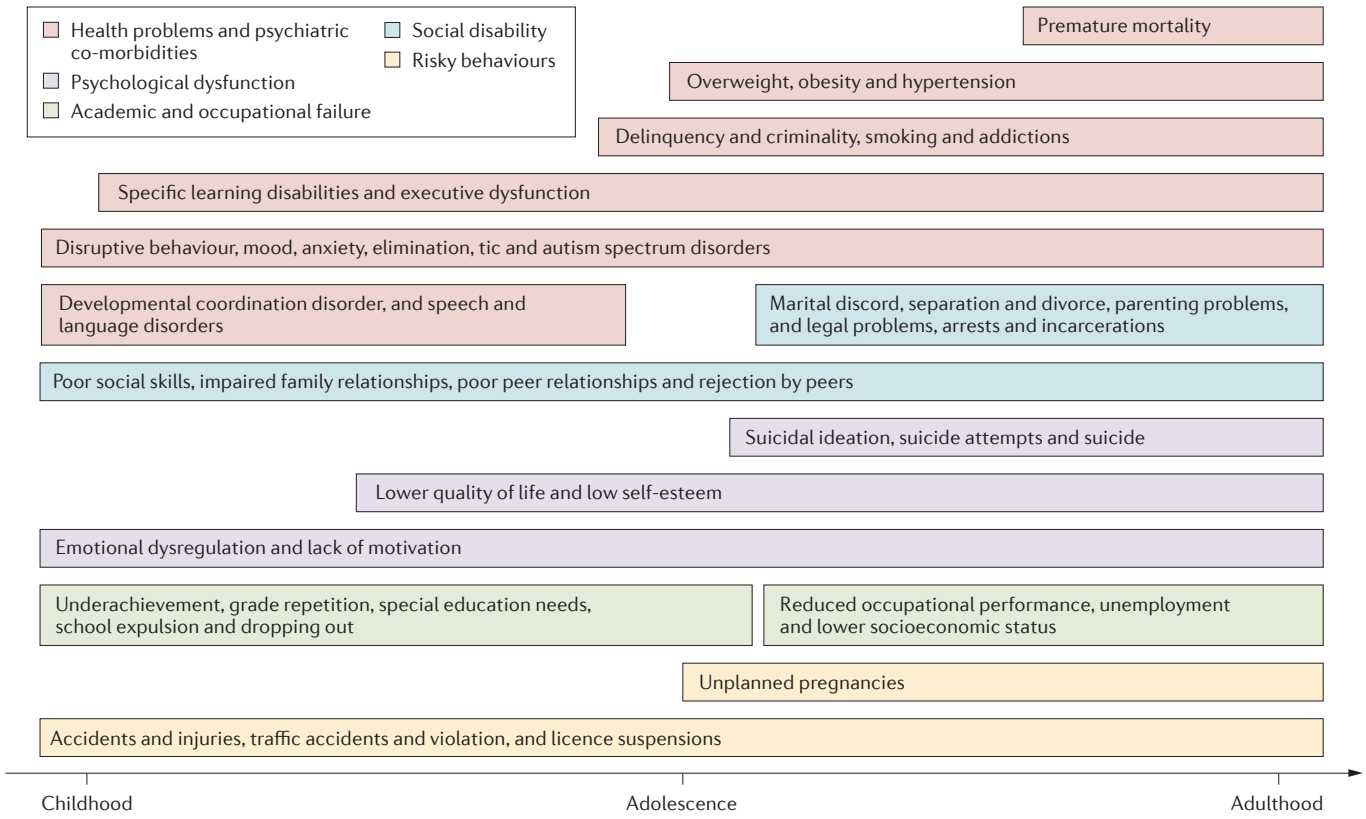

Figure 8 | **Quality of life and attention-deficit/hyperactivity disorder.** Throughout the lifetime of the patient, the impairments of attention-deficit/hyperactivity disorder manifest in psychiatric co-morbidities, health problems, psychological dysfunction, academic and occupational failure, social disability and risky behaviours.

Neurocognitive interventions. Neurofeedback interventions use adaptive reward-based techniques to normalize specific elements of a patient's aberrant electrophysiological profile that are thought to mediate problems with attention[208]. Such interventions target either specific electroencephalogram frequency bands or slow or late components of event-related potentials. Some RCTs have provided evidence for the value of neurofeedback for reducing ADHD symptoms, with the most pronounced effect of neurofeedback found for treating inattention[209]. However, recent meta-analyses have concluded that more evidence is required before neurofeedback can be endorsed for treating ADHD symptoms, owing to the lack of robust effects for blinded measures[191,210].

Other neurocognitive approaches target functions such as working memory and inhibition. Using computers, such approaches train these functions over multiple sessions that continuously challenge the patient's competence by increasing difficulty as performance improves[211]. Recent meta-analyses have demonstrated only small effects on ADHD symptoms when different training approaches were grouped together and effects were measured using blinded outcomes[138,210]. Evidence was weakest for working memory training and strongest for interventions targeting multiple neurocognitive deficits. Effects on targeted deficits, such as working memory in training trials, were positive and highly significant, although no evidence supported the transfer of these effects to non-targeted deficits, ADHD symptoms or other areas of impairment[138]. Alternative non-computerized meditation-based approaches — such as mindfulness training — seek to improve the regulation of attentional processes[212]. However, owing to insufficient evidence from well-designed trials, mindfulness training cannot be recommended as a treatment for ADHD.

Quality of life

ADHD impairs psychosocial functioning in a range of contexts that include social, academic and occupational settings, and the disorder directly affects perceptions of well-being (FIG. 8). For instance, children and adolescents with ADHD are at high risk of school failure, parental and family conflict, social rejection by peers, low self-esteem and delinquent behaviour. In addition, compared with the general population, the risk of smoking and substance use disorders is increased in patients with ADHD, especially among patients who also have conduct or antisocial personality disorder[213,214]. Adverse outcomes in adolescence and adulthood for people with ADHD include academic and vocational underachievement, reduced occupational functioning, obesity[215], emotional dysregulation[103], unemployment and suicide attempts[121,216]. Traffic accidents and violations are more frequent in drivers with ADHD[121,217,218] than in those without the

disorder, and family relationships involving individuals with ADHD might be characterized by discord and negative interactions compared with families unaffected by ADHD[217,219–221]. Finally, patients with ADHD or a history of childhood ADHD, particularly from non-medical causes, have higher mortality rates than those without ADHD, as consistently documented in longitudinal studies[222,223] and a recent registry study[224].

These functional impairments reduce the psychological and social well-being and health-related quality of life (HRQOL) of patients with ADHD[225]. For example, in the pan-European ADHD Observational Research in Europe (ADORE) study, parents reported low HRQOL for their children across a broad range of psychosocial, achievement and self-evaluation domains, which accords with findings from clinical studies[225,226]. Both inattentive and hyperactive–impulsive symptoms diminished HRQOL ratings. The strongest effects on HRQOL measures were found in the psychosocial, achievement and family life domains. Children with ADHD also rated their HRQOL to be lower than that of their peers without ADHD[225]. Similarly, adults with ADHD have a low HRQOL both in adulthood[227,228] and in their retrospective reports from childhood[229].

Although increases in ADHD symptom severity and functional impairment predict poorer HRQOL, the correlations are moderate, which indicates that ADHD symptoms, functional impairment and HRQOL are related but distinct constructs. Accordingly, HRQOL is an important component of a comprehensive assessment. For instance, in the ADORE study, several family factors, such as having a parent with a health or mental health problem, the child living in a single-parent household and maternal smoking during pregnancy, also predicted poorer HRQOL[226].

Table 4 | **Outlook for attention-deficit/hyperactivity disorder research and practice**

Area	Approach	Comments
Technological advances	GWAS, exome sequencing and whole-genome sequencing	• GWAS will discover genome-wide significant common DNA risk variants and quantify the polygenic risk for ADHD • Sequencing will discover rare, functional DNA variants • Expect insights into causal biological pathways relevant to treatment and biomarkers
	iPSCs	• iPSCs derived from peripheral tissue of patients with ADHD who carry known mutations will be used to create brain cells • Studying these cells will clarify mechanisms and provide insights for treatment
	Epigenomics, transcriptomics and proteomics	• Epigenomics will show how genes and the environment combine to modify gene expression • Mapping these pathways will describe the molecular mechanisms underlying the pathophysiology of ADHD
	Small animal models (such as zebrafish and fruitfly) and iPSCs	• Drug discovery requires faster and cheaper model systems to screen molecules for activity against targets identified by 'omic' studies
Clinical research	Therapeutic games and computer technologies	• Computer training methods could target specific deficits and adapt to the needs of patients • Incorporating game features should improve acceptability and adherence
	Treatment adherence protocols	• Mobile technologies such as text messaging should improve adherence to ADHD treatments
	Development of screening and prevention models	• Screening methods might decrease the lag between onset of symptoms and treatment, and thus improve outcomes
	Neurobiological subtypes of ADHD	• Neuropsychological, neuroimaging and genetic studies might parse the heterogeneity of ADHD to aid the development of better diagnostic and treatment strategies
	New ADHD drugs	• Biological research will yield new drug targets for drug development
Longitudinal research	Studies beginning at conception	• Environmental effects on the fetus need to be studied prospectively to better quantify risk and clarify developmental trajectories associated with ADHD genotypes
	Longitudinal neuroimaging	• Clarify the reasons for the persistence and remission of ADHD • Future work will solidify these findings and use multimodal imaging to show how aberrant neurodevelopment is associated with symptom trajectories
International collaboration	PGC	• Provides a platform for large-scale data sharing of large samples • Enables highly powered studies for the discovery of potential biomarkers and treatment targets
	ENIGMA	• Enables large-scale studies of how genetic risk variants affect brain structure and function • Will provide insight into brain-based biomarkers and the neural pathways underlying ADHD symptoms
Altered funding priorities	The RDoC project of the US NIMH	• Encourages researchers to study dimensional constructs that underlie the expression of multiple disorders • Might lead to a change in how psychiatric disorders are viewed and classified
	The EU Horizon 2020 programme	• European funding is increasingly organized around traits and characteristics shared among diseases and disorders • This will direct research to focus on larger, potentially more quantitative disease definitions

ADHD, attention-deficient/hyperactivity disorder; ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis; EU, European Union; GWAS, genome-wide association studies; iPSCs, induced pluripotent stem cells; NIMH, National Institute of Mental Health; PGC, Psychiatric Genomics Consortium; RDoC, Research Domain Criteria.

Treatments for ADHD reduce functional impairments and improve HRQOL. This evidence is, so far, almost entirely limited to pharmacological treatments. Epidemiological and clinical studies have found beneficial effects of medication on functioning and HRQOL for stimulants and for atomoxetine[230]. These effects — which were reported for both youths and adults — mirror, to some extent, medication effects on symptoms of ADHD, although with smaller effect sizes. Medication effects on HRQOL have been found across multiple domains, including key domains relating to achievement in school[231]. Moreover, findings from national registry studies indicate that the use of medication, particularly stimulants, reduces the risk of accidents and trauma-related emergency department admissions and might have protective effects on substance abuse, suicidal and delinquent behaviour[175,214,232,233]. Given that few data are available on longer-term treatment effects[234,235], the extent to which changes in HRQOL are mediated by symptom changes, changes in functional impairment or other factors remain unclear[146]. For example, one study found that medication-related improvement of HRQOL persisted following medication withdrawal, even when symptom severity increased[236], indicating that any potential cause–effect relationships between medication use, symptom and functional impairment reduction and HRQOL require further investigation.

Outlook

In 2011, the Grand Challenges in Global Mental Health Initiative (GCMHI) defined a set of 25 urgent research priorities[237]. Four GCMHI themes are of high relevance to ADHD: clarifying the causes of the disorder, improving diagnosis and treatment, developing preventive strategies and defining the global burden of disease. These research themes are intertwined. Clarification of the causes of ADHD and identification of the mechanisms underpinning pathophysiology will be the most direct path towards improving therapeutic strategies and identifying biomarkers to create objective diagnoses that can select participants for primary prevention protocols (TABLE 4).

Ongoing and planned research in the next 5 years should yield robust information about which genes and regulatory regions increase the risk of ADHD. This information will come from more powerful GWAS and the use of exome sequencing or whole-genome sequencing technologies[238]. To translate genetic findings into mechanisms and to map the biological pathways from genetic variation to disease risk[50] calls for various approaches that encompass bioinformatics, cell-based and animal model research, neuroimaging and behavioural genetic analyses. Although many animal models of ADHD have been developed[239], very few lend themselves to the much-needed medium-throughput or high-throughput analyses of the effects of genetic risk variants. Promising first steps include models of ADHD that are based on zebrafish[240] and fruitflies[241]. Cellular models of ADHD will benefit from advances in induced pluripotent stem cell technology[242]. The ultimate goal of this work will be to discover new targets for treatment.

Research in humans will be needed to validate the relevance of cell-based and animal model studies. Neuroimaging genetic studies could fill this gap but will require large international collaborations, such as the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium[243]. More importantly, tissue resource centres should prioritize the preservation of brain tissue from patients with ADHD; post-mortem studies of the brains of patients with ADHD are essential for progress in understanding the molecular mechanisms of the disorder. In addition, neurobiological studies will need to implement systematic and statistically sophisticated biological subtyping approaches to clarify the clinical and biological heterogeneity of ADHD.

Future work will first improve the behavioural diagnosis of ADHD and, in the long run, set the stage for diagnoses that are assisted by biomarker technologies. Current diagnostic criteria will probably be refined to improve the developmental sensitivity of diagnostic criteria from childhood through to adulthood. Research into the best symptom threshold for ADHD in adults will continue. For example, studies have shown that among adults who had at least six out of nine symptoms in childhood, having only four out of six symptoms in adulthood predicts substantial impairment later in life[244]. Future studies should consider balancing symptom thresholds and functional impairment to define valid diagnostic algorithms for more-refined age groups (for example, preschool, childhood, adolescence and adulthood). There is also a need to learn more about the validity of the ADHD diagnosis when onset occurs after 12 years of age. Such research will increase diagnostic accuracy and provide screening methods for clinicians. Finally, the evolution of diagnostic approaches will be influenced by a renewed focus on dimensional clinical and cognitive constructs, such as those described in the Research Domain Criteria (RDoC) project of the US National Institute of Mental Health[245]. These approaches discard diagnostic categories when looking into the cognitive and clinical features of ADHD and other related disorders.

The discovery of biomarkers that objectify the diagnosis of ADHD will reduce stigma and might foster 'precision medicine' approaches that are tailored to individual patients. No proposed biomarker currently meets the criteria for validity[246], but the future application of machine learning[247] might reveal multivariate patterns in biomarker data that have better predictive accuracy. Given the heterogeneity and multifactorial aetiology of ADHD, a successful biomarker will probably incorporate multiple domains of measurement.

Several new drugs for ADHD have passed safety tests and are being tested in humans. Some of these agents have mechanisms of action previously unexploited in ADHD; others are new formulations of existing medications that will provide new options for the timing and duration of efficacy throughout the day. Whereas current medications have dopaminergic or noradrenergic targets, future work might capitalize on studies that implicate the nicotinic acetylcholine[58], glutamate[44], γ-aminobutyric acid (GABA)[248], serotonin[249], neurite

outgrowth[50] or endosomal[250] systems. For example, a mouse model has demonstrated that fetal exposure to nicotine yields hyperactivity, reduces cingulate cortex volume, reduces dopamine turnover and responsiveness to methylphenidate and might thereby lead to the identification of new pharmacotherapies[58]. New drugs for ADHD could help clinicians to target specific symptom domains.

Further improvements to non-pharmacological approaches involving diet, mindfulness training, neurofeedback, cognitive training and specific computer gaming might yield innovative approaches. Even if they do not treat the core symptoms of ADHD, they might complement medication and behavioural approaches by treating associated symptoms. Novel approaches to improve adherence to treatment are also being developed. These strategies might have immediate clinical impact given the low level of adherence to ADHD treatments[251]. Interventions are also needed to prevent the misuse and diversion of ADHD medications, especially on university campuses[176].

Increased patient involvement in research will yield treatment studies of 'real-world' or 'patient-centred' outcomes, such as academic performance, driving, social functioning and QOL. Given that such issues are difficult to address in RCTs, the cautious application of pragmatic clinical trials[252] should lead to a better understanding of how to manage ADHD. It is good news for people with ADHD that the goal of treatment studies is evolving from reducing ADHD symptoms to eliminating all ADHD symptoms and achieving functional remission and improved QOL[151].

An important research principle explicitly named by the GCMHI is the implementation of a life-course perspective. With some notable exceptions, research into child and adult forms of ADHD has been carried out in isolation; certain age groups, especially preschool-aged children, adolescents and the elderly, have a relatively small research base. Longitudinal studies are, therefore, needed to define the developmental course of ADHD and to understand why some children with ADHD achieve functional normality in adulthood but others continue to experience a chronic, severely impairing form of the disorder. New research is indeed beginning to define neural predictors and correlates of remission[94,95,253]. Defining predictors and correlates of remission might eventually lead to a better allocation of treatment resources to children and adolescents who are at highest risk for persistent and complicated ADHD.

Research innovations along with international and interdisciplinary collaborations promise a bright future for ADHD research. By applying an integrated, bench-to-bedside approach, we can make great strides in understanding the aetiology of ADHD, refining its diagnosis, optimizing treatment outcomes and improving the QOL of patients of all ages with ADHD.

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Competing interests

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