Attention-deficit/hyperactivity disorder (ADHD) in adults: evidence base, uncertainties and controversies

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Attention-deficit/hyperactivity disorder (ADHD) was once thought to be solely a childhood condition. Now it is well established that it can persist into adulthood, with an estimated worldwide prevalence of around 2.5%. Additionally, up to 70% of individuals with childhood-onset ADHD continue to experience impairing symptoms as adults, even if they no longer meet the criteria for a formal diagnosis. The validity of adult ADHD initially faced strong criticism. Today, empirical research supports its descriptive validity (identifying characteristic signs and symptoms), predictive validity (concerning specific outcomes, courses, and responses to treatment), and concurrent validity (evidence related to its underlying causes and biological mechanisms). Despite this progress, unresolved questions and ongoing debates about adult ADHD persist. This paper summarizes current empirical evidence, alongside uncertainties and controversies, regarding the definition, epidemiology, diagnosis, etiology, neurobiology, and management of ADHD in adults. Crucially, we also include perspectives from individuals with lived experience of this condition, highlighting their views on unmet needs and priorities for improving care. Key uncertainties and controversies on adult ADHD include: a) the possibility of late-onset ADHD; b) the significance of emotional dysregulation as a core symptom; c) the definition and characterization of functional impairment; d) the persistence of comorbid psychiatric and somatic conditions after accounting for confounders; e) the relevance of executive dysfunction in the definition of the condition; f) the use of objective diagnostic measures; g) the long-term effects of treatments; and h) the role of non-pharmacological interventions. Further research on adult ADHD is urgently needed. Funding for studies on this condition lags behind that for childhood ADHD and other mental disorders in adulthood. Hopefully, efforts by clinicians, researchers and other stakeholders will ultimately help ensure that adults with ADHD are better understood, supported, and empowered to thrive.

Key words: Adult attention-deficit/hyperactivity disorder, descriptive validity, predictive validity, controversies, diagnosis, epidemiology, etiology, management, people with lived experience

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Attention-deficit/hyperactivity disorder (ADHD) is conceptualized as a neurodevelopmental disorder marked by developmentally inappropriate, pervasive and impairing inattention and/or hyperactivity-impulsivity[1-3]. It was initially considered a childhood disorder, with the nosological developments and clinical awareness of ADHD in adults lagging behind that of the childhood condition[3,4].

Although it is claimed that a very early depiction of a condition resembling what is nowadays referred to as ADHD can be found in the Greek texts of the philosopher Theophrastus in the 4th century BC[5], the first descriptions of children who would likely receive today this diagnosis appeared in French, German and Scottish texts in the 18th century[6]. The first report in a scientific journal was published in 1902, when the British paediatrician G. Still described 43 cases of children and adolescents who would qualify for an ADHD diagnosis today[7]. Many of these individuals were reported to struggle with sustained attention, and most were overactive[7,8].

The condition was initially referred to as "minimal brain damage", assuming that it was associated with brain lesions, which evolved into "minimal brain dysfunction", acknowledging that excessive levels of physical activity and inattention might not necessarily be associated with structural brain lesions[6]. It entered the official nosology in the DSM-II as "hyperkinetic reaction of childhood", followed by a series of nosological reconceptualizations, first as "attention-deficit disorder (with or without hyperactivity)" in the DSM-III, and later as "attention-deficit/hyperactivity disorder" in subsequent DSM editions, up to the current DSM-5-TR. The condition first appeared in the ICD-9 as "hyperkinetic syndrome of childhood", later renamed "hyperkinetic disorder" in the ICD-10, and "attention deficit hyperactivity disorder" in the ICD-11.

While all the above descriptions and diagnostic labels referred

to children and adolescents, the idea that ADHD could also affect adults is not new. Scattered reports from the 1950s and 1960s[9-11] described the symptomatic evolution of "minimal brain dysfunction" in adulthood, and a more systematic article published in 1976[12] sought to define this condition in a group of 15 adults. This definition was based on the presence of impulsivity, irritability, inattentiveness, restlessness, and emotional lability, in the absence of schizophrenia, primary affective disorder, organic brain syndrome, or intellectual disability. A history of long-standing impulsiveness, inattentiveness, restlessness, short temper, and emotional lability – based on self-report and information provided by third parties (e.g., parents) – was also required for the diagnosis of the condition in adults.

Building on this work, the Wender Utah criteria[13] were proposed in the 1990s for what we would today call ADHD in adults. These criteria required a retrospective childhood diagnosis of minimal brain dysfunction, ongoing difficulties with inattentiveness and hyperactivity, and at least two of the following five symptoms: mood lability, irritability and hot temper, impaired stress tolerance, disorganization, and impulsivity. However, the Wender Utah criteria have progressively diverged from conceptualizations of ADHD in the DSM and ICD, and have been criticized for their limited scope, excluding individuals with predominantly inattentive ADHD and those with coexisting mood disorders, as well as for conflating ADHD with conditions such as oppositional defiant disorder and bipolar disorder[14].

The importance of ADHD in adults has gained progressively more traction in the various editions of the DSM, as new data from longitudinal studies of youth and clinical studies of adults have placed the validity of the condition on a firm footing. The DSM-III introduced the category "attention deficit disorder, residual type" for adults diagnosed in childhood who continued to exhibit clinically significant levels of symptoms and impairment. The DSM-III-R recognized that ADHD could persist into adulthood in up to 30% of cases. Despite presenting a unique set of criteria across ages, the DSM-IV provided examples of how ADHD symptoms change in expression during adulthood. The DSM-IV also warned against relying solely on self-report for diagnosis and emphasized the importance of collateral information.

Based on field trials conducted specifically with adults, the DSM-5 changed the threshold of symptoms required for the diagnosis. Starting at age 17, five (rather than six) symptoms of inattention and/or hyperactivity-impulsivity were required. This change aligned with evidence showing that mandating at least six hyperactive-impulsive symptoms excludes a significant percentage (almost half) of adults who are at least 1.5 standard deviations above the population mean on a dimensional measure of hyperactivity-impulsivity[15].

Despite the progressive characterization of adult ADHD, its validity initially met with strong criticism. Beyond general arguments, such as the claim that the prevalence of ADHD has grown rapidly in some countries due to it representing an "expanding and lucrative market" for stimulants and related medications[16], specific concerns revolved around four main aspects[17]: a) the reliability of recalling childhood symptoms; b) the possibility that ADHD symptoms are accounted for by other disorders; c) uncertainty about the effectiveness of medications in adults; d) the fact that ADHD in adults can be a self-diagnosed condition and that some individuals may fake symptoms to obtain stimulants for misuse or diversion.

However, accumulating evidence has shown that: a) symptoms self-endorsed by adults with ADHD correlate with both parental rating scale scores and responses to methylphenidate[18,19]; b) there are individuals who exhibit ADHD symptoms without coexisting conditions that might otherwise explain the presentation[20]; c) medications with a proven efficacy in youth with ADHD are efficacious in clinical trials[21] and effective in real-world settings[22] for ADHD in adults; d) although fake diagnoses and stimulant misuse do occur, self-diagnosis may reflect gaps in the mental health system's ability to recognize legitimate conditions[14].

Furthermore, empirical research supports the descriptive validity (documentation of characteristic signs and symptoms), predictive validity (regarding specific courses, outcomes, and treatment responses), and concurrent validity (concerning etiology and pathophysiology) of adult ADHD[14].

However, while research has clarified many aspects, unresolved issues and controversies surrounding adult ADHD continue to emerge. In this paper, we summarize the empirical evidence, as well as the uncertainties and controversies, related to the definition, epidemiology, diagnosis, etiology, neurobiology, and management of ADHD in adults. Importantly, we also present the views of representatives from associations of individuals with lived experience, focusing on their perceptions of key unmet needs and priorities for adults with ADHD.

CLINICAL MANIFESTATIONS

Inattention, hyperactivity and impulsivity are currently considered the core symptoms of ADHD. Although most health care decisions – for example, those about who should be referred to treatment – involve categorizations (i.e., yes or no), ADHD symptoms, as those of most mental disorders and several somatic diseases, lie on a continuum.

Table 1 presents a list of the main ADHD symptoms across the lifespan. Manifestations of inattention are numerous, including mind wandering while performing a task, lack of persistence in low-motivating activities, forgetfulness, distraction by irrelevant stimuli, and disorganization. Hyperactivity manifests as excessive, inappropriate activity; fidgeting, tapping, restlessness or talkativeness. Impulsive symptoms include making decisions or actions without thinking or considering consequences, difficulty waiting turns, and social intrusiveness. In order to diagnose ADHD, according to current diagnostic systems, these symptoms must have specific characteristics in terms of age of onset, duration and pervasiveness, as detailed in Tables 2 and 3 and discussed in the section below on diagnosis.

Core ADHD symptoms may manifest differently in adults. Thus, hyperactivity in adults often manifests as inner restlessness, overscheduling, or not being able to relax properly. Impulsive behavior may manifest as acting without thinking or blurting things out,

Table 1 List of symptoms of attention-deficit/hyperactivity disorder (ADHD) across the lifespan

Inattention symptoms

- Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
- Often has trouble holding attention on tasks or play activities.
- Often does not seem to listen when spoken to directly.
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).
- Often has trouble organizing tasks and activities.
- Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
- Often loses things necessary for tasks and activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- Is often easily distracted.
- Is often forgetful in daily activities.

Hyperactivity/impulsivity symptoms

- Often fidgets with or taps hands or feet, or squirms in seat.
- Often leaves seat in situations when remaining seated is expected.
- Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
- Often unable to play or take part in leisure activities quietly.
- Is often "on the go" acting as if "driven by a motor".
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often has trouble waiting his/her turn.
- Often interrupts or intrudes on others (e.g., butts into conversations or games).

spending too much money or spending it too quickly, carrying out plans immediately, resigning from jobs in a flurry, starting relationships quickly, and not being able to postpone need gratification. Older adolescents and adults frequently report "sensation-seeking", "novelty-seeking", or seeking out excitement[23].

Most investigations assessing the factor structure of ADHD symptoms in various cultures have relied on samples of children and adolescents, using different information sources (e.g., teachers and parents). These findings have suggested a two-factor model for ADHD, with inattention and hyperactivity/impulsivity as two independent but correlated dimensions[24]. Some investigations using more sophisticated mathematical modeling have suggested that a bifactor model, with one general factor and three specific factors (inattention, hyperactivity, impulsivity), might fit the data better[25]. Studies with adult samples have supported this finding, suggesting separate factors for inattentive, hyperactive and impulsive symptoms[26].

Table 2 Diagnostic criteria for attention deficit hyperactivity disorder (ADHD) according to the ICD-11

- A persistent pattern (e.g., over at least 6 months) of inattention symptoms and/or a combination of hyperactivity and impulsivity symptoms that is outside the limits of normal variation expected for age and level of intellectual development. Symptoms vary according to chronological age and disorder severity.
- Evidence of significant inattention and/or hyperactivity-impulsivity symptoms prior to age 12, though some individuals may first come to clinical attention later in adolescence or as adults, often when demands exceed the individual's capacity to compensate for limitations.
- Manifestations of inattention and/or hyperactivity-impulsivity must be evident across multiple situations or settings (e.g., home, school, work, with friends or relatives), but are likely to vary according to the structure and demands of the setting.
- Symptoms are not better accounted for by another mental disorder (e.g., an anxiety or fear-related disorder, a neurocognitive disorder such as delirium).
- Symptoms are not due to the effects of a substance (e.g., cocaine) or medication (e.g., bronchodilators, thyroid replacement medication) on the central nervous system, including withdrawal effects, and are not due to a disease of the nervous system.

Table 3 Diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) according to the DSM-5-TR

A. A persistent (at least 6 months) pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Based on the preponderance of clinical manifestations, major classification systems (DSM and ICD) propose three different clinical presentations for ADHD: *combined presentation*, when both hyperactive-impulsive and inattentive symptoms are clinically significant aspects of the current clinical picture; *predominantly inattentive presentation*, with a preponderance of inattentive symptoms; and *hyperactive/impulsive presentation*, with a predominance of hyperactivity-impulsivity symptoms. In the past, these clinical presentations were known as ADHD types or subtypes. However, for a variety of reasons, mainly the lack of developmental stability, this terminology has been abandoned[27]. The ICD-11 refers to them as "specifiers", and the DSM-5-TR as "presentations". The developmental stage of the individual must be considered when characterizing the ADHD clinical presentation. Since hyperactive/impulsive symptoms decrease more significantly than inattention in clinical and population samples[28], the most frequent presentation found in older adolescents and adults is ADHD with predominantly inattentive symptoms.

Motivation, relevance, and attractiveness of the task influence symptomatic manifestations. Individuals with ADHD may be able to remain focused when performing specific tasks such as playing videogames. Thus, overconcentration or "hyperfocus" in highly motivating situations are frequent in individuals with this condition. ADHD can thus be viewed as an attention *dysregulation* (rather than *deficit*) disorder. Many patients with ADHD can concentrate in some contexts, but they cannot deploy concentration at some ordinary moments in which it is needed.

Regarding effects of context, careful parents may provide structured environments and stimulation for their children with ADHD, creating a situation in which symptoms only manifest later in adolescence and young adulthood, when more autonomy is needed.

In addition, culture shapes the expression and expectations of behaviors and symptoms[29]. Thus, assessment of ADHD symptoms must always consider cultural aspects.

In addition to what are currently conceptualized as the core symptoms of the disorder, individuals with ADHD may often present with additional problems/dysfunctions. Problems with peers, already evident in childhood, tend to become more pronounced during adolescence and young adulthood, contributing to social rejection and fewer friendships.

Substance experimentation during adolescence is also common, and individuals with ADHD are at a significantly higher risk for substance use disorders, as well as being more vulnerable to engage in other risky behaviors such as unprotected sex, with consequent higher rates of sexually transmitted diseases and pregnancies in young adulthood[3].

Despite a large amount of research to date, there are several uncertainties and controversies regarding the clinical manifestations of adult ADHD.

First, should emotional dysregulation be part of the diagnostic construct of ADHD in adults? Although this is a transdiagnostic manifestation (i.e., with low specificity for ADHD), it is extremely frequent in adults with the disorder. Adolescents and young adults with ADHD often exhibit excessive negative and positive responses, along with outbursts of anger and irritability[3]. Indeed, emotional dysregulation was a core part of the first descriptions of adult ADHD[12], and up to 70% of adults with the disorder implement more frequently non-adaptive emotion regulation strategies compared to people without ADHD symptoms. Additionally, emotion dysregulation is clearly associated with both symptom severity and executive functioning[30].

However, emotional dysregulation is currently not part of the core symptoms of ADHD, and there is uncertainty on whether this manifestation in adults with ADHD is not simply the heir of oppositional defiant disorder, an extremely prevalent comorbid diagnosis in children with ADHD often not recognized by adult psychiatrists[31]. Additionally, emotional dysregulation is associated with controversies in the differential diagnosis between ADHD and bipolar disorder. Momentaneous outbursts of anger and irritability followed by quick return to baseline are regarded as characteristic of adults with ADHD by some clinicians, while others see this symptomatic presentation as an expression of the bipolar phenotype[32].

Second, should executive functioning deficits be more represented in diagnostic criteria for ADHD in adults? The key role of this dysfunction in adult ADHD was demonstrated by Kessler et al[33], who documented that executive deficit manifestations – such as difficulty prioritizing work or completing tasks in allotted time, and making careless mistakes – are the most important predictors of a diagnosis of adult ADHD according to the DSM-IV. However, the presence of executive dysfunction is not currently required for the diagnosis of ADHD, and some consider it as a possible associated dimension that is important to assess and address when present, rather than a core symptom[34].

An additional area of uncertainty concerns the relationship between ADHD and a cluster of symptoms comprised of lethargy, underactivity, apathy, daydreaming, slow thinking, excessive sleep, and being easily lost in thoughts, named sluggish cognitive tempo (SCT) and, more recently, cognitive disengagement syndrome[35]. The nosological status of SCT, initially considered similar to ADHD inattentive presentation and now conceptualized as a transdiagnostic specifier across many disorders, needs further refinement, especially in relation to adult ADHD.

SCREENING AND ASSESSMENT

Screening and assessment for ADHD in adults is often more complex than in children, and must take into consideration cultural norms of age- and gender-appropriate behavior, as well as family values and environmental demands. The key message is avoiding rapid evaluations based only on checklists. Relying on multiple information sources for symptom and impairment ratings (e.g., family members, close friends, co-workers) can improve diagnostic accuracy[23,36], particularly with respect to establishing the presence of symptoms before age 12[37,38].

There can be barriers to obtaining informant reports in some clinical settings, but clinicians are nonetheless encouraged to pursue these reports, given the high rates of both false positive and false negative ADHD symptom reporting that may occur. Indeed, individuals may overinterpret normative cognitive variations as ADHD symptoms, or persons with longstanding ADHD may reject their diagnosis despite continuing to display impairing symptoms [39]. When it is not feasible to integrate informant report into the diagnostic process, a structured clinical interview is advised, so that the clinician can probe for concrete examples of reported ADHD symptoms and link these symptoms to impairment, or further question symptoms denied by the person but noted in the clinical record.

There is no age limit for an ADHD diagnosis. The diagnosis is possible and reliable in children as young as three years of age[39] as well as in older adults[40]. However, ADHD diagnoses may be delayed in women, in individuals who identify as ethnic or racial minorities, and in those with high intelligence. Sociocultural factors, barriers to care, and compensatory strategies are known to produce disparities in age of first ADHD diagnosis[41,42].

Since ADHD is defined by the presence of a persistent and age-inappropriate pattern of inattention and/or hyperactivity-impulsivity interfering with normal functioning or development, it is essential to recognize the main symptoms in these two domains (see Table 1). Of note, these behaviors should not be due to defiance or lack of comprehension. Further aspects that deserve attention during the assessment process are the age of onset of symptoms, their temporal stability, their situational pervasiveness, their incongruency with expected developmental patterns, and the extent to which they lead to functional impairment.

ADHD is classified as a neurodevelopmental disorder with childhood onset and a chronic course. However, recent data show that at least some individuals present a fluctuant pattern of ADHD remission and recurrence from childhood to middle adulthood [39,43,44]. While a duration of at least 6 months is helpful to establish

symptom stability, clinicians should expect that some symptoms wax and wane depending on contextual factors.

Individuals without ADHD may experience ADHD-like symptoms that arise as short-term responses to stressors such as family problems or higher academic/occupational demands. In these cases, it is helpful to construct a developmental timeline of the onset and offset of the symptoms, including factors that the person or the clinician perceives to influence symptom severity and expression. In this assessment, it is essential to set a common understanding with the person on a culturally acceptable definition of what is considered to be frequent.

The symptoms must be inconsistent with the developmental stage of the individual under assessment, which may differ from chronological age in adults with developmental disabilities. Since ADHD symptomatology is dimensionally distributed in the population, any clinical cut-off involves a level of arbitrariness, creating uncertainty in the assessment of individuals with milder symptoms. Thus, clinicians are faced with the difficult task of defining the boundaries separating typical from pathological behavior for each individual. In this scenario, extensive knowledge of normal human development and the person's sociocultural context is crucial.

ADHD symptoms in childhood are frequently found in referred adult cases. However, clinicians should be cautious when excluding ADHD only based on onset of symptoms after 12 years of age. Indeed, in some cases, demands from the environment are lower during childhood, and higher individual cognitive resources and/or family structure and support might prevent the expression of symptoms earlier in development. Impairing symptoms may eventually hatch during adolescence and young adulthood, when the individual faces needs of more autonomy or higher demands[45].

In most cases, the origin of symptoms can be linked to childhood (e.g., subthreshold or unimpairing difficulties recollected by the patient or a parent) and their escalation over time can be related to changing environment or developmental demands. When the clinician cannot trace symptom expression back to childhood based on available information, it is critical to perform a thorough differential diagnostic assessment prior to diagnosing adult-onset ADHD. Notably, research suggests that over 90% of apparent late-onset ADHD cases are ruled out once differential diagnostic procedures are applied[36].

Pervasiveness of symptoms in different environments is another key aspect for ADHD diagnosis. The underlying rationale is to avoid diagnosis in cases where symptoms manifest only in relation to environment-specific triggers (e.g., only at home due to severe family conflicts; only at university or work due to tasks/duties inappropriate for individual's capacities). For example, one study found that up to 40% of the population will report ADHD symptoms in a single context[46]. In many cases, single-setting ADHD symptoms are not associated with impairment or risks for negative outcomes[47]. However, some individuals who display impairment in just one setting at one point in time may show impairment in multiple settings at a later point, when facing more challenging demands[45], creating another diagnostic conundrum. As a result, it may be appropriate to apply a provisional diagnosis of Unspecified ADHD to individuals showing single-setting ADHD symptoms, and to monitor whether symptom pervasiveness increases over time.

Evaluation of impairment is a further important area of assessment. Impairment domains for adults with ADHD are broader than in childhood, including risky behaviors, interpersonal difficulties, underperformance at work or in higher education, financial problems, chronic record of motor vehicle accidents or unsafe driving, and impaired parenting. Since ADHD symptoms reflect a dimensional trait in the population, failure to properly incorporate the impairment criterion as part of the diagnostic criteria for the disorder may result in an explosion of prevalence rates[48]. Two clinical challenges here are: a) how to disentangle the source of impairment (is it coming from ADHD symptoms or from the very frequently associated mental disorders?); b) how to decide if impairment is sufficiently severe to warrant diagnosis (do we threshold impairment against the average peer or the hypothetical potential of the individual?). Clinicians may meet adults with mild ADHD symptoms who show negligible impairment but report internal distress, reduced self-esteem, and self-blame as a consequence of their symptoms. Presently, the DSM-5 classification suggests that ADHD cannot be diagnosed in this scenario, but Unspecified or Otherwise Specified ADHD may be an appropriate alternative diagnosis in these cases.

Diagnostic interviews and rating scales

A structured/semi-structured clinical interview with the patient is the gold standard tool in the assessment of adult ADHD. The instrument with the greatest empirical support is the Diagnostic Interview for ADHD in Adults (DIVA-5) (http://www.divacenter.eu/DIVA.aspx), a semi-structured interview based on the DSM-5.

ADHD is often not included or is screened on a limited basis in broadband adult psychiatric interviews, given its recent recognition as a disorder that presents in adults. Several structured and semi-structured interviews can be used for differential diagnosis in adults, such as the Structured Clinical Interview for DSM-5 (SCID-5)[49]. However, their use tends to be restricted to research settings.

There is uncertainty from practitioners, reflected in varying clinical practices and protocols, on the use of rating scales. Though not recommended as a standalone tool for diagnosing ADHD[50], they are helpful in the diagnostic process in adults. Their main utility for clinicians is related to: a) initial screening, that should be followed by clinical assessment, of ADHD symptoms in targeted populations (e.g., adults seeking treatment for substance use problems or another psychiatric disorder); b) obtaining information from collaterals on ADHD symptoms; and c) monitoring symptom trajectories during treatment.

The three rating scales with the best balance among psychometric properties are the Wender Utah Rating Scale-25 (WURS-25)[51], the Conners Adult ADHD Rating Scales (CAARS)[52], and the Adult ADHD Self-Report Scale-18 (ASRS-18)[53]. We focus here on the ASRS, an open-access instrument with two versions: a) a screener version with six items developed by the World Health Organization (WHO), that is suitable for primary care settings

and for a quick screening of ADHD[54]; b) a long version with the eighteen DSM symptoms, probably more useful for specialized settings. Both versions use wording more adequate for adults. A short version adapted for the DSM-5 is also available[55], and has strong properties when applied to screening.

A systematic review and meta-analysis of studies in children and adolescents[56] – that awaits replication in adults – concluded that most included rating scales have excellent overall diagnostic accuracy, as indicated by the area under the curve. However, the use of a single reporter is unlikely to achieve sufficient sensitivity and specificity for clinical use or population screening[56]. The same is probably true in adults.

The role of biomarkers and neuropsychological tests

There are no ancillary tests or biomarkers with sufficient positive and negative predictive power for the diagnosis of ADHD. No evidence supports the inclusion of neuroimaging exams – e.g., magnetic resonance imaging (MRI), single photon emission computerized tomography (SPECT), positron emission tomography (PET) – or electroencephalography in routine clinical assessment of ADHD, although they can be useful in very specific cases for differential diagnosis[57]. A systematic review of studies in children and adolescents[58], which awaits replication in adults, after examining 780 studies across neurodevelopmental disorders (including ADHD), could not find any biomarker with evidence – from two or more studies by independent research groups, showing results in the same direction – demonstrating specificity and sensitivity of at least 80%.

There are controversies and uncertainties in relation to the use of neuropsychological tests (e.g., continuous performance tests, executive function batteries), nowadays administered mainly digitally, in the diagnostic process. Recently, the UK National Institute for Health and Care Excellence (NICE)[59], after systematically reviewing the literature (including available meta-analytic evidence [60,61]) and consulting experts and individuals with lived experience, issued its recommendations on the use of digital technologies for the diagnosis of ADHD. They suggest that the QbTest, a test combining evaluation of motor activity using an infra-red camera with continuous assessment of attention and impulsivity, could be used as an option to support the diagnosis of ADHD in children. However, for adults, none of the available neuropsychological tests (including the QbTest) were endorsed, due to insufficient methodologically sound evidence. The guidance specifically warns against using these tests, which can be costly, as a triage system to assign patients to waiting lists for assessments – a practice common in some health care centers.

Differential diagnosis

One step in the differential diagnostic process is to rule out health conditions that may mimic ADHD symptoms. For example, sleep problems and deficits in visual and/or hearing acuity may be confused for ADHD. Although the relation between ADHD and sleep disorders/problems is complex (i.e., ADHD and sleep disorders such as restless leg syndrome might co-occur; sleep problems such as long sleep onset latency might be part of the ADHD phenotype or the result of ADHD treatment), some sleep disorders such as insomnia or obstructive sleep apnea might lead to inattentive and hyperactive symptoms during the day. Thus, a good assessment of sleep conditions is mandatory in differential diagnostic assessment.

Physical and laboratory investigations can help in excluding other clinical conditions (e.g., hyperthyroidism, traumatic brain injury). Likewise, it is important to rule out the use of any medication that might cause inattentive and/or hyperactivity/impulsive symptoms. Referral for genetic examination is recommended if there is a clear developmental delay and/or if suggestive phenotypes are present (i.e., neurofibromatosis type 1; fragile X syndrome)[63].

Difficulties with attention are among the most common symptoms listed in the DSM-5-TR[64]. Thus, a number of psychiatric conditions – including mood and anxiety disorders, post-traumatic stress disorder (PTSD), psychotic disorders, neurocognitive or other neurodevelopmental disorders, impulse control disorders, and substance use intoxication or withdrawal – must be ruled out.

Some disorders that commonly co-occur with ADHD (e.g., generalized anxiety disorder, bipolar disorder, major depression, learning disorders, and PTSD) must be ruled out as the sole source of ADHD-like symptoms, which can be challenging and create diagnostic uncertainties. Of note, ADHD and autism frequently co-occur, and the presence of ADHD symptoms in patients with autism spectrum disorder generates distinct problems.

In the process of conducting a careful differential diagnosis, some clinical tips might be relevant: a) consider the age of onset of the symptoms (for example, when disentangling inattention as part of ADHD versus a mild chronic depressive disorder, the occurrence of inattentive symptoms before the onset of any mood symptoms reinforces the ADHD diagnosis); b) examine the trajectory of the symptoms (for example, the clearly episodic occurrence of hyperactivity, impulsivity and irritability can suggest bipolar disorder); and c) assess if the way symptoms manifest is better explained by another mental disorder (e.g., inattention only as a consequence of dysfunctional thoughts/rumination related to performance as in generalized anxiety disorder; inattention related to rituals of counting as in obsessive-compulsive disorder; inattention and executive deficits following abuse of cannabis without any previous history of ADHD symptoms; inattention only related to reading in dyslexia)[63].

ASSOCIATED CONDITIONS

Psychiatric comorbid conditions

ADHD is frequently comorbid with other psychiatric conditions. This comorbidity is associated with greater ADHD symptom severity[65], stronger impairments in daily functioning[66], higher health care needs[67], and higher mortality[68]. Robust knowledge on comor-

bid conditions of ADHD is potentially helpful for the prevention of their onset, and for monitoring and treatment decisions when (early signs of) comorbid conditions have already developed[69,70].

In childhood, it is well-established that oppositional defiant disorder, conduct disorder, childhood-onset anxiety disorders and autism are often comorbid with ADHD[71-73]. While none of these conditions are likely to (fully) remit in adulthood, there is an important gap in the literature, as few longitudinal studies have looked at their continuity from childhood through adolescence and into adulthood.

Studies on psychiatric conditions comorbid with ADHD in adults are mostly separate from those in childhood and have predominantly focused on the so-called "common mental disorders", i.e. anxiety, depressive and substance use disorders. A systematic review and meta-analysis of this literature[70] – including findings from general population studies based on national registers, insurance claims data, and large surveys (N>10,000) – showed strong differences in adults with ADHD compared to those without this disorder. The meta-analysis reported pooled odds ratios (ORs) of 5.0 (95% CI: 3.29-7.46) for anxiety disorders, 4.5 (95% CI: 2.44-8.34) for major depressive disorder, 8.7 (95% CI: 5.47-13.89) for bipolar disorder, and 4.6 (95% CI: 2.72-7.80) for substance use disorders. Other, less extensively studied, psychiatric conditions that are more frequent in adults with than without ADHD are (specific) personality disorders, eating disorders and schizophrenia[74,75]. These disorders, together with the potential (heterotypic) persistence of childhood comorbid conditions, need additional general population-based studies.

Somatic comorbid conditions

In children with ADHD, an elevated risk has been found for obesity and asthma[76-78]. Other somatic conditions for which an increased risk has been reported in children with ADHD include rhinitis, food allergy, dermatitis, and type 1 and 2 diabetes mellitus[78,79]. The risk of obesity may be somewhat higher in adults (OR=1.6, 95% CI: 1.3-1.8) than in children (OR=1.3, 95% CI: 1.2-1.5) with ADHD[76], while the risk of asthma seems to be similar (OR=1.4, 95% CI: 1.4-1.4 in adults; OR=1.6, 95% CI: 1.2-2.1 in children)[78,80].

For several years, few somatic conditions have been thoroughly studied in relation to adult ADHD beyond obesity and asthma[81]. More recently, there has been a surge of studies, based particularly on Swedish health registers. A study[82] reported associations of adult ADHD with obesity (OR=2.7, 95% CI: 2.6-2.8), asthma (OR= 2.4, 95% CI: 2.3-2.5), sleep disorders (OR=4.6, 95% CI: 4.4-4.8), migraine (OR=2.0, 95% CI: 1.9-2.1), epilepsy (OR= 3.0, 95% CI: 2.8-3.2), and chronic obstructive pulmonary disease (OR=3.2, 95% CI: 3.0-3.6). Studies digging deeper into specific somatic disease categories showed that adult ADHD was associated with a diagnosis of any of 13 investigated autoimmune diseases (OR=1.3, 95% CI: 1.3-1.4), with estimates ranging from 1.1 (95% CI: 1.0-1.2) for ulcerative colitis to 1.8 (95% CI:1.4-2.3) for Sjögren's syndrome[83].

Another study[84] showed an increased risk across all types of cardiovascular diseases, even when use of stimulants and other psychotropic drugs was accounted for (hazard ratio, HR=2.1, 95% CI: 2.0-2.1), with the highest risk for cardiac arrest, hemorrhagic stroke and peripheral vascular disease/arteriosclerosis. A meta-analysis on type 2 diabetes mellitus showed an OR of 2.29 (95% CI: 1.48-3.55), which was confirmed in that same paper by an HR= 2.35 (95% CI: 2.14-2.58) based on data from the Swedish registers[85]. A strong association was also found between adult ADHD and sleep disorders, with ORs ranging from 6.4 (95% CI: 6.0-6.7) in mid-to-older adulthood to 12.6 (95% CI: 12.1-13.1) in young adulthood[86]. All these findings were confirmed in a study based on insurance claims data from Germany[80], which also included data from primary care, reflecting an overall poorer somatic health in adults with ADHD. Finally, two studies[80,82] found an enhanced risk of Alzheimer's disease and Parkinson's disease (OR range: 5.2-7.1, aggregated 95% CI: 4.5-9.3).

General considerations

The associations with these psychiatric and somatic conditions have important implications for the management of ADHD (see below). However, some uncertainties remain that require additional studies or novel research strategies. One uncertainty is the extent to which comorbid psychiatric and somatic conditions persist after controlling for a series of important confounders. A study on the association between ADHD and asthma first retrieved all significant confounders with a systematic review and then assessed the association using health registers while controlling for all those confounders[87]. Second, temporal links of ADHD with psychiatric and somatic conditions are mostly unclear, with some prominent exceptions[69,75]. Assuming that ADHD may predate most comorbid conditions, prospective studies are particularly important for knowledge on the age of onset of comorbid conditions and therefore for optimal timing of preventive programs. However, cross-sectional studies on psychiatric and somatic comorbidities that report on different developmental periods from childhood to old age are a reasonable alternative[67,80].

Third, psychiatric comorbid disorders are potentially part of the pathway between ADHD and onset of somatic conditions. This is clear for alcohol-related liver disease (OR=4.7, 95% CI: 3.7-5.6)[82] and likely holds for other somatic conditions as well. Finally, the idea that we could prevent adult-onset conditions that are highly comorbid with ADHD assumes that aspects of ADHD are causal factors in these onsets. This needs more research, including study of possible mediators between ADHD and the comorbid condition, for instance through Mendelian randomization approaches. A recent example[88] focused on the pathway between ADHD, mediators including obesity, and type 2 diabetes mellitus.

EPIDEMIOLOGY

Among school-aged children, the prevalence of ADHD, based on epidemiological studies representative of the general population, is estimated at around 5.5%[89]. Although there is some varia-

tion among studies due to methodological differences, most notably the application of impairment criteria, the prevalence of the disorder is similar across geographic regions[90,91]. By contrast, the administrative prevalence – i.e., that determined based only on administrative records, e.g., billing records – varies across regions, based on multiple factors, including awareness of ADHD, training of clinicians, and conceptualization of the disorder. Only half of individuals with ADHD are diagnosed before age 14[92].

Longitudinal studies[93] have documented an age-dependent decline in symptoms from childhood through adulthood, such that most children with ADHD will no longer meet full criteria for the disorder by age 30. This decline is more marked for hyperactivity and impulsivity compared with inattention[94]. Persistence of ADHD is predicted by disorder severity, psychosocial adversity and psychiatric comorbidity[95-98].

The most recent meta-analysis points to an overall prevalence of 2.5% in adults, with a gradual decline to 1% by age 60[95]. Population studies show that, when the age at onset criterion for the disorder is ignored, prevalence increases to about 9% in early adulthood and 4% at age 60[95].

There are several challenges and uncertainties when estimating the prevalence of ADHD in adults. First, while most individuals with a diagnosis of ADHD in childhood will not meet formal diagnostic criteria in adulthood, about 71% will present with ADHD symptoms, and 65% with functional impairment[93]. Therefore, a crucial issue is whether formal criteria or functional impairment are assessed.

Second, there is an ongoing debate on the existence of cases with late onset, i.e., starting in late adolescence or later on. Indeed, although diagnostic criteria for ADHD require onset prior to age 12, some have argued that adult-onset ADHD is common and distinct from childhood-onset ADHD[38]. It is likely that most of these late-onset cases had indeed symptoms of ADHD in childhood that they were able to compensate for until adulthood. In fact, many individuals in the late-onset group exhibit some ADHD symptoms during childhood or display an externalizing disorder such as oppositional defiant disorder[29]. Moreover, current studies indicate that the majority (if not all) of late-onset ADHD cases emerge between the ages of 12 and 16, classifying them as adolescent or early adult onset ADHD[29].

However, the idea that some cases present with ADHD onset in adulthood remains an area of controversy[99]. Overall, caution should be urged in diagnosing ADHD when onset occurs in adulthood[99], although such onsets can occur due, for example, to traumatic brain injury[100].

Third, while ADHD has traditionally been considered a stable, chronic condition, more recent follow-up studies indicate that, after ADHD remits, it can recur[39]. An analysis of the Multimodal Treatment Study of ADHD, in which patients underwent eight assessments during follow-ups ranging from 2 to 16 years after baseline, showed that about 60% of them experienced a recurrence of ADHD after the initial period of remission[39]. Another study of three independent cohorts suggested that about a quarter of ADHD youth will have a fluctuating course[101].

ADHD is two to three times more common in males than females in the general population[90]. The sex difference in clinics is much larger, because girls – who tend to be inattentive and not disruptive – are less likely to be referred for treatment[102,103]. The sex ratio decreases with age, so that by adulthood it is close to 1[104].

In a meta-analysis of epidemiological population studies comprising 218,445 participants[105], no significant differences in the prevalence of ADHD were found between Black, White, Asian and Latino individuals. There was substantial heterogeneity for each minority subgroup, but meta-regression could not find the reason for it. Moreover, significant publication bias was detected. Data regarding clinical diagnoses are more consistent. Several studies suggest that underdiagnosis occurs in Black and Hispanic groups in the US[106-109]. In Europe and Israel, immigrants are less likely to be diagnosed with ADHD compared to non-immigrants[109]. Lower treatment rates have also been documented for minority groups [108-110].

ADHD treatment in children has increased rapidly in recent years[111,112]. The number of published studies in adults is far lower than in children. In a register study based on the entire adult population in Denmark, Finland, Iceland, Norway and Sweden[113], the annual prevalence of ADHD drug use increased during the study period for both genders and all age groups (from 2.4 to 5.3 per 1,000 men, and from 1.8 to 4.4 per 1,000 women). Another multi-national study using population-based databases from 14 countries[112] reported that, among adults aged 19 years or older, the prevalence of any ADHD medication use in 2010 varied between 0.003% and 1.48% (0.05% in Asia and Australia, 1.42% in North America, 0.47% in Northern Europe, and 0.03% in Western Europe). The absolute increase in ADHD medication use prevalence per year ranged from 0.0006% to 0.12%. So, the available evidence suggests that use of ADHD medications in adults is rising in many countries. This may be associated with an increased awareness and diagnosis of adult ADHD. Furthermore, many children that grow into adulthood are continuing their ADHD medication, hence increasing the prevalence of medication use in adults.

BURDEN

Functional impairment

One controversy about defining impairment in adults with ADHD is whether clinicians should compare a patient's functioning to that of the general population or to the patient's potential as indicated by measures such as IQ or aptitude tests. Using the population as a benchmark has the advantage of being objective, especially where there are standards for what constitutes impairment. For example, chronic unemployment is easier to see as impairment than a moderately successful physician struggling to maintain a practice. Assessing impairment relative to potential recognizes that ADHD symptoms may limit a person's ability to meet his/her own goals or expectations, even if he/she performs adequately compared to the population. Indeed, research has validated the diagnosis of ADHD in highly intelligent patients[114-117]. A highly intelligent adult may meet average workplace standards, yet underperform

relative to his/her potential, leading to frustration, dissatisfaction, and a lack of fulfilment. In practice, clinicians should balance these perspectives by first assessing impairment relative to the general population and then gathering information about the patient's potential, expectations, goals, and self-perceived limitations, which often reveal struggles that standardized measures miss.

It can also be difficult to define and assess functional impairment in older adults[118]. This issue is particularly challenging given the overlap between ADHD symptoms and other problems common in older age, such as cognitive decline and physical health issues, as well as the effects of long-standing compensatory strategies. Traditional definitions of impairment in ADHD focus on domains such as occupational performance, educational achievement, and parenting responsibilities. These domains do not fully capture the challenges faced by older adults, for whom impairment manifests more prominently in areas such as social functioning, health management, financial organization, or maintaining independence.

Another complicating factor is that many older adults may not recognize their struggles as impairments because they have lived with these challenges for decades. This can result in underreporting of challenges and underestimation of their impact. Furthermore, social expectations and norms for older adults may lower the perceived significance of certain impairments, such as difficulty managing time or multitasking.

When evaluating older adults for ADHD, a comprehensive assessment should include an exploration of functional difficulties across age-relevant domains. Collateral information from family members or close friends is especially valuable, as older adults may have difficulty identifying their own impairments. It is essential to evaluate the patient's quality of life and goals. For some older adults, even mild impairments in functioning may have a significant impact on their sense of well-being and autonomy. Clinicians should take these subjective experiences into account when assessing the need for a diagnosis and potential interventions.

Economic impact

Several studies have estimated the economic burden of ADHD. For instance, a study estimating the incremental costs of ADHD (i.e., excess costs over and above those of individuals without ADHD) in the US – in relation to health care, productivity and income losses, education, and justice system – reported costs of $1,137-4,100 per adult per year[119], which is similar to that of chronic complex somatic conditions[120].

Comorbidities, including somatic diseases, are common in ADHD and are important cost drivers. A study[121] that prospectively followed a cohort of 445,790 adults from ages 18 to 26 found that the annual per capita costs associated with multimorbidity were $1,223 for individuals with a childhood ADHD diagnosis. Among these, costs were higher for persisters ($1,456) compared to remitters ($837). The costs for individuals without an ADHD diagnosis were significantly lower, at $418. The main drivers of the above costs were inpatient hospital admissions, primarily due to drug abuse and injuries. Another study in Sweden[122] found that middle-aged adults (30-45 years) newly diagnosed with ADHD had significantly higher health care costs and utilization compared to those without ADHD. Data from individuals born 1966-1978 showed greater outpatient, inpatient and medication costs for psychiatric and somatic comorbidities, with females incurring higher medication costs than males.

Using data from the Danish National Registers in 5,269 adults diagnosed with ADHD in adulthood, a cross-sectional analysis[123] for the year 2010 compared costs incurred by adults with ADHD and their siblings, using data from health, education, crime, employment, and social care registers. Adults with ADHD were found to have significantly lower disposable incomes and paid less tax than their siblings. They received more state benefits and incurred higher costs related to health care, social care, and crime.

Overall, the available evidence highlights that ADHD imposes substantial economic costs on both individuals and the state. This underscores the need to consider the broader economic implications of ADHD, extending beyond income and health care-related expenses.

ETIOLOGY

The etiology of ADHD has been investigated using multiple approaches. Genetics has been the most frequently applied among these approaches, both based on family and twin studies as well as using molecular genetics methods. More recently, also other types of molecular "omics" have been explored, including analyses of the epigenome and transcriptome as well as the microbiome. In all those studies, childhood ADHD has thus far been the main topic, but studies of adult ADHD have also been conducted at least in some areas of research.

Genetics

Twin and family studies

Twin and family studies show that genetics contributes substantially to the etiology of ADHD, with heritability estimated at 70-80% [124]. Twin studies of ADHD in adults have reported lower heritability (30-40%). However, this is not the case in studies using multiple informants[125] or clinical diagnosis[126], in which the heritability of ADHD is >70% also in adults[127].

Large-scale cross-generational analyses indicate a genetic correlation of approximately 0.5 between child and adult presentations of ADHD, suggesting that developmental changes in ADHD presentation may be partly underpinned by genetics[128]. Nonetheless, few longitudinal twin studies of ADHD extend beyond young adulthood, preventing definitive conclusions of whether all forms of adult ADHD represent a continuation of childhood ADHD[29,128]. Twin and family data exploring the etiology of ADHD in later life are lacking.

Twin studies in childhood support the dimensional nature of

ADHD, with the genetic correlation between diagnosed ADHD and ADHD symptoms in the general population estimated to around 0.6[129]. While such conclusions are expected to extend to ADHD in adults, this remains to be tested. The high rates of psychiatric comorbidity in ADHD (e.g., for depression, eating disorders, bipolar disorder, and substance use disorders) are partly mediated by shared genetics, with cross-condition genetic correlations estimated at about 0.5 in both children and adults[130,131].

While much less researched, recent family studies also support genetically mediated links between adult ADHD and somatic conditions, including asthma, obesity, migraine and cardiovascular diseases[82,132], and provide tentative support for a link with neurodegenerative conditions.

Molecular genetics

In the largest available meta-analysis of genome-wide association studies (GWAS) of ADHD (comprising data on 38,691 patients and 186,843 controls), 27 significant loci were found, implicating 76 genes, many of which are upregulated in early neurodevelopment[133]. This meta-analysis primarily comprised children diagnosed with ADHD. Only two GWAS of ADHD in adults[134,135] have been conducted so far, both reporting a strong genetic correlation (>0.8) between ADHD in children and adults. Thus, current evidence from research of common genetic variants indicates a largely similar genetic background of ADHD in adults and children, particularly when adult ADHD is defined by persistence from childhood into adulthood.

No large-scale genetic studies have yet looked into well-defined adult-onset ADHD. However, some studies have reported differences in genetic profiles of common variants between individuals with persistent ADHD and those either first diagnosed with ADHD in adulthood or with symptoms first emerging in adolescence. The latter two appear to have a lower genetic burden for ADHD (as determined based on polygenic scores), stronger positive genetic links to depression and substance misuse, and stronger negative genetic links to education and cognition[29,134,136,137]. Yet, definitive conclusions cannot be drawn, as the studies on clinical diagnoses lack data on symptoms in childhood, and no longitudinal studies of sufficient sample size are yet available.

Studies using GWAS data and ADHD polygenic scores for genetic correlation analyses suggest a strong genetic link between clinically diagnosed ADHD and ADHD symptoms in the population[138], as well as a genetic link between ADHD and several psychiatric and somatic conditions, negative health behaviors (e.g., smoking initiation), psychosocial risk factors (e.g., low socioeconomic status), phenotypes in cardio-metabolic (e.g., higher body mass index and cardiovascular risk) and reproductive (e.g., lower age at first childbirth) domains, and even reduced longevity[133,138-140]. This implies that genetic variation identified in the GWAS largely based on childhood ADHD also confers risk for important health and behavioral outcomes measured across the lifespan.

In addition to common genetic risk variants, rare variants (with potentially larger effect sizes) have also been analyzed to explain ADHD etiology. Individuals with ADHD carry an increased burden of rare, protein-truncating variants in evolutionarily constrained genes[141]. One study suggested a higher rare variant burden in individuals diagnosed with ADHD in childhood, compared to those first diagnosed as adults[134]. Around 10-15% of individuals with ADHD carry rare copy number variants (CNVs)[124,142,143]. Many of these CNVs are also implicated in autism spectrum disorder and schizophrenia, and thus seem to exert effects across disorders with different ages of onset[142,144].

Epigenetics and transcriptomics

Epigenetic modification of DNA (DNA methylation) is an important factor in the regulation of gene activity, influenced by both genetic and environmental variables. Various epigenome-wide association studies (EWAS) have been performed for ADHD[145], analyzing between 450,000 and over 800,000 sites of variable DNA methylation. Most studies have focused on children with clinical diagnosis or symptoms of ADHD. However, the largest EWAS, with over 4,500 participants, was on ADHD symptoms in adults[146]. Though several interesting candidate genes were identified, no findings reproducible across the three analyzed cohorts were observed. Larger sample sizes are clearly needed before significant findings can be expected from EWAS. Moreover, epigenetic modifications are cell type-specific. Although we consider ADHD a brain disorder, epigenetic studies make use of DNA isolated from blood or buccal cells, which has to be considered in data interpretation.

The "transcriptome" represents the output of active genes – the DNA template of a gene is transcribed to produce RNA. Studies of the transcriptome in ADHD are of two types[147]: those that compare RNA isolated from the blood of people with and without ADHD[148,149], and those that integrate GWAS findings with transcriptome data from more relevant tissues/cell types (i.e., different brain areas/cell types) in so-called transcriptome-wide association studies (TWAS)[137,150-153]. All of the latter studies identified novel candidate genes for ADHD. Only one of these studies discriminated between childhood and adult-diagnosed ADHD in the GWAS they used as input information[137]. Though different genes were identified in the two resulting TWAS, the study was underpowered to test significance of differences between the two groups.

Emerging picture of the molecular biology of ADHD

Based on the results of the above-mentioned studies, we are starting to get a first glimpse of the molecular biology of ADHD. Enrichment analyses are being used to link genetic, epigenetic and transcriptomic findings to biological pathways, developmental stages of brain development, and even individual brain cell types. Gene enrichment analyses based on the results of the latest GWAS [133] link early brain development to ADHD and indicate a role for dopaminergic and GABAergic systems and glial cells in ADHD etiology. Integration of candidate genes from epigenetic studies sug-

gests involvement of neurogenesis, neuronal differentiation, cell adhesion, and axon guidance processes in ADHD[145]. TWAS reveal enrichment for several biological pathways as well, including dopaminergic neuron differentiation, noradrenaline release cycle, and triglyceride lipase activity[152]. Since the studies are heavily focused on children with ADHD, we will have to await confirmation of findings for adults.

In summary, twin and molecular studies are greatly advancing our understanding of the etiology of ADHD, and suggest that genetic factors play a substantial role and are largely shared across ages. Nonetheless, well-powered studies of ADHD in adults which contain both "omics" data and information on developmental symptom trajectories are scarce. As such, we are yet to discover if there are more nuances in the etiology of ADHD with increasing age. In addition, genetic risk interplays in complex ways with environmental exposures.

Environmental risk factors

While a large number of studies have found correlations between ADHD and environmental risk factors, such as maternal pre-pregnancy obesity and smoking during pregnancy, such associations must be interpreted with caution[154]. Alternative explanations such as familial confounding (i.e., genetic or other familial variables contributing to both the risk factor and ADHD) need to be addressed to strengthen causal inference. Twin, sibling and family studies have been used to disentangle the effects of environment from genetics, demonstrating that low birth weight, gestational age, and family income in childhood are associated with ADHD even after adjustment for familial confounding[155]. In contrast, several putative risk factors, including pregnancy-related factors (e.g., pre-pregnancy obesity and maternal smoking during pregnancy) were primarily explained by familial confounding[155]. The majority of gene-environment interplay research in ADHD has focused on early development, leaving a large knowledge gap about how environmental hits across the lifespan may interact with dynamic genetic risk to shape the expression of ADHD in adults.

A factor that has received increasing attention is the microbiome. The role of the gut microbiome in adult ADHD remains controversial and uncertain, due to inconsistencies in research findings. Studies differ in the phenotypes analyzed, sequencing methods, statistical approaches, and reported results, making comparisons difficult. A meta-analysis[156] pooling data from four adult ADHD case-control studies (N=617) found that beta diversity was associated with ADHD diagnosis. Specific microbial genera showed robust associations with ADHD: *Ruminococcus torques* was more abundant in ADHD and linked to hyperactivity/impulsivity, while *Eubacterium xylanophilum* was less abundant. These genera may influence inflammatory processes. However, significant heterogeneity between cohorts persisted despite harmonized analyses, underscoring the need for larger meta-analytic studies. Moreover, further research is essential to clarify the possible role of microbiome in ADHD pathophysiology and its potential as a therapeutic target.

NEUROPSYCHOLOGY AND NEUROBIOLOGY

Neuropsychology

Acquired damage to the frontal lobes typically gives rise to a dysexecutive syndrome, in which patients have problems with executive functioning[157] (a constellation of cognitive processes which allow humans to behave in a goal-directed manner). Dysexecutive syndromes are characterized by difficulties in planning, in inhibiting unwanted or inappropriate responses under various environmental circumstances, in using working memory to guide behavior purposively, or in maintaining consistent performance over time, particularly in routine scenarios[157].

The striking parallels between these features of the dysexecutive syndrome and the symptoms of ADHD (e.g., inattention, impulsivity) has spurred decades of research aimed at isolating patterns of cognitive difficulties in individuals with ADHD. It is hoped that discovering reliable signatures of neuropsychological difficulty in ADHD will not only inform knowledge of the underlying neural substrates, but also reveal candidate processes for remediation and rehabilitation, and even aid diagnosis.

Meta-analyses have found that ADHD is indeed associated with difficulties in executive functions – including working memory, reaction time variability, response inhibition, and planning/organization – compared to controls[158]. For adults with ADHD, meta-analyses indicate deficits in domains including decision making[159], working memory[160], focused and sustained attention[161], verbal fluency[162], set shifting[162], and verbal memory[163,164].

Different patterns of activation on functional MRI during neurocognitive tasks between individuals with ADHD and controls have been found. For example, a meta-analysis of 23 studies of response inhibition found decreased activation in the supplementary motor area, insula, caudate, and precentral gyrus, and increased activation in the postcentral gyrus, inferior frontal gyrus, and precuneus in people with ADHD[165]. There were greater decreases in children versus adults with ADHD in the right caudate.

A recent meta-analysis explored the effect of stimulant (methylphenidate) and non-stimulant (atomoxetine) medication use (minimum 3 days) on the executive functions of people with ADHD [166]. This study found a significant effect of methylphenidate for all neurocognitive domains, with the largest effect for attention and the lowest for reaction time (i.e., overall speed). The meta-analysis for atomoxetine found beneficial effects for all neurocognitive domains except for working memory. There were no significant differences in effect sizes between adults and children. An outstanding question resulting from this study is the extent to which the effects of medications on cognitive function were related to changes in symptoms and/or quality of life measures.

It is important to note that there is much heterogeneity in neuropsychological performance in individuals with ADHD[167], which may reflect multiple pathways in the brain that are relevant to the etiology of the disorder. Average effect sizes between controls and people with ADHD are much smaller for neuropsychological tests than for ADHD symptoms, indicating that differences in neuropsychological performance may be minimal in many people with

ADHD[158].

There are uncertainties and controversial views on the value of neuropsychology for clinical practice. While neuropsychological tests can differentiate people with ADHD from controls, there are no tests that can differentiate ADHD from other clinical cohorts, resulting in these tests not being useful in the diagnosis of ADHD[168], nor recommended as such by evidence-based guidelines[169]. Nevertheless, neuropsychological testing can be helpful in understanding a person's unique pattern of cognitive strengths and difficulties, thereby contributing to guide treatment, education and occupational choices.

Neuroimaging

Neuroimaging studies in ADHD have primarily focused on the paediatric population, although studies in adults are gradually increasing, highlighting age-related differences[170-172]. Structural MRI meta- and mega-analyses reported diffuse volumetric and morphometric alterations in cortico-subcortical brain regions in children, but reduced or absent case-control differences with growing age[173-175], in line with the frequently observed symptomatic improvement or remission in adulthood[176]. Conversely, a recent meta-analysis of diffusion-weighted imaging studies reported that the identified case-control differences in the corpus callosum did not survive when restricting the analyses to paediatric studies[172]. These apparently contrasting findings may be related to the distinct developmental trajectories of the gray and white matter, so that a maturational delay of gray matter may be more evident in childhood whilst that of the white matter may be more pronounced later in life. Therefore, longitudinal studies are needed to clarify the life course of brain alterations in ADHD and their relationship with its variable outcome in adulthood.

Another striking aspect of the imaging literature in ADHD is the limited convergence of results when pooling case-control studies in meta-analyses[170-172]. This has been related to both methodological and clinical heterogeneity. Suboptimal MRI acquisition and pre-processing may potentially lead to spurious results, and the substantial variation in data acquisition, pre-processing and analysis, as well as in study design and statistical procedures, limits comparisons among studies[170-172]. Ongoing methodological developments may improve reliability of findings. On the other hand, ADHD is also a highly heterogenous condition both clinically and neurobiologically[176], with preliminary evidence of brain differences between ADHD presentations, sexes, and treated vs. untreated individuals[172,177-179]. Further, more pronounced alterations may be associated with comorbidities or symptom persistence[180,181]. Most neuroanatomical investigations have focused on group comparisons with controls, yielding inconsistent or no results, especially in adults. Thus, there is an increasing need to move beyond case-control comparisons and parse neurobiological heterogeneity, perhaps especially in individual characteristics relevant to clinical practice, such as symptom persistence and treatment response[179-181].

From a functional standpoint, one of the most innovative models of ADHD is the default mode network theory[182], according to which the brain's default mode network, which is normally active during rest and self-reflection, is overly active in individuals with ADHD. This leads to difficulties in sustaining attention and regulating behavior, as the individual is distracted by internal thoughts rather than focusing on external tasks. However, two meta-analyses[171,183] aimed at testing this hypothesis in children, adolescents and adults have reached contrasting conclusions, probably due to different methodologies. As such, the default mode network theory of ADHD deserves further testing, particularly in adults.

Neuropsychopharmacology

Medications used for ADHD include stimulants (amphetamines and methylphenidate) and non-stimulants (such as atomoxetine, clonidine, guanfacine and viloxazine)[184].

The primary mechanism of action of amphetamines is to elevate extracellular dopamine and noradrenaline levels at the synapse. This occurs through the inhibition of dopamine and noradrenaline transporters, which decreases the reuptake of these neurotransmitters from the synaptic cleft[185,186]. Amphetamines also enhance vesicular dopamine release in a dose-dependent and region-specific manner, by inhibiting the vesicular monoamine transporter 2. Additionally, they inhibit monoamine oxidase activity, reducing the breakdown of cytosolic monoamines[185,188]. The striatum seems to be the primary site of action of amphetamines, although direct effects have also been observed in the cortex and the ventral tegmental area[185,186].

The direct effects of methylphenidate involve inhibiting dopamine and noradrenaline transporters, exhibiting agonist activity at the 5-HT1A receptor, and redistributing vesicular monoamine transporter 2. These effects result in increased extracellular levels of dopamine and noradrenaline[185]. Several studies also indicate that methylphenidate directly interacts with adrenergic receptors, and activation of alpha-2 adrenergic receptors has been shown to stimulate cortical excitability[185,189].

Atomoxetine selectively inhibits the noradrenaline transporter, and increases extracellular synaptic levels of noradrenaline and dopamine in the prefrontal cortex. Clonidine and guanfacine stimulate the postsynaptic alpha-2 adrenergic receptors[184], but the neural mechanisms by which they improve ADHD symptoms are still not entirely clear[181]. Viloxazine inhibits the reuptake of noradrenaline in the synapse, which increases the extracellular levels of this neurotransmitter. Additionally, the drug has a serotonin modulating activity, whose role in its effectiveness for ADHD is still being explored[190].

PHARMACOLOGICAL TREATMENT

ADHD simplex

Pharmacological treatment represents the cornerstone of the management of adult ADHD[184]. However, recommendations on

the choice of medication vary somewhat across available guidelines, reflecting not only the evidence base but also the licensed medications in the various countries. For instance, the 2018 (updated in 2019) UK NICE guidelines[59] recommend methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine is not well tolerated) as first-line, followed by atomoxetine as second-line. The 2018 guidelines of the Association of the Scientific Medical Societies in Germany[191] state that medication is the first-line treatment, without specifying the class/formulation or a ranking. The guidelines of the Canadian ADHD Resource Alliance (CADDRA)[192] provide a recommended ranking for children: long-acting stimulants are first-line treatment agents; atomoxetine, guanfacine XR, and short/intermediate-acting psychostimulants are second-line; and bupropion, clonidine, imipramine and modafinil are examples of third-line treatment agents. At the time of writing, the first US guidelines on the assessment and management of ADHD in adults are in the process of being developed[193].

In terms of the evidence base, a network meta-analysis of 113 randomized controlled trials (RCTs) examining pharmacological and non-pharmacological treatments for adult ADHD[21] reported that, with respect to efficacy (i.e., reduction in ADHD symptom severity) in the short term (i.e., at about 12 weeks of treatment), stimulants and atomoxetine were the only treatments to perform better than placebo in both clinician-rated and self-reported assessments. Effect sizes for stimulants ranged from 0.39 to 0.71, while atomoxetine showed effect sizes ranging from 0.38 to 0.51. A previous network meta-analysis in children[194] reported slightly higher effect sizes. Additionally, while the network meta-analysis concerning adults[21] found no significant differences in efficacy between methylphenidate and amphetamines, earlier findings in children[194] indicated higher effect sizes for amphetamines.

Regarding acceptability (i.e., trial dropout rates due to any cause), the network meta-analysis concerning adults[21] reported that stimulants were as acceptable as placebo, whereas atomoxetine was less acceptable. However, in terms of tolerability (i.e., dropout rates due to adverse events), all medications performed worse than placebo. Both stimulants and atomoxetine also improved emotional dysregulation in adults in the short term (up to 12 weeks), but they were not effective in improving other relevant outcomes such as executive dysfunction and quality of life, contrary to the findings of a previous meta-analysis of RCTs in children and adolescents[195].

It is important to note that the effects observed in network meta-analyses, as well as guideline recommendations, are based on averages at the group level. At the individual level, patients may respond preferentially to specific medications, but currently there are no reliable predictors of response. As a result, prescribing ADHD medications remains a trial-and-error process, highlighting a critical gap in the field.

Alongside the choice of medication, dose optimization is another crucial factor. Some guidance documents (e.g., the CADDRA guidelines[192] and the British National Formulary[196]) recommend maximum doses higher than those licensed by regulatory bodies such as the US Food and Drug Administration (FDA). This creates uncertainty regarding the effective and tolerable maximum dose. A dose-response meta-analysis[197] of 47 RCTs addressing this issue found that, for methylphenidate, increasing doses led to additional symptom reductions, though these gains diminished with higher doses and were accompanied by increased risks of adverse events and dropouts. Unlicensed doses provided slightly greater symptom reductions compared to licensed doses, but these gains were small and associated with a higher risk of dropout due to adverse events. For amphetamines, the dose-response curve plateaued, indicating no additional symptom reduction with higher doses, while the risk of adverse event dropouts continued to increase.

A further crucial aspect that remains controversial is the long-term efficacy and effectiveness of ADHD medications. Notably, the majority of the RCTs included in the above-mentioned network meta-analysis concerning adults[21] had a duration of less than 12 weeks, and it is challenging from an ethical and practical standpoint to conduct longer-term RCTs. The available evidence does not support any medication as being more efficacious than placebo in the long term when relying on both self- and clinician-rated scales. Atomoxetine was more effective than placebo at 26 weeks according to self-reported ratings, while stimulants were more efficacious than placebo on clinician-reported ratings. At about 52 weeks, no medication has supporting evidence of being more efficacious than placebo. In clinical practice, patients may report that the medication that was once effective seems to no longer work. Some studies suggest the possibility of a change in the availability of dopamine transporters, which might underlie decreased efficacy and effectiveness of medications over time[198].

A study design that may be informative regarding longer-term effects is the discontinuation-controlled trial, in which patients who have been treated with ADHD medication for years are randomized to either continue the medication or switch to placebo. Given the scarcity of such trials of ADHD medications in adults[199,200], more are needed to better estimate long-term outcomes. Furthermore, since individuals with severe ADHD may tend to decline participation in such studies, these RCTs may include only milder cases. Thus, the extent to which medications are effective in the longer term remains to be better elucidated.

ADHD with comorbidities

While limited evidence exists for adults, a larger literature in children shows that stimulant and non-stimulant agents are effective in treating ADHD in individuals with autism spectrum disorder, particularly in the context of higher intellectual functioning[201]. Generally, lower-functioning autism spectrum disorder is linked to less ADHD improvement and more adverse effects with both non-stimulants and stimulants compared to individuals with ADHD alone[201].

There is a dearth of studies of medications in adults with ADHD and prominent anxiety. Controlled data for atomoxetine in adults with ADHD and social anxiety demonstrated robust improvement in both conditions with tolerable adverse effects[202], supporting findings in youth[203]. A multisite RCT comparing paroxetine

and amphetamine, each alone and in combination, with placebo showed that paroxetine alone improved anxiety symptoms, being ineffective for ADHD[204]. In contrast, amphetamine alone worked somewhat for anxiety and worked well for ADHD, both in monotherapy and with paroxetine[204]. Reviews of stimulants in the context of anxiety in youth with ADHD have reported generally benign outcomes[205]. However, limited evidence in adults remains mixed [206,207].

Older data suggest that untreated mood symptoms result in lower ADHD response and more adverse events if using stimulants [208]. The aforementioned RCT comparing paroxetine and amphetamine indicated improvement in both depression and ADHD ratings only when paroxetine was combined with amphetamine[204]. Other trials have shown that the addition of stimulants to serotonin reuptake inhibitors and the use of bupropion monotherapy are effective in treating ADHD and depression[209-211].

Regarding bipolar disorder, data suggest that mood stabilization is essential prior to medicating ADHD[212]. Though treatment data in adults are lacking, RCTs in youth have shown successful treatment of ADHD without manic activation when amphetamine or methylphenidate is given together with mood stabilizing agents[213,214]. These clinical trial data have been supported by larger registry studies demonstrating the destabilizing tendency of stimulants over 6 months in adults with bipolar disorder not receiving mood stabilizing agents, whereas there was no manic activation when stimulants were combined with mood stabilizers[214].

Overall, there is a need for additional methodologically sound evidence to inform the treatment of ADHD comorbid with psychiatric disorders.

ADHD and substance use disorders

At present the literature is limited regarding how to best treat individuals with ADHD and a substance use disorder. Most studies that have focused on assessing the efficacy of medications for adult ADHD have either excluded or restricted those with past or current substance misuse. Given that most clinicians are more likely to feel comfortable using a non-stimulant in a patient with an active substance use, it is notable that there are so few trials assessing these medications, and that the results are mixed.

Prescribing stimulants to patients with ADHD and a substance use disorder still remains controversial, due to the risk of misuse and/or development of tolerance[219]. Extended-release formulations – particularly lisdexamfetamine and osmotic-release oral system formulations of methylphenidate (OROS-MPH) – are considered preferential over immediate-release preparations, as they contribute significantly less to the development of drug abuse or dependence[220]. A large Internet population survey[221] confirmed that extended-release methylphenidate and amphetamine formulations are less likely to be misused.

Safety concerns arise with prescribing of ADHD medication in the presence of ongoing substance use. In a meta-analysis evaluating stimulants and non-stimulants for treatment of ADHD with substance use disorders, there were no statistically significant differences in adverse events between those receiving active medication and those receiving placebo[222]. Also, all-cause treatment discontinuation was not different between the two groups. While elevations of blood pressure and heart rate have been noted in some clinical trials at a greater rate than those on placebo, untoward effects can be minimized when patients are monitored closely, and doses are adjusted or discontinued if necessary[223,224].

At present, if a patient has both ADHD and a substance use disorder, it is prudent to require the engagement of the patient in a specific treatment for the latter condition, particularly if a stimulant is being considered. In addition to using extended-release stimulant formulations, risk of misuse and diversion can be mitigated by limiting the number of pills provided, increasing the frequency of visits, monitoring for signs of misuse, discussing safe storage of medications, and obtaining urine toxicology if clinically indicated.

Naturalistic studies of medication effects

Significant questions remain regarding the representativeness of RCTs. Indeed, a recent study found that up to 70% of adults with ADHD from the Swedish registries would be ineligible for RCTs[225]. Moreover, RCTs provide limited evidence on serious and long-term outcomes such as injury and suicidality. Pharmacoepidemiology research is needed to collect better real-world evidence regarding the broader risks and benefits of ADHD medication.

Some pharmacoepidemiology studies have used a within-person design, comparing outcomes during medicated and unmedicated periods for the same individual. These studies found that, during periods on ADHD medication, patients had significantly fewer negative outcomes – such as unintentional injuries, motor vehicle accidents, substance use disorders, and criminal acts – and showed improvements in academic performance[22].

Another pharmacoepidemiology study[226] based on Swedish registries found that, among individuals diagnosed with ADHD, medication initiation was associated with significantly lower all-cause mortality, particularly for deaths due to unnatural causes.

Side effects of ADHD medications and their management

A balanced consideration of the side effects of medications is warranted. On the one hand, overlooking side effects may expose the patient to unwanted risks. On the other, excessive concerns about side effects may prevent a patient from receiving a potentially effective treatment, where side effects can be managed.

Table 4 presents a summary of the most significant adverse effects of ADHD medications, and of the recommendations for their management provided by the European ADHD Guidelines Group[227]. These recommendations were focused mainly on the use of ADHD medications in children. Although they can be extrapolated to adults, there is a need for specific guidance in this population.

Table 4 Adverse effects of medications for attention-deficit/hyperactivity disorder (ADHD) and recommendations for their management

Decreased appetite; height and weight gain deficit	• Measure height and weight every 6 months. • If weight loss is of clinical concern: take medication either with or after food, rather than before meals; take additional meals or snacks early in the morning or late in the evening when stimulant effects have worn off; obtain dietary advice; consume high-calorie foods of good nutritional value; take a planned break from treatment; or change medication.
Increased blood pressure/heart rate	• Do not offer routine blood tests or ECG unless there is a clinical indication. • Measure heart rate and blood pressure after each dose change and every 6 months. • If there is sustained resting tachycardia (>120 beats per minute), arrhythmia, or systolic blood pressure >95th percentile (or a clinically significant increase) measured on two occasions, reduce the dose and refer to hypertension specialist or adult physician. • If there are sustained orthostatic hypotension or fainting episodes during treatment with guanfacine, reduce the dose or switch to another ADHD medication.
Sleep disturbance	• Implement sleep hygiene. • If behavioral measures are insufficient and it is not convenient to stop medication, review the possible causes of sleep problems: a) treat restless legs syndrome if present; b) if there is rebound effect with stimulants, add small doses of short-acting stimulants in the evening; c) if stimulant is the current treatment, consider reducing dose, alternative classes or formulations of stimulants, or atomoxetine. • Consider adding melatonin.
Tics	• Monitor tics over a 3 months period before any decision regarding ADHD treatment. • If tics are stimulant-related, reduce the stimulant dose, or consider changing to atomoxetine or clonidine, or stopping medication, or add an antipsychotic.
Seizures	• If there are new seizures or worsening of existing seizures, review ADHD medication and stop any medication that might be contributing to the seizures. Cautiously reintroduce ADHD medication if it is unlikely to be the cause of the seizures.
Psychotic or manic symptoms	• If they occur with therapeutic doses of ADHD medications, reduce the dose or discontinue the ADHD drug. • Once the psychotic or manic symptoms resolve, consider a re-challenge with ADHD medications.

NON-PHARMACOLOGICAL TREATMENTS

Psychosocial interventions

Among psychosocial interventions, current guidelines recognize and recommend cognitive-behavioral therapy (CBT) in the treatment of adults with ADHD, either as a first-line approach in conjunction with medication, or as an alternative monotherapy when medication is not indicated for a particular patient[59,228]. However, CBT is not designed to treat the core symptoms of ADHD. Instead, its goal is to mitigate the impact of ADHD symptoms on the internal and external experiences of everyday life[229]. CBT for adults with ADHD involves a collaborative process between the clinician and the patient that can be delivered in a group, individual, or asynchronous online setting[230]. Protocols generally include the identification of environmental modifications or lifestyle changes that can support ADHD symptom management[229,231,232].

With respect to the "B" in CBT (i.e., behavioral components), adults with ADHD work with clinicians to generate coping strategies that mitigate ongoing impairments due to their ADHD symptoms (e.g., interpersonal challenges, work performance problems, difficulties managing finances, parenting). This may involve teaching executive functioning skills to support self-regulation (e.g., problem-solving, organization, time management) and planning supports to enhance preparation for everyday life situations.

With respect to the "C" in CBT (i.e., cognitive techniques), clinicians help clients identify and restructure maladaptive cognitions formed through years of negative feedback from others and subsequent self-blame (e.g., "I can't do anything right", "No one will want to be my friend", "I am inadequate"). These negative cognitions are thought to undermine self-esteem, motivation and hope in individuals with ADHD[229].

It is believed that by improving behavioral skills and thinking patterns related to oneself, the future and the world (i.e., the "cognitive triad"[233]), adults with ADHD will show greater self-regulation, which may in turn lead to an abatement of symptom severity[234]. However, the above-mentioned network meta-analysis of treatments for adult ADHD[21] showed that, in the short term (i.e., at time points close to 12 weeks), CBT was better than placebo only according to clinicians' assessments, but not to self-reported ratings of ADHD symptoms severity. Data from a very limited number of trials showed that, at about 52 weeks, CBT had supporting evidence of being more efficacious than placebo on self-reported ratings only. These discrepancies between rater assessments warrant further investigation. Furthermore, heterogeneity of ADHD symptom effects likely reflects high intervention heterogeneity with respect to content (emphasis on skills training vs. psychological change), dose/duration of care (brief vs. long-term interventions), format (group vs. individual), and involvement of family members[235].

Third-wave CBTs – including mindfulness and dialectical behavior therapy (DBT) – have also been applied for the treatment of ADHD in adults[236,237], although research evidence remains in its infancy[230]. In the above-mentioned network meta-analysis[21], mindfulness therapy was more efficacious than placebo in the short term (about 12 weeks) on clinicians' assessments but not self-ratings, and on self-report but not clinicians' ratings at 26 weeks.

Other psychosocial interventions widely marketed for adults

with ADHD in certain countries (e.g., ADHD coaching) are yet to be tested by RCTs, signalling a critical need for high-quality research on publicly available non-pharmacological interventions for ADHD in adults.

One practical issue in the application of psychosocial treatments to adult ADHD is the challenge of retaining patients in consistent clinical care. Across the lifespan, individuals with ADHD struggle to complete therapy homework assignments, demonstrate variable participation in activities during sessions, experience difficulties following through on intentions, and may show low or fluctuating self-efficacy and motivation to change behavior, which may lead to premature termination of treatment[238]. In children and adolescents, these challenges are often overcome by engaging parents as central participants in CBTs, often teaching them to reward youth engagement and participation. However, as adults with ADHD transition from a family-based to an individual care model, clinicians may struggle to cultivate client engagement.

To address engagement challenges, motivational interviewing techniques are increasingly being integrated into CBT models for adult ADHD[239]. These techniques may include exploring patients' self-awareness of their personal values and priorities, promoting personally meaningful therapy goals, and implementing a strength-based framework that bolsters self-efficacy[240]. Professionals may devote extra time in sessions to helping clients with ADHD develop specific and detailed implementation plans for intended actions, and use techniques such as advanced problem-solving to identify and address barriers to follow-through prior to their appearance[240].

Other non-pharmacological treatments

A recent pairwise meta-analysis[241] included RCTs of cognitive training across the lifespan (36 trials, eight in adults). Benefits for adults with ADHD were found only on laboratory measures of working memory (moderate effect size). There was no evidence of significant effects on ADHD core symptoms. Another pairwise meta-analysis[242], focusing on neurofeedback (38 RCTs, three in adults), could not find evidence of significant and clinically meaningful effects. While, to date, there is no support for the use of cognitive training and neurofeedback as treatment strategies for ADHD in adults, future studies may identify subgroups of patients who could benefit from these treatments.

SPECIAL GROUPS

Females

Until recently, ADHD in females has often been overlooked in clinical and research settings[243], as the disorder has historically been considered a male dominant one. Prevalence rates of ADHD favour males 3:1 in childhood, but this difference decreases during adolescence, and the rate in adulthood is nearly equal[244,245]. The diagnosis in females is often delayed compared to males[243,246,247], and females are more likely to be diagnosed later in life[248].

The reasons for the less frequent and later diagnosis of ADHD in females remain unclear. Some studies hypothesize that this is due to the difference in phenotypic expression of the disorder. Indeed, females often present with predominantly inattentive symptoms and less overt disruptive behaviors[102,249,250]. Therefore, male patients are more likely to be referred to clinical services[251]. However, recent evidence challenges these "traditional" views[252,253], suggesting that females with ADHD have comparable symptoms of hyperactivity to males. Nonetheless, other studies indicate that females must present with more severe symptoms with greater impairment compared to males to be referred for an ADHD assessment[254].

Another area of consideration is the notion of compensatory and masking behaviors reported more in women. This area of research is outlined in the autism literature, reporting that women, more often than men, utilize strategies to passively mask or hide their difficulties and actively compensate or adapt their behavior, particularly in social situations, which ultimately has detrimental long-term consequences[255,256]. There is limited evidence of this in adult ADHD[257]. Future research to explore the compensatory behaviors and masking techniques used by women with ADHD may improve diagnostic accuracy and help to reduce the harmful consequences of these strategies.

The prevalence of psychiatric comorbidities in females with ADHD has been reported to differ from males, with some studies showing that males are more likely to present with externalizing conditions (i.e., conduct disorders, substance misuse) and females having more internalizing comorbidities (i.e., anxiety and depression)[102,243,258]. This has been suggested to be a factor contributing to the lower rates of referral and diagnosis of ADHD for females compared to males, with depression and anxiety being diagnosed prior to ADHD, the so-called "diagnostic overshadowing"[249,250]. Self-harming behaviors, also more common in women with ADHD compared to males[259], have also been hypothesized to overshadow and distract from an ADHD diagnosis in women.

The recommendations for treatment of ADHD are the same in females as in males. However, females with ADHD are less likely to receive treatment with medication compared to males (independent of the severity of ADHD symptoms)[260]. A meta-analysis[261] confirmed this finding, but also showed that the difference in prescription frequency between males and females was less evident in adults compared to children.

It is unclear if there are sex-specific pharmacokinetics of ADHD medications, and whether the frequency and type of adverse events differ between males and females. Hormonal level fluctuations have been postulated to effect treatment response to stimulant medication[243,250]. A case series in a small sample of adult females (N=9)[262] reported a reduction in premenstrual worsening of depressive and ADHD symptoms when the current stimulant dose was increased. Currently clinical guidelines do not recommend different doses or treatment regimes according to sex, but developments in this area of research may lead eventually to sex-tailored treatments strategies.

Understanding the sex differences in adult ADHD is crucial

for improving timely diagnostic accuracy and clinical outcomes. There is a need for high-quality research including large numbers of female participants across different phases of life (from prepubertal all the way to post-menopausal).

Elderly

Only recently emerging research has demonstrated the presence of ADHD in adults over age 50[263,264]. In a systematic review and meta-analysis[265], the estimated prevalence of ADHD in older adults was 2.18% when diagnosed through validated scales in community samples and 0.23% when relying on clinical diagnoses in electronic health records. The prevalence of treatment for ADHD was 0.09%.

Diagnosing ADHD in older adults with cognitive complaints is complex, due to the variety of alternative diagnoses that must be considered[263], including traumatic brain injury, mild cognitive impairment, major depression, and cognitive symptoms due to medical illnesses or medications. Neuropsychological testing has been shown not to delineate ADHD from non-ADHD in this population[266].

Clinical features that can distinguish ADHD from other disorders are chronicity vs. variability over time of symptoms/impairments, age of onset (ADHD in childhood), temporal relationship to an event (traumatic brain injury, an infection, a new medication), and quality of cognitive symptoms (word finding/misspelling found in mild cognitive impairment, but not ADHD). It should be taken into account that other causes of cognitive impairment may coexist with ADHD.

There is a paucity of research concerning use of ADHD medications in older adults. A study assessing vital parameters in subjects aged 55-84 years receiving lisdexamfetamine[267] concluded that no trends in pulse and blood pressure were seen by age. However, in a minority of older adults, stimulant treatment may elevate blood pressure levels requiring clinical action. Older patients often have pre-existing somatic conditions and may be taking multiple medications concurrently[268]. The decision to treat older adults with ADHD medications involves balancing the potential improvement in quality of life, which is often substantial, against medical risks. Further research is clearly needed in this area.

ORGANIZATION OF SERVICES

Several studies have highlighted the lack of access to ADHD services as a significant issue in many countries[269-271]. In an ideal scenario, units specialized in the management of ADHD across the lifespan should serve as reference centers[269,272]. These units should provide a comprehensive assessment in complex cases and advanced treatment strategies in patients who do not respond to standard interventions. They should be coordinated with primary care physicians and community centers in order to ensure that all the aspects of patients' care are addressed.

The involvement of primary care physicians in the management of adult ADHD is essential[272]. Patients should have the opportunity of a follow-up of pharmacological treatment at the primary care level in coordination with their psychiatrist. Also, primary care physicians can improve the transition from community paediatricians to adult services. Another important role at this level of care is to screen for ADHD in patients with somatic conditions commonly associated with this disorder in adults, such as obesity, type 2 diabetes mellitus, migraine and epilepsy[269]. In general, it is necessary to improve training and education of primary care physicians on ADHD[272].

At the community mental health level, it is crucial that professionals (including psychiatrists, psychologists, nurses, and social workers) have experience in the assessment and treatment of ADHD in adults[269]. The service portfolio of community centers should regularly include the diagnostic assessment and management of adult ADHD and its psychiatric comorbidities, as well as the implementation of relevant psychological treatments[272].

The involvement of community addiction centers when adult ADHD is comorbid with a substance use disorder or behavioral addiction is pivotal[273]. It is not uncommon that the diagnosis of ADHD during childhood is missed in patients with addictions. Screening for ADHD should be included in the standard assessment of all patients with addictions, also considering that undiagnosed ADHD can impact negatively on the progression of the addictive disorder.

The transition from child community mental health services to adult services is a frequent problem in the management of ADHD in adults[274]. Specific programs are needed to improve this transition, especially in patients with comorbid conditions such as autism spectrum disorder, addictions or conduct disorders.

ADHD in adults can be a complex disorder, with multiple somatic and psychiatric comorbidities. The management of patients frequently requires the involvement of various specialists and health care levels. The coordination between professionals is essential to ensure continuity of care and avoid fragmentation[272]. Electronic health records are a very useful instrument to integrate services, share information among professionals, and optimize resources[270].

Digital health tools are playing an increasingly important role in the management of adults with ADHD[275]. They can increase access to ADHD specialists by people who have difficulties to attend in-person appointments because they live in remote areas or do not have specialized centers in their town[275].

There are several evidence-based guidelines with recommendations for assessment, treatment and monitoring of ADHD in adults[59,269]. The implementation of these guidelines at the different health care levels can improve the standard of care[272]. The care delivery in adults with ADHD needs to be person-centered, with consensus decision-making, to improve adherence to the management plan and ensure better outcomes[276]. The use of patient-reported outcome and experience measures (PROMS and PREMS) can help to empower patients.

The collaboration between professionals and patient organizations can increase awareness of adult ADHD and improve quality of care. Patient education is an integral component of management that can help improve the access to ADHD services[276].

PERSPECTIVES FROM ASSOCIATIONS OF PEOPLE WITH LIVED EXPERIENCE

Representatives of the two largest European and US associations of people with lived experience – N. Hovén (President of ADHD Europe) and J. Didier (President of Children and Adults with ADHD, CHADD) – have contributed to this section. We report verbatim their statements.

Diagnosis and access to treatment

"Access for adults to get in medical research is challenging. Adults come across a lot of understatements, even from professionals, if they have outwardly good functional capacity. That is, they have managed at work, are educated or their relationship matters are in order. Many times they are told that it can't be ADHD. Even 40-50-year-olds are told that they cannot get tested when they have survived without a diagnosis for so long. In all the discussion about overdiagnosis, it is forgotten that there is a great deal of underdiagnosis among adults. The experience of health care is that people want a diagnosis and, by applying correctly, seek it. Few people really want a diagnosis, but need it to get any support. The stigma is still associated with ADHD. Adults do not easily dare to talk about their diagnosis, for example. in the workplace, when they are afraid that attitudes towards them will change."

"As someone diagnosed with ADHD later in life, I often think about how much easier things could have been if I had known sooner. Like many women, especially those who excel outwardly in academic or professional settings, my struggles with ADHD went unnoticed by others. My unseen challenges were masked by perfectionism and an overwhelming drive to achieve. Teachers and peers praised my accomplishments, but my internal reality differed. I battled impulsivity, emotional dysregulation, and a constant sense of being 'on the edge' of chaos. When it finally came, my diagnosis provided clarity and validation, but only after years of self-doubt and self-criticism."

"This is a familiar story among adults with ADHD, particularly those diagnosed later in life. Our strengths – creativity, resourcefulness, intelligence – often camouflage the challenges, leaving us to grapple with the condition in isolation. These experiences underscore a broader issue: adults with ADHD are not just underserved – they are often invisible. Through my role as both a member of Children and Adults with ADHD (CHADD) and President of CHADD's Board of Directors, I've witnessed firsthand the profound gaps in awareness, diagnosis and treatment that adults with ADHD face and the transformative power of education, advocacy and support in addressing these needs."

"For many adults with ADHD, the journey to diagnosis is long and frustrating. Outdated stereotypes about who has ADHD – young, male, struggling academically – continue to exclude those who don't fit the mold. Women are often dismissed or misdiagnosed with anxiety or depression, while Black/Indigenous and low-income individuals face systemic biases that further delay care."

"I know what it's like to live in that gap. For years, I was told that I was 'too smart' to have ADHD or that I needed to 'try harder'. These well-meaning but harmful statements left me feeling like my struggles were a personal failing rather than a neurological difference. It wasn't until my diagnosis that I began to understand how ADHD shaped my life – and, more importantly, how to work with my brain rather than against it. This disconnect between how ADHD is perceived and how it manifests is one of the most significant barriers adults face."

Moving beyond medication: the need for comprehensive treatment

"Receiving an ADHD diagnosis is often framed as a solution, but for many, it's just the beginning of a complex process. While medication can be life-changing, it is rarely sufficient on its own. ADHD impacts nearly every aspect of life, from managing time and emotions to navigating relationships and careers. Many adults find that medication alone doesn't address their root challenges; so additional tools and support – like executive function coaching, peer support groups, disability accommodations, and occupational therapy – are needed."

"I've seen this firsthand, both personally and professionally. Cognitive behavioral therapy helped me reframe unhelpful thought patterns, while ADHD coaching and executive function skills training gave me practical strategies to manage my day-to-day life. These tools transformed how I approached everything, from prioritizing tasks to managing emotional overwhelm."

"Unfortunately, these helpful resources are not accessible to everyone. Many clinicians are not trained in ADHD-specific therapies, and insurance coverage for coaching or skills training is inconsistent at best. Even when these resources are available, individuals are often unaware of their existence. Few people diagnosed with ADHD receive education about how to create a comprehensive treatment plan, leaving them to navigate their condition with incomplete support. Organizations like CHADD help adults access resources and programs designed to fill this gap, connecting individuals with evidence-based strategies, webinars, peer support groups, and tools to help them better understand the complexities of ADHD."

The intersection of ADHD and substance use disorder

"One of the most critical yet under-addressed areas in ADHD care is the link with substance use disorder (SUD). Research shows that individuals with ADHD are significantly more likely to experience substance misuse, often to self-medicate for symptoms like impulsivity, emotional dysregulation, or restlessness."

"In my clinical work, I've seen how untreated ADHD can fuel cycles of addiction and relapse. Many individuals in recovery feel unsupported because traditional addiction programs rarely address the role ADHD plays in their behavior. Yet the research indicates that treating both ADHD and addiction helps people stay safer and sober longer. This gap in care perpetuates frustration and

prevents meaningful progress."

"*ADHD rarely travels alone. In fact, as many as 80% of adults with ADHD have at least one coexisting psychiatric disorder. The clinical community needs to continue advocating for integrated care that addresses both ADHD and co-occurring conditions like SUD. Clinicians can reshape how these conditions are treated together by promoting research, training professionals, and sharing resources tailored to these unique challenges."*

Family-centered care: a missing link

"*ADHD doesn't just affect individuals – it impacts entire families. When one person in a household is diagnosed, it often prompts a ripple effect of recognition and adjustment. Parents may realize they share similar traits, siblings may struggle to understand changing dynamics, and partners may face new challenges in communication and support."*

"*Despite this, family-centered care is rarely prioritized. Few treatment models include resources for loved ones, even though understanding ADHD as a shared experience can dramatically improve relationships and outcomes. Families need education, tools, and emotional support to navigate the complexities of ADHD together. My younger brother and sister were diagnosed with ADHD decades before I was diagnosed. How might things have been different if our entire family had been assessed back then? By addressing the whole family's needs, we can create environments where individuals with ADHD feel understood and supported at every stage."*

Addressing systemic inequities in ADHD care

"*For adults in marginalized communities, the barriers to ADHD care are even higher. Black/Indigenous and low-income individuals are often underdiagnosed or misdiagnosed, while women frequently have ADHD symptoms dismissed as stress or poor coping. These disparities perpetuate cycles of inequity, leaving many without the diagnosis and support they need to live well. These systemic issues also extend to justice-involved populations, where ADHD is disproportionately represented but rarely acknowledged and/or treated. Providing proper diagnosis and treatment in correctional settings could improve individual outcomes and reduce recidivism rates. This is a critical area for advocacy and reform."*

CONCLUDING REMARKS

Nowadays, after a period of criticism, ADHD is generally accepted as a valid nosological entity in adulthood. However, several uncertain or controversial aspects remain in the symptomatology, classification, epidemiology, comorbidity, etiology, pathophysiology, treatment, and service organization of the care for adults with ADHD, which we have highlighted in this paper. Therefore, there is a need for additional research on adult ADHD.

Notably, as of January 2023, data from the US National Institutes of Health (NIH) Reporter indicated just under $5.5 million in active funding for adult ADHD research, compared to over $42 million for paediatric ADHD research[277]. Remarkably, the NIH Reporter pointed out that funding for depression research exceeds ADHD research by at least tenfold, despite the two conditions having only slightly different population prevalence rates[277]. This highlights a critical need to expand ADHD research to develop effective public health strategies for identifying and treating its diverse presentations, using both pharmacological and non-pharmacological interventions.

Beyond the specific aspects that we discussed in each of the sections of this paper, there is an emerging potential change in ADHD conceptualization, under the influence of the neurodiversity movement. Neurodiversity, which originated as a social justice movement (rather than a clinical initiative), was initially proposed in relation to autism in the late 1990s by J. Singer[278], an Australian sociologist who identified as autistic herself. She introduced the term to describe the idea that neurological differences, such as autism, are part of natural human diversity rather than disorders to be cured. This concept is currently being extended to other nosologic entities, such as ADHD. From this perspective, impairments result not from intrinsic deficiencies but from a mismatch between the individual and a neurotypical environment. This mismatch can exacerbate challenges and undervalue the strengths of neurodiverse individuals, fostering stigma, shame, and mental health issues.

The neurodiversity movement emphasizes equality and highlights the unique strengths that neurodiverse people can contribute, such as creativity in ADHD or attention to detail in autism. Advocates encourage shifting the research and clinical focus from "fixing deficits" to understanding how environments and societal attitudes create barriers. This approach promotes adapting workplaces, schools and social settings to better suit neurodiverse needs, reducing stigma and discrimination through public education and policy changes.

Some authors in the field[279] have highlighted that, while extreme interpretations of neurodiversity that dismiss diagnosis and treatment should be avoided, integration of neurodiversity alongside traditional approaches should be explored. Combining interventions that address individual needs with societal efforts to accommodate diversity may offer a balanced path forward, enhancing both well-being and inclusion for neurodiverse individuals. We look forward to evidence-based and balanced discussions of these issues.

From a lived experience perspective, adults with ADHD need more than awareness – they need systems that actively support them. This means expanding access to affordable diagnosis and treatment, prioritizing family-centered care, and addressing co-occurring conditions such as substance use disorders through integrated models. It also means challenging outdated stereotypes and ensuring that marginalized communities have equitable access to care. Organizations of people with lived experience of ADHD play a vital role in this vision, advocating for systemic and policy-related changes while also creating peer support spaces where individuals and families can connect, learn and grow.

Ultimately, adults with ADHD require understanding, support, and the right tools to thrive. Continuing education, advocacy and collaboration are needed to create a world where adults with ADHD feel seen, supported and empowered.

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