REVIEW

Approach to Evaluating and Managing Adult Attention-Deficit/Hyperactivity Disorder in Primary Care

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Abstract: Requests for the evaluation of potential adult attention-deficit/hyperactivity disorder (ADHD) is on the rise across primary care clinics. Many health care providers, however, may feel ill equipped to diagnose and manage adults presenting with inattention and impulsivity. The diagnosis of ADHD is often complicated by medical and psychiatric conditions that can contribute to inattention symptoms. In this article, the authors provide a pragmatic clinical approach for evaluating and managing adult ADHD in the primary care setting.

Keywords: attention-deficit/hyperactivity disorder (ADHD), attention-deficit disorder (ADD), primary care

Adult attention-deficit/hyperactivity disorder (ADHD), with a prevalence of about 2.8%,[1] is currently conceptualized as the persistence of childhood ADHD symptoms into adulthood that is associated with impairments in social and occupational functioning.[2] Clinical presentation of adults with inattention requesting evaluations for ADHD has been growing recently. In the past ten years, the prevalence of adult ADHD has increased, and stimulant prescriptions in young adults has exceeded that of children.[3] Many health care professionals may feel ill prepared to diagnose and treat adult ADHD. This clinical review will provide a pragmatic approach to the diagnosis and treatment of adult ADHD in primary care settings.

PRESENTATION

Adults typically present in primary care describing struggles with attending to work, school, or home duties. They report symptoms of poor concentration, general disorganization, tendency to leave projects incomplete, inattention, impulsivity, poor school performance, difficulty functioning at work, problems with time management, difficulty controlling their temper, and anxiety.[4] The majority come in on their own, and a small percentage (5%) are referred by family, therapists, or others.[4] These individuals will sometimes have a childhood diagnosis of ADHD or past treatment with stimulants.

ADULT ADHD DIAGNOSIS IN CONTEXT

The diagnostic validity of any disease is based on four criteria: symptoms, course, genetics, and biological markers.[5] In adult ADHD, the course of illness should be given careful consideration. Does ADHD in adults reflect the continuation of symptoms from childhood, independent of other diagnoses? It is one matter to see adults with inattention and executive dysfunction, consistent with the ADHD clinical picture. It is another matter to ascribe these symptoms to adult ADHD as opposed to other diagnoses.

In prospective studies, adults often meet *Diagnostic and Statistical Manual of Mental Disorders* [DSM]–5 criteria for current ADHD with no history of childhood ADHD. Two such studies showed that approximately 90% of adults who meet criteria for ADHD did not have ADHD in childhood.[6,7] Since those studies were prospective, some lasting three decades, researchers knew definitely whether or not those patients had childhood ADHD. In clinical practice, the matter is different, since clinicians must rely on recall on the part of patient. These prospective studies suggest that such recall is mostly false. The same two studies also found that most children with ADHD did not experience symptoms into adulthood. For instance, one study found that only 17% of children with ADHD continue to meet criteria for ADHD as young adults.[6]

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Furthermore, these studies found that about one-half of patients with adult ADHD also had other psychiatric or substance use diagnoses that cause similar inattention/executive dysfunction. Among those with late-onset ADHD symptoms, most experienced these symptoms in the context of psychiatric conditions and substance use.[8] Thus, the apparent prevalence would need to be halved when other psychiatric causes of cognitive ADHD-like symptoms were taken into account. In short, adult ADHD symptoms in themselves usually do not mean that someone has ADHD.

DIAGNOSIS

The diagnosis of adult ADHD is a clinical one, arrived at based on a carefully collected history of symptoms (ruling out other causes), without placing too much weight on neuropsychological testing or screening instruments. Clinical assessment should focus on (1) evaluating current inattention or hyperactivity/impulsivity symptoms, (2) establishing that these symptoms cause impairment, affecting function across multiple domains, and (3) excluding medical, psychiatric, or other causes of inattention or hyperactivity/impulsivity. For a flow chart regarding diagnosis and treatment, see Figure 1.

According to DSM-5, ADHD occurs when one has inattention or hyperactivity/impulsivity across multiple settings that interferes with one's life.[9] Impairments in adults with ADHD tend to manifest in various domains of life—for example, work, academic settings, and relationships. Adults with ADHD tend to have low job stability and behavioral problems and poor performance at work, and they are more likely to be fired than those without ADHD.[10] In evaluating occupational impairment, we like to ask, "Do you have problems getting along with bosses or coworkers? How are your performance reviews? Have you changed jobs a lot?" Adults with ADHD are more likely to have higher rates of divorce and separation, problems in relationships, and difficulty fulfilling parental responsibilities.[2,11]

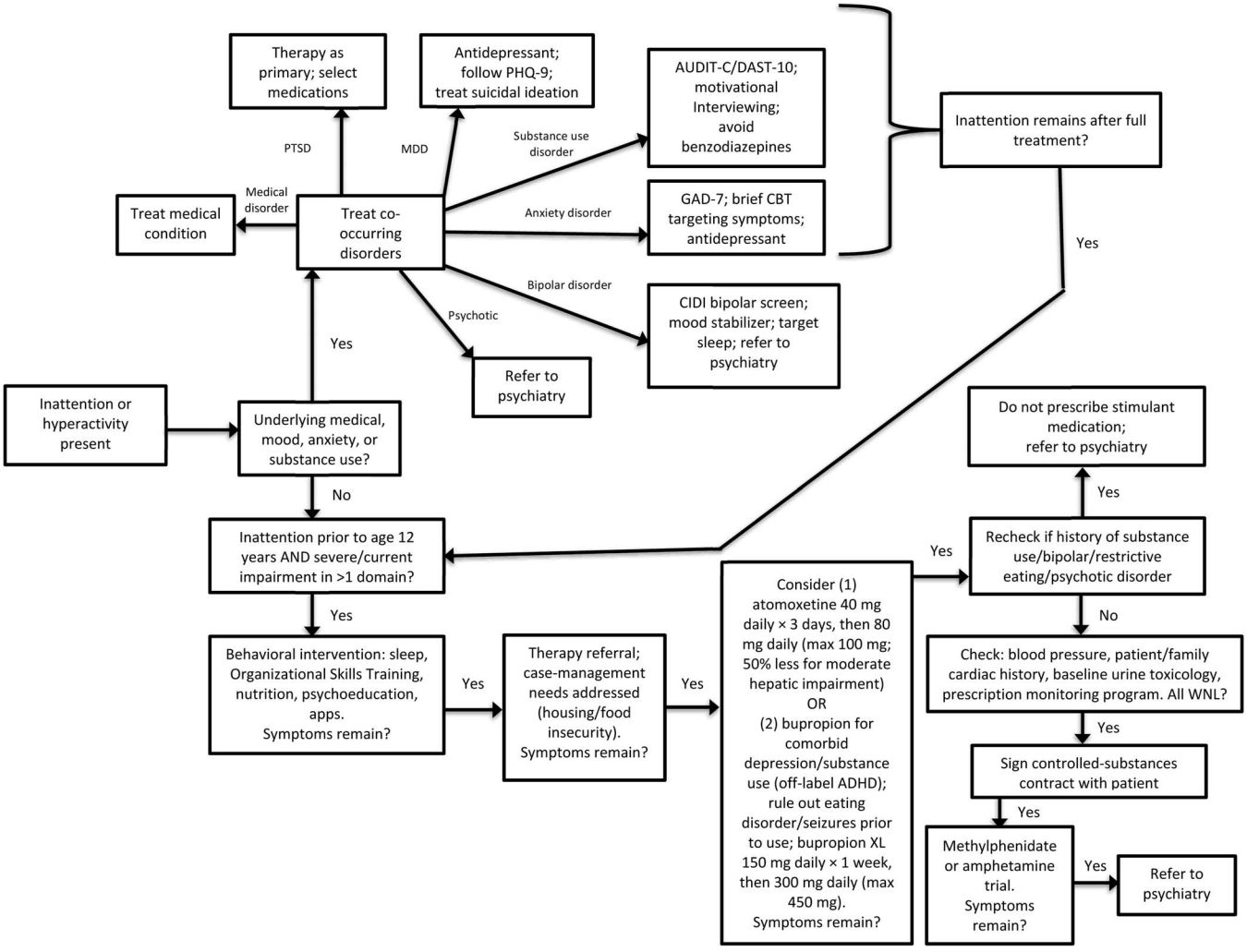

Figure 1. AUDIT-C, Alcohol Use Disorders Identification Test–C; CBT, cognitive-behavioral therapy; CIDI, Composite International Diagnostic Interview; DAST-10, Drug Abuse Screening Test–7; GAD-7, Generalized Anxiety Disorder–7; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire–9.

In evaluating relational problems, we may ask patients about past relationships/marriages and whether they struggle as parents.

Given the current conceptualization of adult ADHD as persistence of childhood symptoms into adulthood, diagnosing ADHD in adults requires establishing the presence of ADHD symptoms in childhood (prior to the age 12 in DSM-5). Unfortunately, access to childhood medical records documenting inattention symptoms is often not possible. Accuracy of self-report of such early symptoms has not been found to be valid, making reliance on this criterion for adults questionable.[12] It would thus be worthwhile to use collateral sources such as family members to describe the patient's childhood symptoms that would be suggestive of ADHD.

One may also indirectly assess childhood symptoms through inquiry of childhood academic impairment. Children with ADHD do not perform as well in school (lower grade point average and class ranking), and are more likely to have had any of the following in their histories: grade retention, required tutoring, an individualized education program (IEP), reading disability, disciplinary actions (being suspended or expelled), and dropping out.[13,14] In evaluating for childhood academic impairment, clinicians may ask what grades were obtained in elementary, middle, and high school; whether the patient was ever diagnosed with a learning disability or had an IEP; and whether he or she was ever held back or had disciplinary problems involving suspension or expulsion.

RATING SCALES AND NEUROPSYCHOLOGICAL TESTING FOR ADULT ADHD

A variety of instruments are cited as being useful for detecting positive cases of adult ADHD—including the Wender Utah Rating Scale, Conner's Adult ADHD Rating Scale, and Adult ADHD Self-Report Scale (ASRS).[15] These instruments are screening tools and not diagnostic. They tend to have limited utility in clinical practice since most adults who present with inattention will likely screen positive due to the nature of the questions. However, the ASRS can be helpful in ruling out ADHD, as its negative predictive value is 98%. Although neuropsychological testing is a way to objectively identify the presence of executive dysfunction, current evidence does not support a role for neuropsychological testing in the diagnosis and evaluation of ADHD.[16]

ASSESSING FOR PSYCHIATRIC COMORBIDITIES

It should be noted that DSM-5 ADHD functional criteria specify that symptoms of inattention or hyperactivity/impulsivity cannot be better explained by another psychiatric disorder. Given the high rates of psychiatric comorbidity associated with ADHD, ruling out other psychiatric causes of inattention in order to diagnose ADHD can be challenging. In a nationally representative sample, among those with adult ADHD, 38% had mood disorders, 47% had anxiety disorders, and 15% had substance use disorders (SUDs; especially alcohol use disorder).[17] This high degree of correlation between adult inattention and other psychiatric conditions would suggest that the symptoms of inattention may reflect an underlying psychiatric disorder. Although it has been postulated that symptoms of inattention cause mood disorders, no diagnostic studies actually support this causal claim.[2] By contrast, studies have shown that mood states and anxiety conditions are associated with poor concentration and impaired attention.[18] In fact, the DSM-5 includes the symptom of poor concentration as one of its diagnostic criteria for mood and anxiety disorders.[9]

Since mood disorders contribute to symptoms of inattention in adults seeking ADHD evaluations, these conditions should be screened with validated instruments that are feasible for use in primary care settings. Positive results on the screens can then be followed by an evaluation by the health care provider that would include a history of illness, family history, mental status exam, neurologic/physical exam, and laboratory tests when indicated. The Patient Health Questionnaire (PHQ)–9 can be used both for screening for clinically relevant depressive symptoms and for serial measurement to follow depression treatment response.[19] The Composite International Diagnostic Interview scale can be used by primary care providers (PCPs) to screen for bipolar spectrum disorder.[20] A negative result can be helpful in guiding their depression or ADHD management decisions, while positive results may benefit from a psychiatric consultation for further diagnostic clarification or treatment recommendations for bipolar disorder.

Another common condition that can present with symptoms of inattention in the primary care setting is posttraumatic stress disorder (PTSD), mainly due to difficulties with memory, avoidance, and changes in arousal and reactivity.[21] The 4-question primary care PTSD screen (PC-PTSD)[22] or 20-item PTSD Checklist for DSM-5 (PCL-5)[23] can be used to screen for this disorder.[24]

Sleep disturbance is highly associated with individuals presenting with inattention/hyperactivity.[25] A careful sleep history should therefore be performed during the evaluation for ADHD to discover possible sleep or other disorders. Such a sleep history could include a description of bedtime routines (e.g., which may include exposure to blue light from the use of phones, tablets, laptops, or television in the evening), caffeine use (quantity and time of use), presence of restless leg symptoms when falling asleep, sleep latency, the number of times the patient awakens overnight, whether the patient awakens overnight gasping for breath, presence of snoring, presence of nightmares, time of awakening, and whether the patient feels refreshed in the morning. The presence of frequent nightmares may be indicative of trauma-related reexperiencing. If a sleep history reveals the patient has symptoms suggestive of obstructive sleep apnea, the STOP-Bang sleep apnea questionnaire can be administered to determine if a sleep study would be indicated.[26]

ASSESSING FOR UNDERLYING MEDICAL AND NEUROPSYCHIATRIC CONDITIONS

In evaluating adults with ADHD, it is important to consider a broad differential diagnosis. While there are no standard recommendations for the medical evaluation of ADHD, in our practice the medical workup is guided by relevant clinical history. We routinely consider common conditions such as thyroid disease, obesity, and sleep disorders (as described above). In women, we consider hormonal changes experienced during menopause or pregnancy. Neuropsychiatric causes of inattention/executive dysfunction can include brain injury, stroke, vascular disease, and dementia. We take substance use into consideration, especially cannabis since there is a known association between cannabis use and difficulties with attention.[27] Certain medications can also contribute to attentional difficulties—such as antihistamines, anticholinergics, benzodiazepines, sleeping aids, narcotics, anticonvulsants, and muscle relaxants.

TREATMENT AND MANAGEMENT

Evidence-based treatments available for adult ADHD include pharmacologic agents (which can be categorized as stimulants and nonstimulants) and psychotherapy. Stimulants, which are FDA approved for adult ADHD, are often touted as the first-line treatment for adult ADHD. A recent Cochrane Review of 19 amphetamine studies, however, reveals that these studies are either of low or very low quality and that none of them had low risk of bias.[28] In addition, the mean length of the studies was just over five weeks, which means we do not have long-term data on the efficacy of this class of medications for adult ADHD.

It is easy to underappreciate the risks associated with stimulant exposure—including neurotoxicity (in animals),[29] worsening of anxiety states (which can, in turn, worsen focus and further impair concentration),[30] amphetamine-induced mania,[31] and possible cardiovascular events in adults.[32] The relevance of neurotoxicity in animals should not be underestimated. Amphetamines and methylphenidate have been shown repeatedly to cause neuronal cell death, both in tissue cultures and in living brain—and especially hippocampal atrophy, which itself would worsen cognition. These findings have been replicated over decades in dogs, mice, rats, and other mammals. Human data are limited, but patients should be informed of this neurotoxic harm in animals and of the lack of definitive counteracting data in humans.

The worsening of anxiety as a prominent side effect of all amphetamines and methylphenidate should be emphasized since anxiety itself is a major cause of inattention and executive dysfunction. Hence, a vicious cycle can occur, with amphetamines given for inattention/executive dysfunction for purported ADHD (which often is due to anxiety or mood illnesses), causing further anxiety that then worsens inattention/executive dysfunction, leading to more amphetamine treatment. It is common (and relevant to the following comments on abuse) for amphetamine treatment to lead to benzodiazepine treatment for concomitant or worsened anxiety. Many clinicians do not appear to appreciate such anxiety as iatrogenic.

Another prominent concern related to stimulant prescribing is the risk for abuse, misuse, and diversion. In 2015 and 2016, 6.6% of U.S. adults used prescription stimulants, with one in three users (31.2%) reporting misuse at least once and 2.7% meeting criteria for prescription stimulant use disorders.[33] Among those misusing stimulants, the most common sources of prescription stimulants were friends or family (56.9%), and the most common reason for misuse was to improve performance (78%). Interestingly, evidence suggests that nonmedical use of prescription stimulants is not associated with performance improvement.[34,35]

Before deciding to initiate a prescription for a stimulant medication, we suggest carefully weighing the benefits of improved focus against the risks elaborated above. An evaluation of cardiac risk is warranted; it would include checking and monitoring vitals, collecting a personal and family history of cardiac disease, and in some cases obtaining an electrocardiogram. When stimulant pharmacotherapy is started, it would be reasonable to have a controlled substance contract in place, to order a baseline urine toxicology screen (to detect current substance use), and to check random urine screens after stimulant treatment has started to detect subsequent substance use and possible diversion. We recommend renewing the controlled substance contract every 2–3 years and checking random urine screens at least once yearly. Since we have limited long-term safety data on stimulant exposure in humans,[36] it may make sense to consider time-limited treatment with this class of medications. Atomoxetine, the only nonstimulant approved by the Food and Drug Administration (FDA), is a medication option for treating adult ADHD, especially for individuals with SUDs. The starting atomoxetine dose is 40 mg daily for three days, with an increase to 80 mg daily (the maximum daily dose is 100 mg). It should be noted that a dose reduction of 50% is needed for those with moderate hepatic impairment. Some evidence suggests that bupropion (which is not FDA approved for treating ADHD) can help improve symptoms of inattention in those with adult ADHD.[37] This option could be considered for those presenting with clinical depression that is marked by impaired concentration/focus. Before starting bupropion treatment, patients should be asked about a history for eating disorders and seizures, which are contraindications for bupropion. The extended-release (XL) formulation of bupropion may improve medication adherence as it is dosed once daily. Bupropion XL can be started at 150 mg daily for one week and then increased to 300 mg daily (the maximum daily dose is 450 mg).

The available evidence suggests that for patients taking medications for adult ADHD, cognitive-behavioral therapy improves outcomes for at least 12 months.[38,39] This therapy can be offered in either group or individual settings, with the evidence indicating that groups are more cost-effective.[40,41] Empirically supported protocols can be used to help the clinician walk the patient through modules such as

(1) psychoeducation and organizational planning, (2) problem solving, (3) distractibility, (4) environmental strategies, (5) adaptive thinking, (6) procrastination, and (7) therapy with a spouse/partner.[42] Health care providers can also share with patents helpful strategies aimed at improving focus and concentration for adults with inattention. These strategies include breaking down large tasks into smaller ones, minimizing distractions in the environment, and taking time (instead of rushing) when performing tasks. The employment of these strategies may be aided by the use of alarm functions and productivity apps on smartphones. In addition to using psychopharmacologic and nonpharmacologic treatments, patients can benefit from support groups for ADHD.[43]

TREATMENT OF UNDERLYING MEDICAL AND PSYCHIATRIC DISORDERS

Major Depressive Disorder

Both antidepressants and psychotherapy are effective for treating major depressive disorder.[44] The decision to initiate an antidepressant should take into account the severity of depressive symptoms and the history of depressive episodes. When an antidepressant is prescribed, one could also consider a time-limited course; this class of medication may offer only limited protection against relapse in depressive illness.[45]

Anxiety Disorder

Evidence-based treatments for anxiety disorders (including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder) are similar to those for depressive disorders. Treatments include psychotherapy and medications from the antidepressant class.

Bipolar Disorder

Maintenance treatments for bipolar disorder include lithium, anticonvulsants, and some atypical antipsychotics.[46] The role of antidepressants in treating bipolar disorder is controversial, with most randomized trials failing to find efficacy; as a result, these agents are generally not recommended. Importantly, stimulants, like standard depressants, can also cause mania, with a consequent negative impact on inattention.[47] Although guidelines exist for managing bipolar disorder in primary care, PCPs may have limited confidence in using some mood stabilizers, such as lithium. Since PCPs are often experienced with prescribing anticonvulsants such as lamotrigine, divalproex, and carbamazepine, it may be reasonable to start patients on one of these agents when bipolar illness is diagnosed, and then to refer to a psychiatrist if the first mood stabilizer trial is ineffective or not tolerated.

Posttraumatic Stress Disorder

The mainstay of treatment for PTSD is trauma-informed therapy.[48] Evidence-based therapies include prolonged exposure therapy, cognitive processing therapy, and eye-movement desensitization and reprocessing (EMDR). Medications can be used alone in primary care if appropriate therapy is unavailable or if the patient has a strong preference for pharmacotherapy.[48] Sertraline and paroxetine are FDA approved as antidepressant treatment for PTSD, although other medications in this class have also shown benefit.

Insomnia

Appropriate treatments for obstructive sleep apnea should be offered when this condition is present. For patients presenting with chronic insomnia, cognitive-behavioral therapy for insomnia (CBT-I) should be offered; sleep agents should be used judiciously as they have limited efficacy in improving sleep.[49]

SPECIAL CONSIDERATIONS IN THE TREATMENT OF ADULT ADHD

Pregnancy and Breast Feeding

In evaluating risks and benefits of treatment of patients in the perinatal period, one must consider the impact of untreated ADHD to the mother/infant pair and of medication exposure to the infant. Limited data are available on the effects of stimulants, atomoxetine, and bupropion on human pregnancy, neurodevelopment, and breastfeeding. Data on methylphenidates and amphetamines indicate no increase in the rate of major congenital anomalies.[50] Data for atomoxetine are limited to a few case reports and a small cohort study (n = 34) indicating no congenital anomalies.[51] A recent systematic review found that first-trimester use of bupropion was linked with a small elevation in the risk of cardiovascular defects; the absolute risk was low, however, and confounding could not be excluded.[52] No data are available on long-term neurodevelopmental effects on children with prenatal exposure to these medications.

Stimulants are secreted in breast milk. When the relative infant dosing (RID) of a medication is <10%, breastfeeding is considered acceptable. Case reports of methylphenidate use during breastfeeding demonstrated RIDs ranging from 0.16% to 0.7%.[50] One study examining dextroamphetamine use in breastfeeding mothers showed that RIDS ranged from 5.7% to 14%.[53] There are no available data on atomoxetine and lactation. Exposure to infants is theoretically reduced by coordinating the medication-dosing and infant-feeding schedules.[54]

Co-occurring Substance Use Disorder

Meta-analyses show a 23.1% prevalence of ADHD in adults with SUDs (excluding nicotine), higher than what is found in the general population.[55] Although an earlier review of the literature suggested that stimulant treatment for children with ADHD is protective against the development of SUDs in later life,[56] a more recent meta-analysis has shown that stimulant exposure for this population neither increases nor decreases the risk for SUDs in adulthood.[57]

No clear treatment guidelines are available for adults with comorbid SUDs and ADHD. Given the abuse potential for stimulants, a major concern arises when treating these individuals—substantial enough, we would argue, to warrant

a black box warning. Motivational interviewing and appropriate substance abuse treatments, such as screening, brief intervention, and referral to treatment (SBIRT), are indicated for patients with comorbid ADHD and SUD.

CONCLUSION

Requests to evaluate potential adult ADHD are increasingly common in primary care. Diagnosis of ADHD in adults is made clinically, with a focus on establishing impairment across multiple domains and excluding other causes of inattention and hyperactivity/impulsivity. The DSM-5 ADHD diagnostic criteria are of limited use in adults, as is neuropsychological testing. Primary psychiatric and substance use disorders are common causes of adult inattention, which calls for the treatment of those conditions before diagnosing ADHD and initiating treatment (in which case the risks/benefits of stimulant use must be carefully considered). The risks of stimulant treatment for adult ADHD are generally underappreciated, as long-term efficacy and safety data on stimulant use in adults with ADHD are lacking.

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Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist Instructions

The questions on the back page are designed to stimulate dialogue between you and your patients and to help confirm if they may be suffering from the symptoms of attention-deficit/hyperactivity disorder (ADHD).

Description: The Symptom Checklist is an instrument consisting of the eighteen DSM-IV-TR criteria. Six of the eighteen questions were found to be the most predictive of symptoms consistent with ADHD. These six questions are the basis for the ASRS v1.1 Screener and are also Part A of the Symptom Checklist. Part B of the Symptom Checklist contains the remaining twelve questions.

Instructions:

Symptoms

1. Ask the patient to complete both Part A and Part B of the Symptom Checklist by marking an X in the box that most closely represents the frequency of occurrence of each of the symptoms.

2. Score Part A. If four or more marks appear in the darkly shaded boxes within Part A then the patient has symptoms highly consistent with ADHD in adults and further investigation is warranted.

3. The frequency scores on Part B provide additional cues and can serve as further probes into the patient's symptoms. Pay particular attention to marks appearing in the dark shaded boxes. The frequency-based response is more sensitive with certain questions. No total score or diagnostic likelihood is utilized for the twelve questions. It has been found that the six questions in Part A are the most predictive of the disorder and are best for use as a screening instrument.

Impairments

1. Review the entire Symptom Checklist with your patients and evaluate the level of impairment associated with the symptom.

2. Consider work/school, social and family settings.

3. Symptom frequency is often associated with symptom severity, therefore the Symptom Checklist may also aid in the assessment of impairments. If your patients have frequent symptoms, you may want to ask them to describe how these problems have affected the ability to work, take care of things at home, or get along with other people such as their spouse/significant other.

History

1. Assess the presence of these symptoms or similar symptoms in childhood. Adults who have ADHD need not have been formally diagnosed in childhood. In evaluating a patient's history, look for evidence of early-appearing and long-standing problems with attention or self-control. Some significant symptoms should have been present in childhood, but full symptomology is not necessary.

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date	

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.

	Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?					
3. How often do you have problems remembering appointments or obligations?					
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					

Part A

7. How often do you make careless mistakes when you have to work on a boring or difficult project?					
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
10. How often do you misplace or have difficulty finding things at home or at work?					
11. How often are you distracted by activity or noise around you?					
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
13. How often do you feel restless or fidgety?					
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?					
15. How often do you find yourself talking too much when you are in social situations?					
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
17. How often do you have difficulty waiting your turn in situations when turn taking is required?					
18. How often do you interrupt others when they are busy?					

Part B

The Value of Screening for Adults With ADHD

Research suggests that the symptoms of ADHD can persist into adulthood, having a significant impact on the relationships, careers, and even the personal safety of your patients who may suffer from it.[1-4] Because this disorder is often misunderstood, many people who have it do not receive appropriate treatment and, as a result, may never reach their full potential. Part of the problem is that it can be difficult to diagnose, particularly in adults.

The Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist was developed in conjunction with the World Health Organization (WHO), and the Workgroup on Adult ADHD that included the following team of psychiatrists and researchers:

- **Lenard Adler, MD**
  Associate Professor of Psychiatry and Neurology
  New York University Medical School

- **Ronald C. Kessler, PhD**
  Professor, Department of Health Care Policy
  Harvard Medical School

- **Thomas Spencer, MD**
  Associate Professor of Psychiatry
  Harvard Medical School

As a healthcare professional, you can use the ASRS v1.1 as a tool to help screen for ADHD in adult patients. Insights gained through this screening may suggest the need for a more in-depth clinician interview. The questions in the ASRS v1.1 are consistent with DSM-IV criteria and address the manifestations of ADHD symptoms in adults. Content of the questionnaire also reflects the importance that DSM-IV places on symptoms, impairments, and history for a correct diagnosis.[4]

The checklist takes about 5 minutes to complete and can provide information that is critical to supplement the diagnostic process.

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Hyperactive Child Syndrome and Estimated Life Expectancy at Young Adult Follow-Up: The Role of ADHD Persistence and Other Potential Predictors

Russell A. Barkley[1] and Mariellen Fischer[2]

Abstract

Objective: We examined if ADHD Combined Type or Presentation (ADHD-C) reduced estimated life expectancy (ELE) at young adulthood and if the persistence of ADHD to adulthood further adversely affected ELE. **Method:** A young adult follow-up of 131 hyperactive and 71 control cases was used to derive 14 variables that were entered into a life expectancy calculator to generate ELE scores. Both ratings of executive function (EF) in everyday life and tests of EF and IQ were measured along with comorbid psychopathologies. **Results:** Childhood ADHD-C was associated with a 9.5-year reduction in healthy ELE, and a 8.4-year reduction in total ELE relative to control children by adulthood. The persistence of ADHD to adulthood was linked to a 12.7-year reduction in ELE. Several background traits accounted for more than 39% of variation in ELE. **Conclusion:** Childhood ADHD-C predicts a significantly reduced ELE by adulthood, which is further reduced by the persistence of ADHD to adult follow-up. *(J. of Att. Dis. XXXX; XX*[*X*] *XX-XX)*

Keywords

ADHD, estimated life expectancy, young adult follow-up, behavioral inhibition

ADHD is a neurodevelopmental disorder (American Psychiatric Association [APA], 2013) affecting 5% to 10% of children and 3% to 5% of adults (Willcutt, 2012). The disorder persists into adulthood in approximately 40% to 65% of cases diagnosed in childhood (Faraone et al., 2015; Owens, Cardoos, & Hinshaw, 2015). The condition was previously known as hyperkinetic reaction of childhood or hyperactive child syndrome (Barkley, 2015c). Despite the focus on motor activity in the term, descriptions of the syndrome also emphasized the importance of symptoms of inattention and impulsivity (APA, 1968; Cantwell, 1975) just as do current descriptions of ADHD Combined Type or Presentation (ADHD-C; APA, 2013).

Estimated life expectancy (ELE) refers to the number of years of life remaining at a specific age and is based on actuarial life tables of large population samples, such as those provided by the U.S. Social Security Administration (SSA). ELE can then be further adjusted by disability conditions and health-related variables based on their demonstrated impact on life expectancy in population samples apart from age and sex effects. These adjustments are known as Disability Adjusted Life Years (DALY) and Health Adjusted Life Years (HALY) calculations of ELE. There are at least five empirical reasons to hypothesize that hyperactive child syndrome, or ADHD-C, would be associated with a reduction in ELE so adjusted by adulthood:

1. Some longitudinal studies of hyperactive child syndrome, or those diagnosed with ADHD, are beginning to document increased death rates by young adult follow-up even if not yet significantly different from control groups (Barbaresi et al., 2013). However, others have not yet shown such differences by young adulthood (Barkley, Murphy, & Fischer, 2008). This lack of significance could be related to inadequate lengths of follow-up periods to detect differential death rates. As evidence of such, the longest running follow-up study that has followed their participants to midlife has reported a small but significant group difference (7.2% vs. 2.8%, respectively) by a mean age of 41 years (Klein et al., 2012).
2. ADHD is linked to increased adverse consequences in nearly every major domain of life activity studied to date (Barkley et al., 2008), some of which are

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linked to shortened life expectancy. For instance, ADHD is associated with higher risks for accidental and self-inflicted injuries in childhood and adulthood (Nigg, 2013) and that lead to increased emergency room admissions (Cuffe, Moore, & McKeown, 2009). Adverse driving outcomes, including more vehicular crashes (Barkley, 2015b; Barkley & Cox, 2007), are also associated with ADHD. ADHD is also associated with an increased risk for suicidal ideation, attempts, and completions (Barbaresi et al., 2013; Barkley et al., 2008). While comorbid depression in such cases is the major predictor of the greater risk for suicidal ideation, it is the impulsivity linked to ADHD-C that accounts for its greater risk for suicide attempts and completions (Barkley et al., 2008). All of these adverse outcomes intimate a likely reduction in ELE being associated with ADHD-C by adulthood.

3. ADHD is associated with various adverse medical conditions, including increased rates of seizures, obesity, eating pathology, traumatic brain injury, tobacco, alcohol, and marijuana use; dental trauma and caries; sedentary behavior or low rates of exercise;, sleeping problems, migraines, and risk for future coronary heart disease, as well as decreased involvement in preventive health, nutrition, and dental hygiene activities (Barkley, 2015a; Barkley et al., 2008; Nigg, 2013). Many of these conditions, well-known correlates of reduced ELE, are used in making DALY and HALY adjustments in calculations of ELE. They are also the focus of various societal efforts at their improvement by public health authorities in efforts to improve quality of life generally and life span specifically.
4. Teens and adults with ADHD-C are far more likely to be involved in interpersonal hostility generally and antisocial activities specifically that include violent crimes, reactive aggression, and intimate partner violence even when conduct disorder is not present or is statistically controlled (Buitelaar, Posthumus, & Buitelaar, 2015; Mohr-Jensen & Steinhausen, 2016; Saylor & Amann, 2016). All of these variables would predispose to an increased risk for greater morbidity and likely earlier mortality by violent means.
5. A few recent studies have specifically examined the issue of greater mortality in ADHD, using large epidemiological samples or even entire populations. In most cases, they show that in childhood the mortality risk is nearly doubled that of the typical comparable population, and in adulthood, that risk is more than quadrupled (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015; Jokela, Ferrie, & Kivimaki, 2009; London & Landes, 2016). This risk of earlier mortality seems to be largely a result of not only a greater proneness to accidental injury but also, to a lesser extent, from an elevated risk for suicide (Barbaresi et al., 2013; Dalsgaard et al., 2015). However, a much smaller study of 1,489 adults with ADHD enrolled in drug trials did not find significantly elevated mortality during the period of the drug evaluations (Khan, Faucett, Morrison, & Brown, 2013). But these results could be due to the smaller samples, shorter duration of the ascertainment window, and screening of study participants for health risks that might preclude study participation thus ruling out the least healthy ADHD adults.

Yet, greater mortality risk ratios in ADHD do not provide a direct estimate of reduced remaining years of life expectancy across adulthood. That is because very early mortality in childhood or young adulthood, such as related to accidental injuries, which has been documented in such cross-sectional studies is not reflective of later longevity risks that may arise from lifestyle factors used in DALY and HALY adjustments to ELE. The impact of those disability and health factors may produce cumulative health risks when chronic, such as excessive smoking, use of alcohol, drug abuse, poor diet, poor sleep, and limited exercise, among other health and lifestyle factors. Such factors caneventually lead to earlier death in mid-to-late life. Thus, it is still valuable to examine the ELE in young adults with ADHD-C that is associated with such health and lifestyle factors apart from what is already known about elevated mortality risk earlier in life in ADHD-C. For all of these reasons, we hypothesized that hyperactive child syndrome (ADHD-C), particularly if it was associated with the persistence of ADHD to adulthood, would be linked to a significant reduction in both total ELE and healthy ELE as well as an increase in unhealthy ELE by young adulthood.

The foregoing health and lifestyle factors that may affect ELE may be thought of as proximal or first order variables that are directly employed in algorithms to predict ELE, as often occurs in epidemiological research concerning public health within and across populations, countries, and ethnic groups. However, no research in ADHD-C has employed health and lifestyle factors for estimating ELE using DALY/HALY calculator algorithms. We propose to do so here.

Research has shown, however, that many of these first order health and lifestyle factors may be partially a function of second order background or more distal variables such as traits inherent in the individual that predispose them more than others to engaging in such health-adverse activities. Those background traits could be related to personality, cognitive deficits, psychopathologies, and even genetics. For instance, twin research has found that while smoking conveys an increased risk of mortality in identical twins discordant for smoking, thus supporting its direct contribution

to reduced ELE, this is not the case for low physical activity or high alcohol use. In those cases, there was no difference in mortality risk despite discordance for these activities (Kujala, Kaprio, & Koskenvuo, 2002). This implies that it is the genetic predisposition for such mortality risk that may underlie reduced ELE associated with low physical activity and heavy alcohol use rather than a direct effect of these adverse health activities.

One personality trait that has been strongly and consistently predictive of ELE and actual longevity and may underlie predispositions to engage in the above lifestyle risk factors is that of Conscientiousness (Bogg & Roberts, 2004; Hampson, 2008). This trait refers to the degree to which one relies on his or her conscience specifically and self-regulation and contemplation more generally to engage in decisions and actions that benefit one's longer term welfare over one's immediate gratification. For instance, low Conscientiousness in childhood (defined as the bottom quartile) is associated with reduced longevity by 7 to 8 years even among gifted individuals followed across their life spans (Friedman et al., 1995). Low Conscientiousness also predicts an increased risk for death by all causes (Bogg & Roberts, 2004; Hampson, 2008). Moreover, risk for coronary heart disease and cardiac arrest increase by 20% for each decrease of 1 *SD* in self-regulation (Kubzansky, Park, Peterson, Vokonas, & Sparrow, 2011) and, by inference, in Conscientiousness. Conscientiousness is negatively correlated with poor self-regulation generally and impulsivity or behavioral disinhibition specifically (Sharma, Markon, & Clark, 2014; Whiteside & Lynam, 2001). As might be expected from this negative association, Conscientiousness is also negatively associated with ADHD symptoms, which include behavioral disinhibition (Brainstorm Consortium, 2018; Martel, Nikolas, Jernigan, Fridericic, & Nigg, 2010). This association of Conscientiousness with ADHD may be due in part to their shared heritability (Brainstorm Consortium, 2018). Thus, it may be through its behavioral disinhibition component (and hence low Conscientiousness) that ADHD-C predisposes to those adverse health and lifestyle factors that reduce ELE.

This argument also provides a theoretical basis to logically hypothesize reduced ELE in ADHD-C. Behavioral inhibition is considered to be one of the seven major executive functions (EFs), along with sustained attention, working memory (both verbal and nonverbal), planning and problem solving, emotional self-regulation, and self-motivation (Barkley, 2012a). One major theory of ADHD-C is that it involves substantial deficits or delays in these EF components and especially inhibition and working memory (Barkley, 1997, 2015d), as has been abundantly evident in research on ADHD and EF (Frazier, Demareem, & Youngstrom, 2004; Hervey, Epstein, & Curry, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Besides these cognitive EFs, individuals also engage in actions in daily life that comprise the five major EFs evident in those daily life activities, such as self-restraint, time management, self-organization and problem solving, emotional self-regulation, and self-motivation (Barkley, 2012a, 2012b). Cognitive tests and rating scales for assessing EF are, surprisingly, not significantly correlated (Toplak, West, & Stanovich, 2013). Individuals with ADHD-C are substantially and pervasively deficient in such everyday EFs in both childhood (Gioia, Isquith, Kenworthy, & Barton, 2002) and adulthood (Barkley & Fischer, 2011; Barkley & Murphy, 2011), with deficient behavioral inhibition being especially prominent (Barkley & Murphy, 2011; Gioia et al., 2002; Thorell, Eninger, Brocki, & Bohlin, 2010). Hence, this theory of ADHD-C as involving deficient EF might also provide another trait or set of traits inherent in the individual that partially explains the proclivity of those with ADHD to engage in more adverse health and lifestyle activities that lead to reduced ELE.

A third inherent trait that could indirectly influence longevity through its impact on health and lifestyle practices is intelligence, another cognitive trait that overlaps to some extent with EF. Reviews of the literature clearly support a role of lower intelligence in the first two decades of life as being associated with increased risk for later mortality, even controlling for confounding factors in early life (Batty, Deaery, & Gottfredson, 2007). This effect may be partially mediated through the effects of IQ on education, occupational income, and other more proximal factors used in estimating life expectancy. ADHD is known to have a small but reliable, meaningful, and inherent negative association with intelligence with which it shares 6% to 12% of its variance (Tillman, Bohlin, Sorenson, & Lundervold, 2009). This relationship is through shared genetic and developmental etiological influences (Mill, Caspi, Williams, Craig, Taylor et al., 2006; Rommel, Rijsdijk, Greven, Asherson, & Kuntsi, 2015) and to some extent (4% to 46%) may be mediated by EF components related to both variables (Tillman et al., 2009). Hence, there is good reason to examine IQ in addition to EF deficits and behavioral disinhibition (low Conscientiousness) as second order traits related to ADHD that are also related to reduced ELE.

To test our hypothesis of reduced ELE in ADHD-C, the present study used health and lifestyle information from a longitudinal study of children diagnosed with Hyperactive Child Syndrome (ADHD-C) followed to young adulthood to estimate remaining ELE by ages 24 to 32 (mean age 27 years) relative to a concurrently followed community control (CC) group of children (Barkley et al., 2008). To test our second hypothesis that persistence of ADHD to adulthood would produce an even greater deleterious effect on ELE, we rediagnosed participants at their young adult outcome as to presence or absence of ADHD using modified *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*; APA, 1994) criteria.

Several additional specific aims were also addressed here. One was to evaluate which first order health and lifestyle factors used to calculate ELE in a DALY/HALY calculator may underlie any reduction found to be associated with ADHD-C. A further aim was to evaluate several second order or background traits inherent in individuals that might be contributing to variation in ELE, given that they predispose to adverse health and lifestyle factors and so to ELE. We therefore evaluated the second order traits of IQ and EF, including behavioral disinhibition. We evaluated EF using both neuropsychological testing and ratings of EF in daily life, given that the information provided by these different methods of evaluating EF have no significant relationship to each other (Toplak et al., 2013). Although we had no direct measure of Conscientiousness in this project, our EF measures of behavioral disinhibition, particularly EF ratings in daily life, could serve as a proxy for low Conscientiousness here given their strong negative relationship. An additional background or second order trait that might predispose to adverse health and lifestyle factors, and hence to reduced ELE in studies of ADHD, is its common comorbid psychopathologies (such as hostility, anxiety, and depression; Nordentoft et al., 2013). Therefore, a further aim of this study was to evaluate any contribution being made to ELE by such psychopathologies apart from those made by the other background trait factors.

Method

Participants

Samples. This study utilized 158 children determined as having hyperactive (H) child syndrome (the diagnostic term for ADHD-C at the time) and a matched CC group ($N = 81$) followed concurrently. The groups were originally evaluated in 1979 to 1980 when they were aged 4 to 12 years (Barkley, Karlsson, Strzelecki, & Murphy, 1984). Most (Hyperactive $n = 123$, or 78%; Normal $n = 66$, or 81%) were evaluated again as teens in 1987 to 1988 when they were 12 to 20 years of age (mean age of 14 years; Barkley, Fischer, Edelbrock, & Smallish, 1990). The participants were reassessed at early adulthood in 1992 to 1996 at 19 to 25 years of age (mean age of 20 years; Barkley, Fischer, Smallish, & Fletcher, 2002). The final follow-up serving as the basis for this article was in adulthood ages 24 to 32 (mean age of 27 years) conducted from 1998 to 2004 (Barkley et al., 2008). A total of 131 of the original H participants agreed to participate in all aspects of the study including the physical exam (83%). Seventy-one of the original 81 CC participants (88%) did so as well. Results from this final young adult follow-up appear elsewhere (Barkley & Fischer, 2011; Barkley et al., 2008).

Recruitment at childhood entry. At childhood entry, all participants were required to (a) have a verbal IQ greater than 80 on the Peabody Picture Vocabulary Test (Dunn & Dunn, 1981), (b) be free of gross sensory or motor abnormalities, and (c) be the biological offspring of their current mothers or have been adopted by them shortly after birth. The original gender composition was 91% male and 9% female; a typical Male: Female ratio for clinic-referred children having ADHD at the time. The racial composition at entry was 94% White, 5% Black, and 1% Hispanic.

The H group was originally recruited from consecutive referrals to a child neuropsychology service in the Midwest that also specialized in the treatment of H children. The CC children were recruited using a "snowball" technique in which the parents of the H children were asked to provide the names of their friends who had children within the age range of interest to the study. These friends of the parents then were contacted about the study. Those eligible were seen for the initial evaluation. At that time, they were asked about other friends of theirs who had children. These families were contacted to participate and so on. As such, this CC group is not a random or necessarily representative sample of the regional population but was intended to try and more closely equate hyperactive and control cases on demographic and socioeconomic factors.

For this young adult follow-up, all participants were contacted by phone, given an explanation of the study, and urged to volunteer to be reevaluated. They were then scheduled for their evaluations over a 2-day period at which time formal written consent was obtained. The battery of measures assessed psychiatric disorders, history of mental health treatments, outcomes in major life activities (education, occupation, dating, sexual activity, driving, money management, etc.), antisocial activities and drug use, and medical history. Some psychological tests and rating scales were also collected. The measures and results are described in detail in other sources (Barkley et al., 2008). Participants were asked to provide the name of another adult who could best describe their current functioning and to give permission for project staff to contact and interview this person about them. These interviews were conducted by an experienced master's-level psychological assistant and supervised by a licensed board-certified doctoral neuropsychologist. This assistant was not blind to original group membership at study entry. However, she was blind to the subgroup designation of having persistent disorder or not. The longitudinal study was reviewed and approved by the medical university institutional review board at each of the follow-up points, and all participants signed statements of informed consent, as did collaterals providing information about the participants. Participants and those collateral sources were paid for their time.

Participant selection criteria at childhood entry. Official diagnostic criteria for ADHD were not available at the time these children were recruited other than the one sentence

describing hyperkinetic reaction of childhood in the *DSM*, Second Edition (DSM-II; APA, 1968). Developmentally referenced research criteria that existed at the time were therefore used for identifying H children at study entry (Barkley, 1982). To be considered for the H group, the children had to (a) have scores on both the hyperactivity index of the Revised Conners' Parent Rating Scale–Revised (CPRS-R; Goyette, Conners, & Ulrich, 1978) and the Werry-Weiss-Peters Activity Rating Scale (WWPARS; Barkley, 1981) that met or exceeded 2 *SD*s above the mean for severity for same age, same sex normal children [the former scale contained items reflecting inattention, impulsivity, and hyperactivity, while the latter scale comprised items mainly reflecting hyperactive behavior in various situations]; (b) have scores on the Home Situations Questionnaire (Barkley, 1990) indicating pervasive behavioral problems in at least six or more of the 14 problem situations on this scale (a score exceeding +1 *SD*); (c) have parent and/or teacher complaints (as reported in a parent interview) of poor sustained attention, poor impulse control, and excessive activity level; (d) have developed their behavior problems prior to 6 years of age; (e) have had their behavioral problems for at least 12 months; and (f) have no indication of autism, psychosis, thought disorder, epilepsy, gross brain damage, or mental retardation. Such criteria are as or more strict than those for ADHD in *DSM-IV* (APA, 1994) available at the young adult follow-up.

In view of the selection criteria used here and the close convergence of rating scale diagnoses with the clinical diagnosis of ADHD (Edelbrock & Costello, 1988), it is likely that all participants would have met criteria for ADHD based on the *DSM-IV* had those been available. In fact, over 70% of them met the highly similar *DSM*, Third Edition, Revised (*DSM-III-R*; APA, 1987) criteria for ADHD 8 to 10 years later at the adolescent follow-up (Barkley et al., 1990).

Eligibility for the CC group was based on (a) no history of referral to a mental health professional, (b) no current parental or teacher complaints of significant behavioral problems, (c) scores within 1.5 *SD*s of the typical mean on both the hyperactivity index of the CPRS-R and the WWPARS, and (d) no evidence of any other psychiatric disorder.

Determining the presence of ADHD in adulthood. A structured interview involving *DSM-IV* criteria for ADHD (APA, 1994) was created and employed at follow-up, given that no structured interview using precisely these criteria then existed for use with adults to evaluate the presence of this disorder. Symptoms of ADHD were reviewed twice, once for current functioning (past 6 months) and a second time for childhood between 5 and 12 years of age, with the requirement that the symptom only be endorsed if it occurred often or more frequently. A symptom count was calculated from each symptom list. The age of onset of symptoms was also determined. Six domains of impairment (functional ineffectiveness) were also reviewed with impairment having to occur often or more frequently and at what age each domain became impaired. The domains were occupational, home, social, community activities, education, and dating/marriage. The interview has been used successfully in other studies of adult ADHD (Barkley et al., 2008).

One could simply apply the *DSM-IV* criteria as written to these adults to identify presence of ADHD in adulthood. If that were done, then 30% of the H group would meet the *DSM-IV* threshold of having at least six of nine symptoms on either symptom list by self-report. Adding the additional criterion of having impairment in at least one or more domains by self-report reduces this figure to 24%. The results for the control group would be 3% using symptoms only and 1% using symptoms and impairment. If the reports of others (the collaterals) are used instead to define ADHD, these figures would be 26% for having six of nine symptoms and 25% for having those symptoms plus impairment for the H group (1% for controls in either case).

Yet there are good reasons to challenge this approach to diagnosing adults with ADHD, especially in follow-up studies of children with ADHD (Barkley et al., 2008; McGough & Barkley, 2004). The *DSM* items and thresholds were designed for use with children, not adults. Given that ADHD symptoms decline significantly with age in both ADHD and typical populations (Owens et al., 2015), symptom thresholds used with children may not be equally applicable for identifying adults with ADHD as they would represent an increasing severity level with age. Previous research (Barkley, 2011) suggests that a threshold of four self-reported symptoms on either list is sufficient to accurately classify ADHD in adults, and represents the 93rd percentile or +1.5 *SD*s above the general population mean. Applying this threshold along with a requirement for impairment resulted in 44% ($n = 55$) meeting these developmental criteria. Henceforth, this group is called ADHD present (or H + ADHD, for H children and currently ADHD in young adulthood). The remaining 80 members of the H group who did not meet these criteria are referred to as ADHD nonpresent (or H – ADHD).

Demographic information. The groups did not differ in their sex composition (84% to 93% males). There were just nine females in the H + ADHD group, 11 in the H – ADHD group, and five in the control group, precluding the examination of potential sex differences having satisfactory statistical power. A slightly yet significantly lower percentage of the two hyperactive groups consisted of self-identified White or European American ethnic identity (81% to 84% White) at follow-up in comparison with the control group (97% White). Groups did not differ in the proportions that were currently single, married, or separated/divorced, with approximately 30% to 43% of our groups being currently

Table 1. Demographic Characteristics by Group for Dimensional Measures.

Group:	(1) H + ADHD		(2) H – ADHD		(3) Community				Pair-wise
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	Contrasts
Age (years)	26.8	1.4	27.2	1.4	26.9	0.8	1.52	*ns*	
Education (years)	12.2	2.2	12.8	2.1	15.8	2.3	51.49	<.001	1,2 < 3
Verbal IQ (WAIS-III vocabulary)	10.5	3.4	10.6	3.3	14.1	2.6	29.55	<.001	1,2 < 3
Nonverbal IQ (WAIS-III block design)	11.6	3.2	11.6	3.4	13.0	2.9	4.85	.009	1,2 < 3
Hollingshead job index	32.3	19.8	40.1	20.6	56.0	27.0	18.11	<.001	1,2 < 3
Hollingshead SES	28.4	11.2	33.2	12.7	45.4	15.1	28.80	<.001	1,2 < 3

Note. H + ADHD = hyperactive group that currently has a diagnosis of ADHD at follow-up. H – ADHD = hyperactive group that does not have a diagnosis of ADHD at follow-up; *ns* = not significant; WAIS-III = Wechlser Adult Intelligence Test–Third Edition; SES = socioeconomic status.

married. Significantly fewer H + ADHD cases were currently employed compared with the H – ADHD and CC groups. The dimensional demographic features are displayed in Table 1. The ages of the groups are comparable (age 27 years). Both of the H groups had less education, lower Hollingshead job index scores, and lower IQ estimates than the CC group consistent with other longitudinal studies of ADHD children.

Treatment history. The vast majority of individuals in the two H groups were not currently receiving any form of treatment nor were they at the last follow-up. That fact likely accounts for why no effects of earlier treatment were evident in any domain of functioning evaluated in this project by young adulthood, either at age-21 or age-27 follow-ups (Barkley et al., 2008). Thus, treatment history was not examined here for any relationship to ELE.

Dependent Measures

ELE Calculator and Output Scores

It is common practice now in public health research to employ disability and health factor adjustments to estimate remaining life expectancy, or ELE (in years of life remaining), such as is done by the World Health Organization[1] in their research comparisons across member countries and by the Centers for Disease Control and Prevention.[2] Large databases on populations are used to calculate initial mortality rates and these rates are then adjusted for various health and lifestyle factors shown to have an impact on life expectancy in those populations. Formulas then combine weightings of such factors[3] to produce an estimate of total, unhealthy, and, more recently, healthy years of life remaining (Crimmins & Saito, 2001; Mathers, Sadana, Salomon, Murray, & Lopez, 2001; Murray et al., 2015; Robine & Ritchie, 1991). Of the various ELE calculators that are available on the Internet and thus are publicly available, we used one (a) not commercially affiliated; (b) of relatively recent origin to insure that the actuarial databases used to construct it and its regression weights were founded on current population samples and their mortality tables; (c) founded on large actuarial databases known as life tables similar to those used in epidemiological research on ELE and in the insurance industry; (d) that used a sufficient number of relevant variables to adjust the calculation of the ELE values for each individual beyond what would merely be available through government actuarial tables based on age, sex, and race; and (e) that contained variables that were collected in our follow-up study or could be extrapolated from them. The ELE calculator at the Goldenson Center for Actuarial Research, University of Connecticut (UCONN) met these requirements (see https://apps.goldensoncenter.uconn.edu/HLEC/).

This ELE Calculator is based on a model employing three input assumptions: (a) for healthy mortality, it used the first year Society of Actuaries select life mortality rates; (b) for the incidence rate of disability, it used the Society of Actuaries annuitant disabled rates; and (c) for the mortality rates of disabled lives, it employed the Social Security disabled mortality rates. The developer then used a multiple-decrement actuarial modeling algorithm to calculate healthy life expectancy (HLE; years left free of disability and ill-health; Jagger & Robine, 2011; Robine & Ritchie, 1991), unhealthy life expectancy (ULE; years left with disability and ill-health, also known as DALY; Murray et al., 2015; Robine & Ritchie, 1991), and total life expectancy (LE = HLE + ULE). The three input assumptions were adjusted for 14 individual health and lifestyle variables (such as education, body mass index [BMI], diet, exercise, sleep, etc.) using a factor approach based on quintiles of the HLE distribution.

The ELE Calculator requires the entry of 14 variables. These are set forth in Table 2 along with the source used from the study database to derive each variable and any adjustments that were required to adapt the information into that format required by the Calculator. Unique to this calculator is its estimation of both healthy and unhealthy years of life remaining rather than just total ELE. It also provides an estimate of the percent difference between the individual

Table 2. Variables Used in the ELE Calculator to Compute Estimated Life Expectancies.

Variable	Units	Source	Adjustments (if any)
Gender	Male/female	Interview	
Age	Years	Interview	
Weight	Pounds	Phys. exam	
Height	Feet and inches	Phys. exam	
Education	Less than HS, HS, college, graduate	Interview	All cases were entered as HS except for those having less education. Then 11 months was added to the HLE and LE output for each additional year of education after high school based on more recent research supporting this adjustment(Joshi et al., 2017)
Income	<US$25K, US$25K-US$50K, US$50K-US$75K, US$75K-US$100K, US$100K+	Interview	
Exercise	Never, rarely, 1-2 days/week, 3-4 days/week, 5+ days/week	Interview	
Current health	Poor, fair, good, very good, excellent	Interview	Based on responses to 59 possible current medical health complaints answered as currently a problem or not as described elsewhere(Barkley et al., 2008). The total number of such complaints was computed. Then the distribution of such scores for the CC group was used to create the five quintile ranges (0-20 percentile, 21-40 percentile, etc.). These ranges then served to determine the category entered for this variable with the highest quintile corresponding to Poor, next highest to Fair, and so on.
Type 2 diabetes	No/yes	Interview	
Diet	Poor, fair, good, very good, excellent	SCLI	This interview (Skinner, 1994) evaluates 16 domains of self-reported lifestyle, one of which is the Nutrition domain score. Scores reflect placement within one of three ranges corresponding to a Risk or Concern, or a Strength. We coded the Risk and Concern output as Poor and the Strength output as Good, thus using only two of the five possible entries.
Sleep	<5 hr, 5-8 hr, or 8+ hr per night	SCLI	Information on the Sleep domain is among the 16 domains assessed in this interview. Output from this assessment coded as a Risk or Concern was entered as the <5 hr category while output coded as a Strength was entered as 8+ hr.
Smoking	Nonsmoker, smoker	Interview	We also had data on how many cigarettes per day the individual reported currently smoking. Recent research shows (Joshi et al., 2017) that ELE can be adjusted further beyond that done in this calculator by determining if an individual also smokes 20 or more cigarettes per day. That study indicates that smoking that amount or more per day reduces LE by 6.4 years. The ELE Calculator already reduces its output by 4 years if someone is a smoker. So the outputs of the calculator for HLE and LE were further adjusted downward by another 2.4 years for any participant also reporting smoking 20+ cigarettes per day.
Driving	0, 1, or 2+	Interview	This is intended as a self-assessment reflecting risky driving. It is usually entered as one of three categories: 0 accidents per year (of driving), 1 accident a year, and 2+ accidents a year. However, as discussed with the ELE Calculator developer, this is a markedly unrealistic index of risky driving as no one in our study had 1 or more accidents per year in their driving career that spanned 10 to 19 years. Given that teens and adults with ADHD are among the riskiest and accident prone drivers studied in prior research (Barkley & Cox, 2007) the fact that none of our participants would be considered a risky driver for this ELE calculator seemed highly unrealistic. In discussion with the developer, it was decided that a far better index of risky driving in our database was the number of times a participant had reported having his or her license suspended or revoked.
Alcohol	Never, rarely, 2-3 drinks/week 3-7 drinks/week, and 8+ drinks per week	Interview	

Note. ELE = estimated life expectancy; HLE = healthy life expectancy; LE = life expectancy; CC = community control; SCLI = Skinner Computerized Lifestyle Interview.

being evaluated and the average of the actuarial population on which the calculator is based. The UCONN HLE Calculator therefore provided four related dependent measures: (a) HLE or healthy years remaining, (b) ULE or unhealthy years remaining, (c) total years of life remaining (ELE), and (d) Relative Healthy Years Percent (RHYP) above or below the norm expressed as a positive or negative percentage. The HLE and ELE outputs were further adjusted for two variables within the calculator that may underestimate their contribution to ELE based on more recent research (Joshi et al., 2017). These were years of education beyond high school (with 11 months added per year) and smoking 20 or more cigarettes per day (with 2.4 years being subtracted; see Table 2). Those adjusted scores are henceforth termed HLE(A) and ELE(A).

Predictor Measures

The following measures were used to conduct the appropriate analyses for addressing the additional specific aims discussed above as possible variables associated with ELE.

Executive functioning in daily life. A self-report interview was created consisting of 91 items intended to reflect deficits in various components of EF as they may occur in daily life. More information on this interview can be found in other research from this study (Barkley & Fischer, 2011; Barkley et al., 2008). The internal consistency of this scale is high (Cronbach's $\alpha = .961$, $p < .001$). A factor analysis in that earlier research showed it to reflect five EF components, these being Time Management, Organization and Problem Solving, Self-Motivation, Self-Activation, and Behavioral Inhibition. Scores were created for each factor by counting an item as an EF symptom if it was reported as occurring often or very often. That earlier study also found that the H + ADHD group had more severe ratings on all of these EF components than did the H – ADHD and CC groups while the H – ADHD group scored more poorly than the CC group on three of the five components. This interview was subsequently transformed, normed, and published as the Barkley Deficits in Executive Functioning Scale (Barkley, 2011), the manual for which provides further information on the psychometric properties of this interview and the subsequent scale created from it.

Neuropsychological tests. The following battery of tests was used to evaluate verbal and nonverbal IQ as well as the EF components of inhibition, verbal and nonverbal working memory, fluency, and planning/problem solving.

Vocabulary and Block design subtests from the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III). Two subtests were chosen from this standardized intelligence test to serve as a quick screening for level of verbal and nonverbal intelligence (Vocabulary and Block Designs; Wechsler, 1997). They were chosen for having among the highest correlations with the Verbal and Nonverbal IQ scores, respectively, derived from the complete test administration. The scaled scores from both subtests were used here.

Digit span from the WAIS-III. This test involves two subtests (Wechsler, 1997). In one, the examinee is given a series of increasingly longer strings of digits by the examiner at a rate of 1 per second. The examiner must repeat them back in the same numerical sequence. In the second subtest, the examinee must repeat increasingly longer strings of digits in a backward order from that given by the examiner. For both tests, the participant is given two trials at each span length. The test is concluded when the participant fails to repeat both trials correctly at that span length. The score is the longest span length the participant was able to perform correctly on at least one of the two trials. The raw scores from both tests were combined to form a single raw score for this measure. This test was chosen to evaluate verbal working memory.

Simon game. This is a commercially available game that consists of a circular plastic device housing four large colored keys on its top surface. Each key is a different color. When depressed, each of these keys emits a different tone. When activated, the game automatically presents a sequence of different tones and lights up the key corresponding to each tone as it does so. The participant must then press the keys in their correct sequence so as to reproduce the melody. With each trial, the sequence of tone/key combinations becomes increasingly longer and thus more complex. The score used here was the longest correctly reproduced sequence. This task was chosen so as to evaluate nonverbal working memory in a manner equivalent to a digit span forward task. It is akin to self-ordered pointing tasks (see Lezak, 1995). Our past research with adults with ADHD (Barkley, Murphy, & Kwasnik, 1996; Murphy, Barkley, & Bush, 2001) found those adults to be impaired relative to a control group on this measure. It is possible that some adults may be more familiar with this game than others, and so we inquired about this issue with our participants. The groups did not differ in their familiarity with this game.

Kaufman Hand Movements Test from the Kaufman Brief Intelligence Test. The Hand Movements Test is a well-standardized and normed test for children based on a traditional measure of frontal lobe function in adults (Kaufman & Kaufman, 1993). Children are presented with progressively longer sequences of three hand movements that they must imitate. The test has acceptable reliability and normative data and three studies have shown it to differentiate groups of ADHD from groups of normal children (Grodzinsky & Diamond, 1992; Mariani & Barkley, 1997)

and from attention deficit disorder (ADD) children who are not hyperactive (Barkley, Grodzinsky, & DuPaul, 1992). Its sensitivity to ADHD may rest in the well-known fine motor coordination difficulties often seen in these children as well as in their inattention to the task itself or deficits in nonverbal working memory, especially as sequences of movements become progressively longer.

The 5 Points Test of design fluency. Originally developed by Regard, Strauss, and Knapp (1982) as an attempt to design a nonverbal version of more commonly used verbal fluency tasks, this test involves a sheet of paper with 40 five-dot matrices on it (Lee et al., 1997). Participants are required to produce as many different figures as possible by connecting the dots within each rectangle within a 3-min time limit. Not all dots have to be used and only straight lines between dots are permitted. No figures are to be repeated. If a violation occurs, participants are given a single warning on the first violation but the rules are not repeated after any further infractions. Scores are the number of unique designs created, the number of repeated designs (perseveration), the number of rule infractions, and the percentage of designs that are repeated designs (percent perseveration). Patients with frontal lobe dysfunction have a significantly higher percentage of perseverative errors than do neurological patients without frontal involvement and psychiatric patients (Lee et al., 1997). Using a modified version of this same task, Ruff, Allen, Farrow, Nieman, and Wylie (1994) also found the task to be sensitive to frontal lobe injuries and perhaps is more sensitive to right than left lobe involvement.

Tower of London Test. This test presents the participant with a stand on which there are three spindles of different heights along with three balls of different colors (red, blue, and green) that are arranged on two of these spindles (Shallice, 1982). The participant is then shown a diagram illustrating the goal or final position in which these balls are to be rearranged. In proceeding to rearrange the balls in that final sequence, the participant most do so in the fewest moves. The task requires that participants look ahead to determine the proper order of moves, and so it is considered a test of planning ability. The test has been used in a number of neuropsychological studies of children with ADHD where planning deficits have been noted (Grodzinsky & Diamond, 1992; Hervey et al., 2004).

Stroop Color Word Test. This test measures the ability to inhibit competing responses in the presence of salient conflicting information (Stroop, 1935; Trenerry, Crosson, Deboe, & Leber, 1989). The version and norms published by Trenerry et al (1989) were used here. The task is comprised of three parts. In the first part, the participant reads a repeating list of color names (e.g., red, blue, and green) printed in black ink. In the second part, the participant names the colors of a repeated series of Xs printed in an ink of those same colors. In the last or Interference condition, the participant must say the color of ink in which a color word is printed. For some words, the color of ink in which it is printed is the same as that of the word while for others, the color of ink differs from that specified by the word. This portion of the task is believed to reflect problems with the capacity to inhibit habitual or dominant responses (reading the word, in this case). We used the score from this last portion of the test (Interference) as a measure of behavioral disinhibition.

The results for the group comparisons on these tests are presented elsewhere (Barkley et al., 2008). They found that both the ADHD groups performed more poorly than the CC group on the verbal and nonverbal IQ subtests (see Table 1), the Simon Game, The 5-Point Design Fluency Test, and the WAIS-III Digit Span subtest, while not differing significantly from each other. Only the H + ADHD group performed more poorly on the Stroop Test compared with both the H – ADHD and CC groups. And the H + ADHD group performed worse than the H – ADHD group that was worse than the CC group on the Kaufman Hand Movements Test. There were no group differences on the Tower of London Test. Subsequent reanalyses covarying IQ did not materially alter these findings.

Comorbid psychopathology: Hostility, anxiety, and depression. To evaluate comorbid symptoms of psychopathology, we employed the Symptom Checklist–90–Revised (SCL-90-R; Derogatis, 1986). This self-report scale provides a global severity index as well as *T*-scores for nine specific scales of maladjustment (e.g., anxiety, paranoid ideation, interpersonal hostility, depression, etc.). Only the scores for the hostility, anxiety, and depression scales were used here as these are the most often elevated in research on adult ADHD (Barkley et al., 2008).

Results

ELE

As a starting point, we needed to show equivalence in ELE between these groups without making adjustments for any of the education, occupation, health, and lifestyle variables entered into the UCONN HLE Calculator. The starting ELE for each participant was determined based on the actuarial tables available for just their age and sex from the SSA tables for 2004 (the year closest to the completion date of this follow-up point) published at the SSA website (see https://www.ssa.gov/oact/STATS/table4c6_2004.html). A one-way ANOVA was used to compare the two diagnostic groups at study entry (H vs. CC) on this ELE score. Differences were not significant ($F = 1.51$, $df = 1/200$, $p = .22$; H: $n = 131$, Mean = 49.99, $SD = 2.10$; CC: $n = 71$,

Table 3. Means, Standard Deviations, and Statistical Test Results for the Four UCONN ELE Calculator Scores for the Hyperactive and Community Control Groups Formed at Study Entry.

Group:	Hyperactive		Control			
Measure	*M*	*SD*	*M*	*SD*	*F*	*p*
Healthy—HLE(A)	45.1	8.8	54.7	7.4	60.57	<.001
Unhealthy—ULE	5.4	2.0	4.2	1.1	21.23	<.001
Total LE(A)	50.5	7.9	58.9	7.2	55.28	<.001
RHYP	−20.2	13.9	−8.5	10.6	38.70	<.001

Note. UCONN ELE = University of Connecticut estimated life expectancy; *F* = results of the *F* test from the one-way ANOVA; *p* = probability value associated with the *F* test; HLE(A) = healthy life expectancy adjusted for smoking amount and years of education after high school; ULE = unhealthy life expectancy; Total LE(A) = total years of life expectancy adjusted for smoking amount and years of education after high school; RHYP = relative healthy years percent.

Mean = 49.66, *SD* = 1.27). Thus, without DALY/HALY adjustments for any other variables, and using government provided actuarial tables, the mean ELEs for these two groups are essentially equivalent.

An ANOVA was then used to compare the initial groups formed at study entry (H vs. CC) on the four measures computed from the UCONN HLE Calculator with adjustments as discussed above. Statistical significance was set a priori at $p < .01$ given the large number of analyses. The results of these group comparisons are shown in Table 3. All comparisons were significant (*p*s < .001), indicating that the H group had differed significantly from CC cases on all four ELE-related scores. On average, the H group demonstrated a nearly 10-year reduction in HLE(A), while having 1.2 years greater in ULE, thus resulting in an overall 8.4year reduction in Total ELE(A). On the RHYP score, the H group placed more than 20% below average compared with the CC group ($M = -8.4\%$).

The three groups that were formed at the young adult follow-up based on persistence of ADHD by that point (H + ADHD, H – ADHD, CC) were then compared on these same four ELE scores using one-way ANOVAs. The results are shown in Table 4 with group differences on all four scores being significant (*p*s <.001). Persistence of ADHD to adulthood had a significant impact on reducing HLE(A) and thus Total ELE(A) as well as on RHYP compared with nonpersistent cases of the disorder. But the persistence of ADHD at adulthood was not associated with a significant difference from the nonpersistent ADHD group in their ULE, with both differing significantly on this score from the CC group at follow-up.

Group Differences on ELE Calculator Variables

The next set of analyses focused on the 14 ELE calculator variables and the two additional ones (education beyond high school, smoking 20+ cigarettes per day) used to make further adjustments to the ELE output. These analyses explored the specific aim of what calculator factors were accounting for this reduction in ELE associated with the ADHD groups. We first compared the three groups formed at adulthood on the six dimensional measures used in the calculator using one-way ANOVAs. The p value was set at _<.05 due to the small sample sizes of these outcome groups and so reduced power. The results are shown in Table 5. The groups did not differ significantly in their age, weight, or height. However, both ADHD groups had significantly less education compared with the CC group. The ADHD+H group also had a significantly lower annual salary and consumed significantly more alcoholic drinks per week than did the CC group, while the ADHD – H group did not differ from either group, placing between the two on these variables.

We next compared the groups on the 10 variables used in the ELE calculator that were categorical in nature, using Pearson chi-squares (see Table 6). The groups did not differ in their sex, diabetes, or nutrition. However, both of the ADHD groups were less likely to graduate from high school and were more likely to be smokers than the CC groups, with neither ADHD group differing from the other in these aspects. The ADHD + H group reported significantly poorer current health than did the ADHD – H group and both ADHD groups reported poorer health than the CC group. This was also the case with regard to getting 8+ hr of sleep per night. Only the ADHD+H group had a higher percentage of smokers consuming 20+ cigarettes per day compared with the other two groups although the difference between the ADHD – H and CC groups was of marginal significance ($p = .053$). Although not significant, the two ADHD groups also had a higher percentage of cases reporting at least 2+ drivers' license suspensions/revocations than did the CC group that was of marginal significance ($p = .06$). These analyses reveal which calculator health and lifestyle factors were resulting in the significant reductions in ELE associated with the ADHD groups that might serve as targets for subsequent intervention efforts so as to improve ELE.

Background Traits Potentially Associated With ELE

Having shown which fisrt order factors in the ELE calculator were adversely affecting ELE in the ADHD-C groups, we then examined several second order trait variables that might be linked to reductions in ELE via their association with the health and lifestyle factors used to compute ELE. These background variables were IQ, EF components as measured via neuropsychological tests, ratings of EF in daily life, and several dimensions of psychopathology often associated with ADHD (hostility, depression, and anxiety). Before examining the relative contributions of these measures to ELE in the entire sample using multiple regression,

Table 4. Means, Standard Deviations, and Statistical Test Results for the Four UCONN HLE Calculator Scores for the H + ADHD, H – ADHD, and Community Control Groups.

Group:	(1) H + ADHD		(2) H – ADHD		(3) Community				Pair-wise
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	Contrasts
HLE(A)	42.0	8.8	47.3	8.2	54.7	7.4	38.94	<.001	1<2<3
ULE	5.8	2.2	5.2	1.8	4.2	1.1	13.20	<.001	1,2<3
Total—LE(A)	47.8	7.9	52.4	7.4	58.9	7.2	35.30	<.001	1<2<3
RHYP	−25.6	13.4	−16.5	13.0	−8.5	10.6	29.48	<.001	1<2<3

Note. UCONN HLE University of Connecticut healthy life expectancy; H + ADHD = hyperactive group that currently has a diagnosis of ADHD at follow-up; H – ADHD = hyperactive group that does not have a diagnosis of ADHD at follow-up; *F* = results of the *F* test from the ANOVA; *p* = probability value associated with the *F* test; pair-wise contrasts = results from the pair-wise comparisons of the three groups; HLE(A) = healthy life expectancy adjusted for smoking amount and years of education after high school; ULE = unhealthy life expectancy; Total LE(A) = total years of life expectancy adjusted for smoking amount and years of education after high school; RHYP = relative healthy years percent.

Table 5. Group Differences for the Dimensional Measures Used in the ELE Calculator.

Group:	(1) H + ADHD		(2) H – ADHD		(3) Community				Pair-wise
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	Contrasts
Age (years)	26.8	1.4	27.2	1.4	26.9	0.8	1.52	NS	
Weight (lb)	209.0	63.7	205.0	50.0	194.6	52.9	1.17	NS	
Height (ft)	5.8	0.4	5.8	0.3	5.8	0.2	0.52	NS	
Education (years)	12.3	1.9	12.9	2.1	15.8	2.3	49.06	<.001	1,2<3
Annual salary (thousands)	25.4	14.5	29.5	19.5	36.6	19.0	5.43	.005	1<3
Alcoholic drinks consumed weekly	9.7	16.8	4.3	6.2	5.5	7.1	4.40	.013	1>3

Note. ELE = estimated life expectancy; H + ADHD = hyperactive group that currently has a diagnosis of ADHD at follow-up; H – ADHD = hyperactive group that does not have a diagnosis of ADHD at follow-up.

Table 6. Group Differences for the Categorical Measures Used in the ELE Calculator.

Group:	(1) H + ADHD		(2) H – ADHD		(3) Community				Pair-wise
Measure	%	*N*	%	*N*	%	*N*	χ^2	*p*	Contrasts
Sex (male)	85	46	86	66	94	67	3.60	*ns*	
High school graduate	63	34	67	52	99	70	28.79	<.001	1,2<3
Exercise (3-4/week)	7	1	12	4	3	1	3.02	*ns*	
Health (excellent)	18	10	36	28	69	49	52.95	<.001	1<2<3
Diabetes (yes)	4	2	1	1	0	0	2.90	*ns*	
Nutrition (good)	31	17	48	37	51	36	6.53	*ns*	
Sleep (8+ hr/night)	48	26	67	52	86	61	20.48	<.001	1<2<3
Smokes cigarettes	65	35	57	44	35	25	12.36	.002	1,2<3
Smokes 20+/day	43	23	23	18	11	8	16.43	<.001	1>2,3
License revoked 2+ times	36	19	30	23	16	11	8.98	*ns*	

Note. ELE = estimated life expectancy; H + ADHD = hyperactive group that currently has a diagnosis of ADHD at follow-up; H – ADHD = hyperactive group that does not have a diagnosis of ADHD at follow-up; *ns* = not significant.

we examined the correlation matrix among the measures for possible collinearity within measures of a trait and multicollinearity across traits. As expected, most measures within each trait were more highly correlated with each other than with those of other traits, yet even then the tolerance for collinearity within traits and multicollinearity across traits appeared acceptable. Specifically, the EF ratings correlated more highly with each other (*r*s = .61-.77) than with EF tests (–.03 to –.31), IQ (–.11 to –.38), and SCL-90 scales (.42 to .59). The SCL-90 scales also correlated more highly with each other (.64-.75) than with EF tests (–.07 to –.21) and IQ (–.15 to –.23). However, the EF tests showed a

Table 7. Regression Analyses of EF Ratings, SCL-90-R Ratings, EF Tests, and IQ Subtests on to Total Life Expectancy (ELE[A]).

Predictors	*B*	*t*	*p*	95% CI	CT
EF Rating—Time management	−.192	−1.83	.069	[–.620, .023]	.267
EF Rating—Self-organization	.122	1.33	.184	[–.102, .527]	.353
EF Rating—Behavioral disinhibition	−.327	−3.13	**.002**	[–.842, –.191]	.269
EF Rating—Self-motivation	.115	1.17	.244	[–.273, 1.07]	.304
EF Rating—Self-activation	−.064	−0.66	.510	[–.743, .371]	.315
SCL-90-R—Depression	−.144	−1.52	.131	[–.236, .031]	.326
SCL-90-R—Anxiety	.120	1.34	.181	[–.040, .212]	.369
SCL-90-R—Hostility	−.168	−2.06	**.041**	[–.245, –.005]	.439
EF Test—WAIS-III digit span	−.021	−0.28	.782	[–.494, .372]	.515
EF Test—Simon: Longest correct	.036	0.55	.581	[0.331, .589]	.706
EF Test—5 points: Unique designs	.120	1.49	.139	[–.031, .219]	.449
EF Test—Stroop interference score	−.075	−1.28	.203	[–.267, .057]	.852
EF Test—Tower of London: Correct	−.069	−1.19	.236	[–.957, .237]	.870
EF Test—KHT: Number correct	.050	0.69	.489	[–.355, .740]	.556
WAIS-III: Vocabulary (verbal IQ)	.205	2.66	**.008**	[.131, .875]	.496
WAIS-III: Block Design (nonverbal IQ)	.028	0.36	.718	[–.336, .487]	.476

Note. EF = executive function; SCL-90-R = Symptom Checklist–90–Revised; ELE = estimated life expectancy; *B* = standardized beta coefficient from the final model; *t* = *t* test, *p* = probability value for the *t* test; 95% CI = confidence interval; CT = collinearity tolerance; WAIS-III = Wechsler Adult Intelligence Scale–Third Edition. Stroop = Stroop Word-Color Test; KHT = Kaufman Hand Movements Test. Estimate in the bold indicate results that were significant at $p<.05$.

similar range of correlations with each other (.13-.55) as they did with IQ (.10-.64); not unexpected given their similarity of measurement and known overlap.

We then used multiple regression with the entire sample (collapsed across groups) to analyze all trait predictor variables simultaneously for their relationship to total life expectancy indexed by Total ELE(A). The results appear in Table 7. The equation was significant ($R = .656$, $R^2 = .430$, $F = 9.14$, $df = 16/194$, $p < .001$) and explained 43% of the variation in Total ELE(A). Individual measures that were significant after controlling for all others as shown in Table 6 were the EF rating of Behavioral Disinhibition, the SCL-90-R rating of Hostility, and the Verbal IQ estimate. Given that this equation was significant, and to evaluate the amount of variance explained by each significant variable, we repeated this regression analysis using stepwise entry. Four of the variables were significantly predictive of Total ELE(A) explaining 40% of the variance, these being the EF rating of Behavioral Disinhibition ($R = .556$, $R^2 = .309$, $R^2\Delta = .309$, $F = 93.50$, $df = 1/209$, $p < .001$), the WAIS Verbal IQ estimate ($R = .607$, $R^2 = .368$, $R^2\Delta = .059$, $F = 19.53$, $df = 1/208$, $p < .001$), the SCL-90-R Hostility scale ($R = .621$, $R^2 = .386$, $R^2\Delta = .017$, $F = 5.90$, $df = 1/207$, $p = .016$), and the 5 Points Test score of Number of Unique Designs assessing nonverbal working memory ($R = .631$, $R^2 = .398$, $R^2\Delta = .012$, $F = 4.10$, $df = 1/206$, $p = .044$). Hence the second order background traits of Behavioral Disinhibition (EF), verbal IQ, comorbid hostility, and nonverbal fluency (EF) appear to make unique contributions to explained variation in total life expectancy.

Discussion

Consistent with our initial hypothesis, this longitudinal study found that children having hyperactive child syndrome, or ADHD-C, manifested a significantly reduced estimated HLE in remaining years, a significantly greater ULE in remaining years, and an overall significantly lower total life expectancy in remaining years than did control children by young adulthood. Also supporting our additional hypothesis, the persistence of ADHD to adult follow-up was associated with an even worse impact on these ELE measures than in cases where the disorder was not persistent in the originally hyperactive children. And both persistent and nonpersistent ADHD cases had significantly lower ELEs by adulthood than did control cases. This is the first study to compute estimated remaining years of life expectancy by adulthood in children with ADHD-C. Yet its findings are quite consistent with a few earlier studies discussed above, demonstrating a greater mortality risk in both children and adults with ADHD relative to the general population.

This study goes further, however, in showing that besides the causes of early mortality in previous research, those being chiefly accidental injuries and suicides, life expectancy by young adulthood in those having ADHD-C as children may be further compromised by various adverse demographic, health, and lifestyle variables that are used in estimating life expectancy. The situation is even worse for those in whom ADHD persisted to adulthood. A number of such adversities related to life expectancy were found here

to be significantly and disproportionately associated with childhood ADHD-C by adulthood even if it had not persisted. These included the demographic factors of not only reduced education, lack of high school graduation, and annual income in the ADHD-C groups but also in the health and lifestyle factors of greater alcohol consumption, poorer overall health, reduced sleep, increased likelihood of smoking and of smoking more than 20+ cigarettes per day, and possibly greater adverse driving consequences resulting in license suspensions/revocations. These results provide insight into the reasons ELE may be reduced in those with ADHD-C. They also suggest avenues by which ELE could be improved via interventions.

Although sobering, the reduced ELEs found in this study to be linked to childhood ADHD-C as well as its persistence to adulthood are not immutable or necessarily stable going forward through adulthood. Many of the factors in estimating life expectancy that were shown to be more adverse in the ADHD-C groups can be changed and so yield significant positive effects on ELE. For instance, losing weight, increasing exercise, getting more sleep, reducing alcohol consumption, and quitting smoking are just a few of the health maintenance and self-improvement activities that might lead to improved ELE (Joshi et al., 2017). Yet such enthusiasm should not be unbounded, given our additional discovery of four background traits that accounted for substantial variation in life expectancy. These are more problematic in cases of ADHD-C and likely predispose those with ADHD-C to those adverse health and lifestyle problems that reduce ELE. Such background or second order traits may be more difficult to modify or ameliorate.

For instance, besides ADHD-C itself, this study showed that behavioral disinhibition (as assessed by EF ratings in daily life), verbal IQ, the comorbid psychopathology of hostility, and the EF of nonverbal fluency (and its association with nonverbal working memory) all uniquely contributed, in descending order, to variation in life expectancy. The largest percentage, however, by far was contributed by behavioral disinhibition. All are known to be more deficient or poorer in those having ADHD. Even so, treating ADHD symptoms and especially the larger domain of behavioral disinhibition might also improve ELE. Specifically, using ADHD medications and evidence-based psychosocial treatments, such as EF-focused cognitive behavioral therapy and Adult ADHD Coaching, could help to reduce ADHD symptoms and improve EF in daily life generally and behavioral disinhibition specifically so as to improve ELE. While lower verbal IQ and deficient nonverbal fluency may be more difficult to improve, they contributed far less to ELE variation than EF in daily life and thus may not be as crucial to change so as to improve ELE. Should any of the fisrt order risk variables or the second order trait factors change with age going forward, then ELE would change accordingly. At the very least, these results argue for more aggressively treating ADHD and its associated EF deficits as well as including health-related recommendations as part of the treatment proffered by clinicians for those with ADHD.

The limitations of this study should not be overlooked. ELE differences between groups may actually be greater than those evident here for two reasons. One is that variables known to affect elevated mortality risk generally (blood pressure, high density lipoprotein [HDL] and low density lipoprotein [LDL] cholesterol, coronary artery disease; Joshi et al., 2017) and those within ADHD samples (accidental injuries, suicide attempts; Barbaresi et al., 2013; Dalsgaard et al., 2015; Nigg, 2013) were not entered in the ELE calculator used here. Another is that young adults with ADHD have been shown to underreport the severity of their symptoms and even some types of impairment, such as driving, relative to reports about them from their parents (Barkley et al., 2002). Both reasons would have biased calculator inputs and hence outputs in a more conservative direction.

Another limitation is the reliance here on a clinically referred sample of children with hyperactivity/ADHD-C. They were defined by research criteria representing a severity of symptoms at or above the 97th percentile for age and so are likely to be more severe in their ADHD-C symptoms and to have higher rates of comorbid psychopathologies than is often the case using community derived samples and current diagnostic criteria for ADHD. Both factors may bias these results toward larger ELE reductions than would be the case in a community sample with ADHD-C or those identified as ADHD-C by current criteria. The overrepresentation of males in the study, our reliance on a largely White sample of Midwestern U.S. origin, and our focus only on ADHD-C cases in childhood all limit the degree to which these findings can be generalized to females with ADHD, to other presentations of ADHD, and to ADHD cases in other ethnic groups or other regions.

With these limitations in mind, the present study demonstrated that childhood ADHD-C (hyperactive child syndrome) is associated with reduced ELE by young adulthood, including healthy remaining years of life, as well as an increased period of unhealthy estimated years of remaining life. This reduction in ELE is worse when ADHD is persistent into adulthood. The reduced ELE linked to ADHD was found to be a function of the first order variables of less education, less annual income, greater consumption of alcohol and tobacco, diminished sleep, and poorer overall health status relative to the control group. Moreover, ELE was also shown to be a function of the second order traits of deficient behavioral inhibition in daily life and, much less so, of low verbal IQ, greater interpersonal hostility, and deficient nonverbal fluency. Our findings in general are consistent with research showing that various mental disorders have adverse effects on ELE (Chesney, Goodwin, & Fazel, 2014; Nordentoft et al., 2013).

Our results extend this earlier work by adding ADHD to this list. Nevertheless, our findings may also argue for the potential value of adding recommendations regarding health and lifestyle related self-improvement programs to the usual package of treatments applied to ADHD across development, given the apparent modifiability of many of these risk factors linked to reduced ELE.

Authors' Note

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Notes

1. https://gateway.euro.who.int/en/indicators/hfa_67-1,080-disability-adjusted-life-expectancy-world-health-report/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2486718/
3. https://en.wikipedia.org/wiki/Disability-adjusted_life_year

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The World Federation of ADHD International Consensus Statement: 208 Evidence-based Conclusions about the Disorder

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The World Federation of ADHD International Consensus Statement: 208 Evidence-based Conclusions about the Disorder

Short Title: The World Federation of ADHD International Consensus Statement

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Highlights

- ADHD occurs in 5.9% of youth and 2.5% of adults.
- Most cases of ADHD are caused by the combined effects of many genetic and environmental risks.
- There are small differences in the brain between people with and without ADHD.
- Untreated ADHD can lead to many adverse outcomes.
- ADHD costs society hundreds of billions of dollars each year, worldwide.

Abstract

Background: Misconceptions about ADHD stigmatize affected people, reduce credibility of providers, and prevent/delay treatment. To challenge misconceptions, we curated findings with strong evidence base**.**

Methods: We reviewed studies with more than 2,000 participants or meta-analyses from five or more studies or 2,000 or more participants. We excluded meta-analyses that did not assess publication bias, except for meta-analyses of prevalence. For network meta-analyses we required comparison adjusted funnel plots. We excluded treatment studies with waiting-list or treatment as usual controls. From this literature, we extracted evidence-based assertions about the disorder.

Results: We generated 208 empirically supported statements about ADHD. The status of the included statements as empirically supported is approved by 79 authors from 27 countries and 6 continents. The contents of the manuscript are endorsed by 362 people who have read this document and agree with its contents.

Conclusions: Many findings in ADHD are supported by meta-analysis. These allow for firm statements about the nature, course, outcome causes, and treatments for disorders that are useful for reducing misconceptions and stigma.

Key Words: ADHD, diagnosis, treatment, course, outcome, genetics, brain

Introduction

Nearly two decades ago, an international team of scientists published the first International Consensus Statement on attention-deficit hyperactivity disorder (ADHD) (Barkley, 2002). They sought to present the wealth of scientific data attesting to the validity of ADHD as a mental disorder and to correct misconceptions about the disorder that stigmatized affected people, reduced the credibility of health care providers, and prevented or delayed treatment of individuals challenged by the disorder (DosReis et al., 2010; Horton-Salway, 2013; McLeod et al., 2007; Mueller et al., 2012).

This paper updates the International Consensus Statement by cataloging important scientific discoveries from the last 20 years. We do not intend to present an encyclopedia of ADHD or guidelines for diagnosis and treatment. The latter can be found in the references cited. Our aim is to provide current and accurate information about ADHD supported by a substantial and rigorous body of evidence.

Methods

We identified evidence-based statements about ADHD through expert scrutiny of published high quality meta-analyses and very large studies. Expert scrutiny was provided by a project Steering Committee (Supplemental Table 1) which included representatives from the following professional groups dedicated to research and clinical care of ADHD: The World Federation of ADHD, EUropean NETwork for Hyperkinetic DIsorderS (Eunethydis), the American Professional Society of ADHD and Related Disorders, the Canadian ADHD Resource Alliance, the Asian Federation of ADHD, the Latin American League of ADHD, the Australian ADHD Professionals Association, the Israeli Society of ADHD, the Saudi ADHD Society, Neurodevelopmental

Disorders Across Lifespan section of the European Psychiatric Association, the ADHD Guidelines Group of the Association of Medical Scientific Societies in Germany, the ADHD Network of European College of Neuropsychopharmacology, the Chinese Society of Child and Adolescent Psychiatry and the ADHD Section of the World Psychiatric Association.

For large cohort studies, we searched PubMed with these search criteria: ADHD [tiab] AND (nationwide [tiab] OR national [tiab] OR register [tiab] OR registry [tiab]) NOT review [Publication Type] NOT meta-analysis [Publication Type]. For meta-analyses, we searched PubMed with these search criteria: ADHD [All Fields] AND (meta-analysis [Title] OR meta-analysis [Title] OR meta-analytic [Title] OR systematic review [Title]). We excluded meta-analyses that did not assess publication bias, except for meta-analyses of prevalence. For network meta-analyses we required that comparison adjusted funnel plots be presented. For treatment studies, we excluded results of meta-analyses including comparisons of treatments with waiting-list or treatment as usual controls.

Apart from statements about the history of ADHD and its diagnostic criteria, we required each evidence-based statement to be supported by meta-analyses or by large registry studies with more than 2,000 participants. We required meta-analyses to report data from five or more studies or 2,000 or more participants.

We describe the magnitude of effect size findings using standard criteria as follows: standardized mean difference: small = 0.20, medium = 0.50, large = 0.80; correlation coefficient: small = 0.10, medium = 0.24, large = 0.37 (Ellis, 2010; Rosenthal and Rosnow, 1984). “Moderate” is used as a synonym for “medium,” and “strong” for “large.” A “small” effect is

generally difficult to observe in an individual but may be very important for public health if it concerns a common exposure that affects many children. A “medium” effect is expected to be noticeable to a careful observer (Cohen, 1988). A “large” effect is generally relevant to clinical practice at the level of the individual.

If a topic is not included in this document, it does not mean the topic is unimportant; rather, it means the evidence found was insufficient to allow firm conclusions. This could be because there were insufficient studies of quality, because no attempt was made to assess publication bias, or because the data available did not support the claims made. After the document was completed, we invited additional colleagues to join as signatories to indicate their support of the document. In what follows, we use the term "evidence-based" to refer to evidence that meets the inclusion/exclusion criteria we used in our literature search. We recognize that other criteria could be applied, such as requiring the absence of severe heterogeneity in meta-analyses or increasing the numbers of research participants.

Overview of Results

Our search strategy generated 208 empirically supported statements about ADHD. For details, see the PRISMA diagram in Supplemental Figure 1. The status of the included statements as empirically supported has been approved by the 79 authors from 27 countries and 6 continents (Supplemental Figure 2). It has been endorsed by 362 people who have read this document and agree with its contents (Supplemental Table 2). Table 1 summarizes our findings along with the item numbers that support each statement. A limitation of this consensus statement is that we do not report well-established research findings for which meta-analyses or very large

studies do not exist. The absence of such a study, is not always an indication of knowledge of absence of an effect.

Table 1: Summary of Findings

Findings	Items
The syndrome we now call ADHD has been described in the medical literature since 1775.	1 - 13
When made by a licensed clinician, the diagnosis of ADHD is well-defined and valid at all ages, even in the presence of other psychiatric disorders, which is common.	14-19
ADHD is more common in males and occurs in 5.9% of youth and 2.5% of adults. It has been found in studies from Europe, Scandinavia, Australia, Asia, the Middle East, South America, and North America.	20-25
ADHD is rarely caused by a single genetic or environmental risk factor but most cases of ADHD are caused by the combined effects of many genetic and environmental risks each having a very small effect.	26-62
People with ADHD often show impaired performance on psychological tests of brain functioning, but these tests cannot be used to diagnose ADHD.	63-70
Neuroimaging studies find small differences in the structure and functioning of the brain between people with and without ADHD. These differences cannot be used to diagnose ADHD.	71-77
People with ADHD are at increased risk for obesity, asthma, allergies, diabetes mellitus, hypertension, sleep problems, psoriasis, epilepsy, sexually transmitted infections, abnormalities of the eye, immune disorders, and metabolic disorders.	78-100

People with ADHD are at increased risk for low quality of life, substance use disorders, accidental injuries, educational underachievement, unemployment, gambling, teenage pregnancy, difficulties socializing, delinquency, suicide, and premature death.	101-136
Studies of economic burden show that ADHD costs society hundreds of billions of dollars each year, worldwide.	137-147
Regulatory agencies around the world have determined that several medications are safe and effective for reducing the symptoms of ADHD as shown by randomized controlled clinical trials.	148-157
Treatment with ADHD medications reduces accidental injuries, traumatic brain injury, substance abuse, cigarette smoking, educational underachievement, bone fractures, sexually transmitted infections, depression, suicide, criminal activity and teenage pregnancy.	158-177
The adverse effects of medications for ADHD are typically mild and can be addressed by changing the dose or the medication.	178-188
The stimulant medications for ADHD are more effective than non-stimulant medications but are also more likely to be diverted, misused, and abused.	189-194
Non-medication treatments for ADHD are less effective than medication treatments for ADHD symptoms, but are frequently useful to help problems that remain after medication has been optimized.	195-208

A Brief History: ADHD is not a New Disorder

The concept of ADHD has a long history, starting with clinical reports from European countries. The clinical significance of the signs and symptoms of the disorder has been recognized for over two centuries. Although these early reports did not use the term “ADHD”, they described children who showed the symptoms and impairments we now recognize as ADHD. For a detailed history see (Lange et al., 2010; Taylor, 2011; Weikard, 1799). Here are highlights from the early history of ADHD:

1. 1775: Melchior Adam Weikard, a German physician, wrote the first textbook description of a disorder with the hallmarks of ADHD.

2. 1798: Alexander Crichton from the Royal College of Physicians (United Kingdom) described a similar disorder in a medical textbook (Palmer and Finger, 2001).

3. 1845: Heinrich Hoffmann, who later became head of the first psychiatric hospital in Frankfurt am Main, Germany, described hyperactivity and attention deficits in a children’s book which documented ADHD-like behaviors and their associated impairments (Hoffmann, 1990).

4. 1887-1901: Désiré-Magloire Bourneville, Charles Boulanger, Georges Paul-Boncour, and Jean Philippe described an equivalent of ADHD in French medical and educational writings (Martinez-Badia and Martinez-Raga, 2015).

5. 1902: George Still, a physician in the United Kingdom, wrote the first description of the disorder in a scientific journal (Still, 1902a; Still, 1902b, c).

6. 1907: Augusto Vidal Perera wrote the first Spanish compendium of child psychiatry. He described the impact of inattention and hyperactivity among schoolchildren (Vidal Perera, 1907).

7. 1917: the Spanish neurologist and psychiatrist Gonzalo Rodriguez-Lafora described symptoms of ADHD in children and said they were probably caused by a brain disorder with genetic origins (Lafora, 1917).

8. 1932: Franz Kramer and Hans Pollnow, from Germany, described an ADHD-like syndrome and coined the term “hyperkinetic disorder”, which was later adopted as a term by the World Health Organization (Kramer and Pollnow, 1932; Neumarker, 2005).

9. 1937: Charles Bradley, from the USA, discovered that an amphetamine medication reduced ADHD-like symptoms (Bradley, 1937).

10. 1940s: ADHD-like symptoms in children described as “minimal brain dysfunction”.

11. 1956-1958: First hint in follow-up study of the persistence of minimal brain dysfunction-related behaviors into adulthood (Morris et al., 1956; O'Neal and Robins, 1958)

12. 1960s: U.S. Food and Drug Administration approved methylphenidate (Ritalin) for behavioral disorders in children.

13. 1970s to today: Diagnostic criteria for ADHD evolved based on research showing that the diagnosis predicts treatment response, clinical course, and family history of the disorder.

How is ADHD diagnosed?

ADHD can only be diagnosed by a licensed clinician who interviews the parent or caregiver and/or patient to document criteria for the disorder (American Psychiatric Association, 2013; Chinese Society of Psychiatry, 2001; Faraone et al., 2015; Feldman and Reiff, 2014; Pearl et al., 2001; Stein, 2008; World Health Organization, 2018). It cannot be diagnosed by rating scales alone, neuropsychological tests, or methods for imaging the brain.

The diagnosis of ADHD has been criticized as being subjective because it is not based on a biological test. This criticism is unfounded. ADHD meets standard criteria for validity of a mental disorder established by Robins and Guze (Faraone, 2005; 1970). The disorder is considered valid because: 1) well-trained professionals in a variety of settings and cultures agree on its presence or absence using well-defined criteria and 2) the diagnosis is useful for predicting a) additional problems the patient may have (e.g., difficulties learning in school); b) future patient outcomes (e.g., risk for future drug abuse); c) response to treatment (e.g., medications and psychological treatments); and d) features that indicate a consistent set of causes for the disorder (e.g., findings from genetics or brain imaging) (Faraone, 2005). Professional associations have endorsed and published guidelines for diagnosing ADHD (Alliance, 2011; Banaschewski T, 2018; Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018; Pliszka, 2007; Schoeman and Liebenberg, 2017; Seixas et al., 2012; Taylor et al., 2004; Wolraich et al., 2011).

The main features of the diagnosis are:

14. The diagnosis requires: 1) the presence of developmentally inappropriate levels of hyperactive-impulsive and/or inattentive symptoms for at least 6 months; 2) symptoms occurring in different settings (e.g., home and school); 3) symptoms that cause impairments in living; 4) some of the symptoms and impairments first occurred in early to mid-childhood; and 4) no other disorder better explains the symptoms (American Psychiatric Association, 2013; World Health Organization, 2018; Yi and Jing, 2015).

15. The clinical presentation of ADHD can be described as primarily inattentive, primarily hyperactive-impulsive, or combined, depending on the nature of their symptoms (American Psychiatric Association, 2013). Meta-analyses indicate that inattention is more strongly associated with academic impairment, low self-esteem, negative occupational outcomes and lower overall adaptive functioning. Hyperactive-impulsive symptoms are associated with peer rejection, aggression, risky driving behaviors and accidental injuries. Patterns of associated disorders also differ between the dimensions (Willcutt et al., 2012).

16. ADHD impairs the functioning of highly intelligent people, so the disorder can be diagnosed in this group. A population-based birth cohort study of over 5,700 children found no significant differences among children with high, average, or low IQ and ADHD in median age at which ADHD criteria were met, rates of learning disorders, psychiatric disorders, and substance abuse, and rates of stimulant treatment (Katusic et al., 2011; Rommelse et al., 2017).

17. In adolescence and young adulthood, many individuals with a history of childhood ADHD continue to be impaired by the disorder, although they often show reduced hyperactivity and impulsivity while retaining symptoms of inattention (Faraone et al., 2006).

18. Many large epidemiologic and clinical studies show that ADHD often co-occurs with other psychiatric disorders, especially depression, bipolar disorder, autism spectrum disorders, anxiety disorders, oppositional defiant disorder, conduct disorder, eating disorders, and substance use disorders (Bernardi et al., 2012; Chen et al., 2018c; Groenman et al., 2017; Nazar et al., 2016; Solberg et al., 2018; Tung et al., 2016; Yao et al., 2019). Their presence does not rule out a diagnosis of ADHD.

19. A meta-analysis comprising 25 studies with over eight million participants found that children and adolescents who are relatively younger than their classmates are more likely to have been diagnosed with ADHD (Caye et al., 2020)

How Common is ADHD?

ADHD occurs throughout the developed and developing world and is more common in males compared with females. It has not become more common over the past three decades although due to increased recognition by clinicians, the disorder is more likely to be diagnosed today than in prior decades.

20. A meta-analysis of 19 studies with over 55,000 participants found that 5.9% of youths meet diagnostic criteria for ADHD (Willcutt, 2012). Another meta-analysis, with 135 studies and about a quarter of a million youths, found no significant differences in prevalence between

North America and Europe, Asia, Africa, South America, and Oceania (Polanczyk et al., 2014).

21. The latter meta-analysis found no increase in the prevalence of ADHD in children and adolescents over the past three decades (Polanczyk et al., 2014). Although the prevalence of ADHD has not changed in this time period, large studies from the US and Sweden indicate that ADHD is more likely to have been diagnosed in recent years, which reflects changes in administrative and clinical practices (Rydell et al., 2018; Song et al., 2019; Xu et al., 2018).

22. A meta-analysis of six studies with over 5,300 participants estimated the prevalence of ADHD in adulthood to be 2.5% (Simon et al., 2009). A meta-analysis of 20 studies encompassing 13 countries and seven regions/metropolitan areas, involving more than 26,000 participants, estimated that 2.8% of adults meet criteria for ADHD (Fayyad et al., 2017). The lower prevalence in adults compared with youth is consistent with a meta-analysis of 21 studies with over 1,600 participants showing that only about one in six youths with ADHD still meet full diagnostic criteria for ADHD at age 25, and about half show signs of residual impairment (Faraone et al., 2006).

23. A meta-analysis of nine studies with a total of over 32,000 older adults found a prevalence of 2.2% based on ADHD rating scales, dropping to 1.5% when limited to persons at least fifty years old. Yet a meta-analysis of seven studies with over 11.7 million participants based on ADHD clinical diagnoses, performed by the same team, reported a prevalence of only 0.2% for persons at least fifty years old. A third meta-analysis performed by the same

researchers, of four studies with over 9.2 million participants, found an ADHD treatment rate of only 0.02% among persons at least fifty years old (Dobrosavljevic et al., 2020).

24. A meta-analysis of 19 studies encompassing over 150,000 U.S. Black youths under 18 years old reported an ADHD prevalence rate of 14 percent. The authors concluded, "Black individuals are at higher risk for ADHD diagnoses than the general US population. These results highlight a need to increase ADHD assessment and monitoring among Black individuals from different social backgrounds" (Cénat et al., 2020).

25. ADHD is more common in males. A meta-analysis of parent ratings of symptoms in 29 studies with over 42,000 participants, and teacher ratings in 24 studies with over 56,000 participants, found a roughly two-to-one male/female ratio in youth (Willcutt, 2012).

What causes ADHD?

For most people with ADHD, many genetic and environmental risk factors accumulate to cause the disorder (Faraone et al., 2015). The environmental risks for ADHD exert their effects very early in life, during the fetal or early postnatal period. In rare cases, however, ADHD-like symptoms can be caused by extreme deprivation early in life (Kennedy et al., 2016), a single genetic abnormality (Faraone and Larsson, 2018), or traumatic brain injury early in life (Stojanovski et al., 2019). These findings are helpful to understand the causes of ADHD but are not useful for diagnosing the disorder. The associations between aspects of the environment and the onset of ADHD have attained a very high level of evidential support. Some have strong evidence for a causal role but, for most, the possibility remains that these associations are due

to correlated genetic and environmental effects. For this reason, we refer to features of the pre- and post-natal environments that increase risk for ADHD as correlates, rather than causes. The genetic and environmental risks described below are not necessarily specific to ADHD.

Genetic Causes of ADHD

26. A review of 37 twin studies from the United States, Europe, Scandinavia, and Australia found that genes and their interaction with the environment must play a substantial role in causing ADHD (Faraone and Larsson, 2018; Larsson et al., 2014a; Pettersson et al., 2019).

27. In a genomewide study, an international team analyzed DNA from over 20,000 people with ADHD and over 35,000 without ADHD from the United States, Europe, Scandinavia, China, and Australia. They identified many genetic risk variants, each having a small effect on the risk for the disorder (Demontis et al., 2019). This study confirmed a polygenic cause for most cases of ADHD, meaning that many genetic variants, each having a very small effect, combine to increase risk for the disorder. The polygenic risk for ADHD is associated with general psychopathology (Brikell et al., 2020) and several psychiatric disorders (Lee PH, 2019).

28. Additional genes have been implicated by meta-analyses, but their status as risk genes remains uncertain until validated in a genomewide study. These genes are *ANKK1* (Pan et al., 2015) *DAT1* (Grunblatt et al., 2019b), *LRP5* and *LRP6* (Grunblatt et al., 2019a), SNAP25 (Liu et al., 2017b), ADGRL3 (Bruxel et al., 2020) DRD4 and BAIAP2 (Bonvicini et al., 2020; Bonvicini et al., 2016).

29. The polygenic risk for ADHD predicts ADHD symptoms in the population suggesting that the genetic causes of ADHD as a disorder, also influence lower levels of ADHD symptoms in the population (Demontis et al., 2019; Taylor et al., 2019).

30. In the population, those with a high polygenic risk for ADHD are more likely to have been diagnosed with ADHD (Li, 2019), anxiety or depression (Martin et al., 2018).

31. ADHD can also be the result of rare single gene defects (Faraone and Larsson, 2018) or abnormalities of the chromosomes (Cederlof et al., 2014). When the DNA of 8,000+ children with autism spectrum disorder (ASD) and/or ADHD and 5,000 controls was analyzed, those with ASD and those with ADHD had an increased rate of rare genetic mutations compared with controls (Satterstrom et al., 2019).

32. Family, twin, and DNA studies show that genetic and environmental influences are partially shared between ADHD and many other psychiatric disorders (e.g. schizophrenia, depression, bipolar disorder, autism spectrum disorder, conduct disorder, eating disorders, and substance use disorders) and with somatic disorders (e.g. migraine and obesity) (Demontis et al., 2019) (Faraone and Larsson, 2018) (Ghirardi et al., 2018) (Lee et al., 2019) (Lee et al., 2013) (Anttila et al., 2018; Tylee et al., 2018) (van Hulzen et al., 2017) (Vink and Schellekens, 2018) (Brikell et al., 2018) (Chen et al., 2019a) (Yao et al., 2019). However, there is also a unique genetic risk for ADHD. Evidence of shared genetic and environmental risks among disorders suggest that these disorders also share a pathophysiology in the biological pathways that dysregulate neurodevelopment and create brain variations leading to disorder onset.

33. Very large studies of families suggest that ADHD shares genetic or familial causes with autoimmune diseases (Li et al., 2019), hypospadias (Butwicka et al., 2015), and intellectual disability (Faraone and Larsson, 2018).

Environmental Correlates of ADHD: Exposure to Toxicants

34. A pair of meta-analyses found small correlations between lead burden and inattention symptoms (27 studies, over 9,300 youths) and hyperactivity-impulsivity symptoms (23 studies, over 7,800 youths) (Goodlad et al., 2013). A more recent meta-analysis of 14 studies with over 17,000 children reported that higher blood lead levels were associated with quadrupled odds of ADHD (Nilsen and Tulve, 2020). A study of over 2,500 youths from the National Health and Nutrition Examination Survey, a cross-sectional, nationally representative sample of the U.S. population, found that those with blood lead levels in the top third were 2.3 times more likely to have ADHD compared with those in the bottom third (Froehlich et al., 2009). A similar study, with over 4,700 youths from the same national survey, found that those with blood lead levels in the highest fifth were four times more likely to have ADHD compared with those in the bottom fifth (Braun et al., 2006).

35. Three meta-analyses with over twenty studies covering more than three million persons have found prenatal exposure to maternal smoking associated with a greater than 50% increase in incidence of ADHD (Huang et al., 2017) (Dong et al., 2018; Nilsen and Tulve, 2020). Although this association has also been seen in large population studies (Joelsson et al., 2016; Obel et al., 2016; Skoglund et al., 2014), it disappears after adjusting for family history of ADHD which indicates that the association between maternal smoking during

pregnancy and ADHD is due to familial or genetic factors that increase the risk for both smoking and ADHD.

36. A meta-analysis of nine studies spanning three continents and over 100,000 participants found that childhood exposure to secondhand cigarette smoke was associated with a 60% greater likelihood of ADHD. It was unclear to what extent the association was causal versus due to confounders (Huang et al., 2020).

37. In a meta-analysis of 15 double-blind, placebo-controlled trials with 219 participants, artificial food dyes were associated with a small increase in hyperactivity in children (Schab and Trinh, 2004). Another meta-analysis, covering 20 studies with a combined total of 794 individuals, found a very small increase in ADHD symptoms, but only when rated by parents, not by teachers or other observers (Nigg et al., 2012).

38. In a Taiwanese study of over 10,000 births, maternal use of acetaminophen during pregnancy was associated with a 33% greater likelihood of ADHD in their children (Chen et al., 2019b). Another study, examining 113,000 offspring from the Norwegian Mother and Child Cohort Study and the Norwegian Patient Registry, including 2,246 with ADHD, found a dose-response relationship between maternal prenatal use of acetaminophen and ADHD (Ystrom et al., 2017).

39. A nationwide study using the Danish national registers looked at 913,000 children born between 1997 and 2011. Prenatal exposure to the anti-epileptic drug valproate was associated with a 50% greater risk of ADHD. No associations were found for other anti-epileptic drugs (Christensen et al., 2019).

40. In a Norwegian registry study, 297 children with ADHD and 553 controls were randomly sampled from an eligible population of over 24,000. Children of mothers in the highest quintile of phthalate metabolite levels were three times more likely to have had ADHD as children compared with those in the bottom quintile, after adjusting for confounders, such as maternal age at delivery, sex of the child, maternal education, marital status, and prenatal maternal smoking (Engel et al., 2018).

41. Organophosphate pesticides are potent neurotoxins. In a sample of 1,139 children from the U.S. population, a tenfold increase in the organophosphate metabolite dimethyl alkylphosphate (DMAP) was associated with 55% increase in the probability of having ADHD. Children with detectable levels of the most-commonly detected DMAP metabolite were twice as likely to have ADHD compared with those with undetectable levels (Bouchard et al., 2010).

42. A meta-analysis found no significant effect of three classes of air pollutants –particulate matter (six studies, over 51,000 persons) and nitrogen oxides (five studies, over 51,000 persons) (Zhang et al., 2020b). A Taiwan-wide longitudinal cohort study geolinking over 16,000 mother-infant pairs to levels of air pollutants found no association between small particulate matter levels, sulphur dioxide levels, or nitrogen dioxide levels during gestation and ADHD diagnoses in the first eight years of their offsprings' lives. It did find a 25 percent greater odds for having ADHD with exposures to nitric oxide, a common traffic pollutant (Shih et al., 2020).

43. A nationwide cohort study used the South Korean national health insurance registry to identify all 7,200 hospital admissions of adolescents with a primary diagnosis of ADHD from 2013 to 2015, and daily readings of three air pollutants from 318 monitoring stations distributed across the country over the same period. It found that spikes in nitrogen dioxide, sulphur dioxide, and particulate matter were associated, respectively, with 47%, 27%, and 12% increases in ADHD related hospital admissions in succeeding days. There were no significant differences between male and female adolescents, or between older and younger adolescents (Park et al., 2020).

44. A meta-analysis of nine European population studies encompassing 4,826 mother-child pairs examined the relationship between exposure to Perfluoroalkyl Substances (PFAS) via breast milk in infancy and development of ADHD. No associations were found with ADHD in offspring (Forns et al., 2020).

45. A meta-analysis of seven studies encompassing a total of over 25,000 participants from six countries on three continents found no evidence of an association between sugar consumption and ADHD in youth (Farsad-Naeimi et al., 2020)

Environmental Correlates of ADHD: Nutrient Deficiencies

46. A pair of meta-analyses found no difference in serum iron levels in youths with ADHD (six studies, 617 participants) but small-to-moderate reductions in serum ferritin, a protein that stores iron (ten studies, over 2,100 participants) (Wang et al., 2017). Another pair of meta-analyses likewise found no difference in serum iron levels (six studies, over 1,700

participants) but small-to-moderate reductions in serum ferritin (12 studies, over 6,000 participants) (Tseng et al., 2018).

47. A meta-analysis of nine studies and 586 people found moderately lower overall blood levels of omega-3 PUFAs in ADHD than non-ADHD youth (Hawkey and Nigg, 2014).

48. A nationwide population-based case-control study using the Finnish national registers compared 1,067 patients with ADHD born between 1998 and 1999 with 1,067 matched controls. Lower maternal vitamin D levels were associated with a roughly 50% greater likelihood of ADHD in their children (Sucksdorff et al., 2019).

Environmental Correlates of ADHD: Events During Pregnancy and Birth

49. A meta-analysis of twelve studies with over 6,000 participants found a threefold increase in the rate of ADHD among very/extremely preterm or very/extremely low birth weight babies (Franz et al., 2018). Another meta-analysis, combining 85 studies with a total of over 4.6 million births, found a small-to-moderate correlation between low birth weight and ADHD (Momany et al., 2018). A Swedish national register study of 1.2 million children found a stepwise increase in the likelihood of ADHD with increasing prematurity. Results were not due to having an ADHD relative or socioeconomic stress (Lindstrom et al., 2011). Similar results were reported from the Finnish national registers when comparing over 10,000 people with ADHD with over 38,000 controls (Sucksdorff et al., 2015).

50. A meta-analysis of six studies combining 1.4 million people found that children whose mothers had hypertensive disorders during pregnancy had a 25% increase in the rate of ADHD (Maher et al., 2018).

51. A nationwide population-based cohort study using Swedish registers and covering more than two million children, 115,000 of them with ADHD, found that maternal preeclampsia during pregnancy is associated with a 15% greater subsequent likelihood of ADHD in offspring, rising to over 40% when the fetus is small for gestational age and exposed to preeclampsia. This pattern in families showed that it is not due to genetic or other family influences (Maher et al., 2020).

52. Two meta-analyses, one with seven studies with over 28,000 participants and another with three studies and over 1.4 million participants, found that children of obese mothers were roughly 60% more likely to develop ADHD (Jenabi et al., 2019; Sanchez et al., 2018). A study of over 80,000 mother-child pairs participating in the Danish National Birth Cohort reported an almost 50% elevated risk of ADHD in children of obese mothers and a doubled risk in children of severely obese mothers (Andersen et al., 2018).

53. A meta-analysis of two large cohort studies with a combined total of over 3.1 million persons found a slight but significant association between maternal hyperthyroidism during pregnancy and ADHD in offspring. A second meta-analysis of four cohort studies encompassing over 3.4 million participants likewise found a slight but significant association between maternal hypothyroidism and ADHD in offspring. No attempt was made to assess the role of confounders (Ge et al., 2020).

54. A nationwide cohort study using Danish national registers examined over a million births, comparing offspring of mothers with a single prior miscarriage and mothers with more than one prior miscarriage with mothers with no history of miscarriage. It found that after adjusting for a wide range of possible confounders which turned out to have little effect,

children of mothers with a single prior miscarriage were 9% more likely to develop ADHD than those of mothers without any miscarriage. Children of mothers with two or more prior miscarriages were 22% more likely to be diagnosed with ADHD. This upward exposure-response trend was statistically significant (Wang et al., 2020).

Environmental Correlates of ADHD: Deprivation, Stress, Infection, Poverty and Trauma

55. A Taiwan-wide longitudinal cohort study based on the country's universal coverage National Health Insurance Research Database compared over 14,000 enterovirus patients (ER71) with an equal number of controls matched by age and sex. After further adjusting for paternal occupation and urbanization level of residence it found the enterovirus patients were 25 percent more likely to subsequently be diagnosed with ADHD (Tseng et al., 2020).

56. A nationwide population-based cohort study using Danish registers compared over 29,000 children born to women who lost a close relative during pregnancy with a million other children in the same cohort and found that boys born to these women were twice as likely to have ADHD (Li et al., 2010).

57. A U.S. population-based study of over 14,000 participants in the National Longitudinal Study of Adolescent Health found that after adjusting for demographic, socioeconomic, and familial risk factors for child maltreatment, ADHD inattentive type was associated with having been exposed to sexual abuse and physical neglect (Ouyang et al., 2008).

58. A nationwide population-based cohort study of over 18,000 children from the South Korean National Health Insurance database found that lower levels of family income were associated with increased rates of ADHD (Choi et al., 2017). A Swedish study of over

800,000 people reported similar results even after adjusting for shared familial/genetic risk factors in families (Larsson et al., 2014b).

59. A Danish national register longitudinal cohort study of a million people found that Rutter's indicators of adversity were predictive of ADHD. Out-of-home care was strongly predictive; low social class, paternal criminality, maternal mental disorder, and severe marital discord were moderately predictive. Large family size had no effect (Ostergaard et al., 2016).

60. A countrywide population study using Danish national registers looked at over 630,000 youths and found dose-response relationships between lower parental educational attainment, parental unemployment, and parental relative poverty and higher risk of ADHD in offspring. Combinations of social disadvantages had cumulative risks. For instance, parental relative income poverty plus completion of no more than compulsory education plus unemployment was associated with a roughly five percent higher risk of ADHD in their offspring (Keilow et al., 2020).

61. A Swedish national register cohort study of over 540,000 people found a dose-response relationship between cumulative indicators of adversity in the family and ADHD. A death in the family increased the subsequent likelihood of ADHD by 60%. Substantial parental substance abuse, criminality, or psychiatric disorder each more than doubled the likelihood as did residential instability and household public assistance (Bjorkenstam et al., 2018).

62. In a sample of 4,122 U.S. youths with ADHD from the 2016 U.S. National Survey of Children's Health, greater family cohesion and community support decreased the risk for moderate to severe ADHD (Duh-Leong et al., 2020).

What Have We Learned from Studying the Brains of People with ADHD?

There are two broad classes of research findings about the brains of people with ADHD. The first comes from studies of the performance of patients on psychological tests that study mental processes. The second comes from methods that directly examine brain structure or function with neuroimaging scans. Although many of these studies have found differences between groups of people who are and are not diagnosed with ADHD, the differences are typically small and do not dramatically differ between people with ADHD and those with other disorders. They are, therefore, not useful for diagnosing the disorder (Thome et al., 2012). These differences are not caused by drug treatment and, for some patients, diminish or change as patients grow out of the disorder.

Performance Deficits in Psychological Processes

63. A meta-analysis of 137 studies with over 9,400 participants of all ages found ADHD to be associated with moderately lower IQ and reading scores and larger decreases in spelling and arithmetic scores (Frazier et al., 2004). Another meta-analysis, spanning 21 studies with over 1,900 adults, concluded that ADHD-associated IQ deficits were small and not clinically meaningful (Bridgett and Walker, 2006).

64. A series of meta-analyses found that people with ADHD had small to moderate difficulties with abstract problem solving and working memory (12 studies, 952 persons), focused attention (22 studies, 1,493 persons), sustained attention (13 studies, 963 persons), and verbal memory (8 studies, 546 persons) (Schoechlin and Engel, 2005). Another meta-

analysis, with 11 studies with 829 participants, reported people with ADHD were moderately more prone to cognitive errors known as “rule violations” (Patros et al., 2019).

65. Two meta-analyses, one with 21 studies and over 3,900 participants, the other with 15 studies with over a thousand participants, found that those diagnosed with ADHD have a moderate tendency to favor small immediate rewards over large delayed rewards (Jackson and MacKillop, 2016; Marx et al., 2018).

66. A meta-analysis of 37 studies with more than 2,300 participants found a small-to-moderate association between ADHD and risky decision-making (Dekkers et al., 2016). Another meta-analysis, combining 22 studies with 3,850 children and adolescents, found those with ADHD exhibited moderately greater impulsive decision-making overall on delay discounting and delay of gratification tasks (Patros et al., 2016).

67. A recent meta-meta-analysis included 34 meta-analyses of neurocognitive profiles in ADHD (all ages) concerning 12 neurocognitive domains. Those with ADHD had moderate impairments in multiple domains (working memory, reaction time variability, response inhibition, intelligence/achievement, planning/organization). Effects were larger in children and adolescents than in adults (Pievsky and McGrath, 2018).

68. A meta-analysis of 49 studies and over 8,200 children and adolescents found moderate impairments in working memory in those with ADHD. These deficits declined with age (Ramos et al., 2020).

69. Among youths with ADHD, a series of meta-analyses found no significant sex differences in either total ADHD symptoms (15, studies, over 3,400 youths), inattention symptoms (26

studies, over 5,900 youths), or hyperactivity-impulsivity symptoms (24 studies, over 4,900 youths) (Loyer Carbonneau et al., 2020).

70. A meta-analysis of randomized controlled trials (RCTs) with preschoolers found that cognitive training led to moderate improvement in working memory (23 studies, over 2,000 participants) and small-to-moderate improvement in inhibitory control (26 studies, over 2,200 participants) (Pauli-Pott et al., 2020).

Differences in the Brain Found by Neuroimaging Studies

71. An analysis of structural magnetic resonance imaging (MRI) data from 36 cohorts with a total of over 4,100 participants found slightly reduced total cortical surface area in children with ADHD. The same team found some subcortical regions of the brain were smaller in children with ADHD, mainly in frontal, cingulate and temporal regions with some reductions in cortical thickness in temporal regions. The same team found some subcortical regions of the brain, i.e., basal ganglia, amygdala, hippocampus and intracranial volumes were smaller in children with ADHD in 23 cohorts of 3,242 participants. The differences seen in children were not seen in adolescents or adults (Hoogman et al., 2017; Hoogman et al., 2019). All of the differences observed were small to very small and subtle.

72. Comparative meta-analyses show that structural grey matter volume reductions in basal ganglia and insula are disorder-specific relative to OCD in 30 data sets with 1,870 participants (Norman et al., 2016) while medial frontal reductions were specific to ASD in 66 data sets with 3,610 participants (Lukito et al., 2020). An analysis of structural magnetic resonance imaging (MRI) data from 48 cohorts with a total of over 12,000 participants

showed that ADHD participants had smaller hippocampus volume relative to OCD which was related to IQ differences and smaller intracranial volume relative to ASD and OCD patients (Boedhoe et al., 2020). The functional under-activations in right inferior frontal cortex and basal ganglia during tasks of cognitive control were disorder-specific relative to OCD in 1,870 participants (Norman et al., 2016), while the inferior frontal dysfunction was specific relative to autism in 3,610 participants (Lukito et al., 2020).

73. A meta-analysis of ten diffusion tensor imaging studies with 947 participants found that the most consistent white matter differences between those with and without ADHD were located in the splenium of the corpus callosum extending to the right cingulum, the right sagittal stratum, and left tapetum, suggesting problems with the connections between the two hemispheres in posterior parieto-temporal attention regions and in long-range fronto-posterior association tracts (connecting inferior frontal, temporal, parietal and occipital regions) involved in attention and perception (Chen et al., 2016).

74. A meta-analysis of 21 functional MRI studies with 607 participants found that those with ADHD showed consistent and replicable under-activation in typical regions of inhibitory control such as right inferior frontal cortex, supplementary motor area and the basal ganglia relative to typically developing individuals (Hart et al., 2013). The inferior frontal under-activation findings were replicated in two further fMRI meta-analyses of inhibitory control with 33 datasets/1,161 participants, and 42 datasets/2,005 participants, respectively (Lukito et al., 2020; Norman et al., 2016). Another meta-analysis including 130 fMRI studies with 1,914 participants found no convergence except for aberrant function in basal ganglia for neutral fMRI tasks and inferior frontal under-function in males only (Samea et al., 2019).

75. A meta-analysis of nine studies with over 1,250 research participants found that elevations in the theta/beta on the electroencephalogram cannot be considered a reliable diagnostic measure for ADHD although it may have prognostic value in some patients (Arns et al., 2013).

76. A meta-analysis of six studies with 148 participants examined mismatch negativity, which assesses the integrity of auditory sensory memory and involuntary attention switching. It reported that ADHD children had small-to-moderate reductions in mismatch negativity amplitude compared with healthy controls (Cheng et al., 2016).

77. Meta-analyses and systematic reviews showed that the medications used to treat ADHD are not associated with observed deficits in brain structure (Hoogman et al., 2017; Hoogman et al., 2019; Lukito et al., 2020; Norman et al., 2016; Spencer et al., 2013), but with improved brain function, most prominently in inferior frontal and striatal regions (Hart et al., 2013; Lukito et al., 2020; Norman et al., 2016; Rubia et al., 2014; Spencer et al., 2013).

What kinds of Non-Psychiatric Medical Problems Commonly Occur among People with ADHD?

A relatively new area of research into ADHD is examining what types of medical problems are more common than expected among people with ADHD. As you read this section, keep in mind that not all people with ADHD will suffer from all, or even only one, of these disorders.

Obesity

78. A Swedish national register study of over 2.5 million people found ADHD patients had a threefold greater risk of obesity relative to their non-ADHD siblings and cousins. It also found a familial co-aggregation of ADHD and clinical obesity, the strength of which varied directly with the degree of genetic relatedness (Chen et al., 2018c).

79. A meta-analysis found that compared with typically developing people, children and adolescents with unmedicated ADHD were about 20% more likely to be overweight or obese (15 studies, over 400,000 participants), and adults with unmedicated ADHD almost 50% more likely to be overweight or obese (9 studies, over 45,000 participants) (Nigg et al., 2016). Meta-analyses of twelve studies with over 180,000 participants found that people with unmedicated ADHD were about 40% more likely to be obese, whereas those who were medicated were indistinguishable from typically developing people (Cortese et al., 2016b).

Allergies and Asthma

80. A Swedish national register study of over 1.5 million people found that those with asthma were 45% more likely to have ADHD even after adjustment for relevant variables (Cortese et al., 2018b). A cohort study of almost a million births using the Danish national registers found that children born to asthmatic mothers were 40% more likely to develop ADHD (Liu et al., 2019b).

81. In a meta-analysis of six longitudinal studies with over 50,000 participants, those with asthma or atopic eczema were a third more likely to have ADHD than controls. A meta-

analysis of three studies with over 48,000 participants found that those with allergic rhinitis were about 50% more likely to have ADHD (van der Schans et al., 2017).

Diabetes Mellitus:

82. A retrospective analysis of over 650,000 children and adolescents in German diagnosis and prescription databases found ADHD was 40% more likely to be diagnosed among children with type 1 diabetes (T1DM) (Kapellen et al., 2016).

83. A German multi-center registry study of over 56,000 children and adolescents found that those with both ADHD and T1DM suffered twice as often from diabetic ketoacidosis compared with diabetic patients without ADHD. They also found significant differences in HbA1c, and concluded, “Pediatric patients with ADHD and T1DM showed poor metabolic control compared with T1DM patients without ADHD” (Hilgard et al., 2017).

84. A longitudinal study using the Taiwan National Health Insurance Research Database enrolled over 35,000 patients with ADHD and over 70,000 age- and sex-matched controls. Adolescents and young adults with ADHD were about three times more likely to develop type 2 diabetes mellitus (Chen et al., 2018b).

85. A cohort study using multiple Swedish national registers looked at over 1.6 million adults aged 50 to 64 years. Prevalence of type 2 diabetes mellitus was 70% greater among adults with ADHD (Chen et al., 2018c).

86. A meta-analysis found that maternal pre-existing type 1 diabetes was associated with a small increased risk of ADHD in offspring (4 studies, over five million people). So was

paternal pre-existing type 1 diabetes (3 studies, 4.7 million people), and maternal pre-existing type 2 diabetes (2 studies, 2.6 million people) (Zeng et al., 2019). A Swedish study looked at all 15,615 children born after their parents were diagnosed with type 1 diabetes. After controlling for confounders, it found that these children had a 30% greater chance of being diagnosed with ADHD (Ji et al., 2018).

Other Somatic Disorders:

87. A meta-analysis of 18 studies with more than 2,500 children and adolescents found a moderate association between sleep-disordered breathing and ADHD (Sedky et al., 2014).

88. A meta-analysis of sleep in adults with ADHD found no significant differences with normally developing adults, as measured by polysomnography. In four studies with 178 participants, sleep onset latency, stage 1 sleep, stage 2 sleep, slow wave sleep, REM, and sleep efficiency were all comparable. Same with total sleep time (3 studies, 130 persons), and with REM latency and wake after sleep onset (3 studies, 121 persons). As measured by actigraphy, there were no significant differences for time in bed and actual wake time (3 studies, 159 persons), true sleep (4 studies, 222 persons). However, sleep onset latency was much greater for those with ADHD, and sleep efficiency was moderately lower (4 studies, 222 persons). Nevertheless, subjective evaluations by those with ADHD reported moderately greater difficulty in falling asleep (8 studies, over 1,700 persons), moderately greater frequency of night awakenings and moderately lesser likelihood of being rested at wake-up (5 studies, over 1,100 persons), and moderately worse sleep quality (5 studies, over 800 persons)(Lugo et al., 2020).

89. In a Norwegian national registry study of over 1.2 million males and over 1.2 million females, males with ADHD were 30% more likely to be diagnosed with psoriasis, and women with ADHD more than 50% more likely to be diagnosed with psoriasis, than normally developing controls (Hegvik et al., 2018).

90. A Taiwan nationwide population cohort study of over 8,000 people with ADHD and 32,000 matched controls explored associations with autoimmune diseases. It reported that those with ADHD had well over twice the prevalence of ankylosing spondylitis, ulcerative colitis, and autoimmune thyroid disease, and over 50% greater likelihood of asthma, allergic rhinitis, and atopic dermatitis (Chen et al., 2017a) .

91. A population-based cohort study of over 900,000 Danish children found that epilepsy was associated with a 2.7-fold increased risk for ADHD (Bertelsen et al., 2016). Another population-based cohort study, of over 12,000 Taiwanese, reported that epilepsy was associated with a 2.5-fold increased risk for ADHD. Conversely, a linked cohort study of over 18,000 Taiwanese found ADHD was associated with a fourfold increase in epilepsy (Chou et al., 2013).

92. A countrywide registry study of 1.9 million Swedes reported that those with epilepsy were three and a half times more likely to have ADHD. The risk of having ADHD was 85% greater if the person's mother had epilepsy, 50-60% greater if the father or a brother or sister did, 15% greater for cousins. Genetics explained 40% of the variance, with non-shared environmental factors explaining another 50% (Brikell et al., 2018).

93. A longitudinal study using the Taiwan Health Insurance Research Database compared almost 18,000 adolescents and young adults with ADHD with over 70,000 age- and sex-matched controls. Those with ADHD were over three times more likely to develop sexually transmitted infections, after adjusting for demographic data, other psychiatric disorders, and ADHD medications (Chen et al., 2018a).

94. A Danish national register cohort study of 1.1 million people found that hospitalization for serious infections was associated with a subsequent doubling in the rate of ADHD diagnosis. Among those treated with anti-infective agents, the risk of subsequent diagnosis with ADHD was halved (Kohler-Forsberg et al., 2019).

95. A Danish national register study of almost a million people found that children with autoimmune disease were 24% more likely to develop ADHD. Maternal autoimmune disease was associated with a 12% greater likelihood of ADHD in their offspring. Paternal autoimmune disease was not associated with any significant effect (Nielsen et al., 2017).

96. Using Taiwan's nationwide population-based dataset, over 116,000 children with ADHD were compared with the same number of randomly selected children without ADHD. Those with ADHD were much more likely to have significant abnormalities of the eye: almost 90% more likely to have amblyopia ("lazy eye"), over 80% more likely to have astigmatism, and twice as likely to have heterotropia, in which the eyes diverge at rest (Ho et al., 2020). A study using the same database matched 6,817 youths diagnosed with amblyopia to over 27,000 age- and sex-matched controls. Those in the amblyopia group had 1.8 times the risk of developing ADHD (Su et al., 2019).

97. In a study of over 2.5 million German youth, those with ADHD were nine times more likely to have metabolic disorders, five times more likely to develop viral pneumonia, four times more likely to have white blood cell disorders, three times more likely to have kidney failure, high blood pressure, or be obese, two and a half times more likely to have type 2 diabetes or migraines, twice as likely to have asthma or atopic dermatitis, and 50% more likely to have glaucoma (Akmatov et al., 2019). A Brazilian population-based study including 5,671 children found those with migraine about four times more likely to have ADHD (Arruda et al., 2020).

98. A study of over 59,000 boys diagnosed with ADHD and over 52,000 healthy boys in Taiwan reported that those in the ADHD group were twice as likely to develop testicular dysfunction (Wang et al., 2019).

99. A nationwide population cohort study using the Swedish national registers compared over 19,000 children with a diagnosis of biopsy-verified celiac disease with over 95,000 matched child controls. It found a subsequent 29% increased risk of ADHD in the celiac patients, rising to 39% when restricting to adult diagnoses of ADHD. However, when comparing 13,000 children diagnosed with celiac disease to their 18,000 non-celiac siblings, the increases became nonsignificant, suggesting the increases were primarily attributable to confounders (Lebwohl et al., 2020).

100. A Swedish nationwide study using national registers examined medical records of all individuals aged 18 to 64 years who were residing in Sweden during 2013 and identified 41,840 who filled at least one prescription for ADHD medicines. Young adults with ADHD

were four times more likely to have somatic co-prescriptions and fifteen times more likely to have psychotropic co-prescriptions than normally developing controls. For middle-aged adults (30-49) the odds were six and 21 times greater, respectively, and for older adults, seven and 18 times greater. Respiratory medications (primarily for allergies reactions and asthma) were the most likely to be dispensed for somatic purposes, followed by alimentary tract and metabolic medications (most frequently proton pump inhibitors indicated for gastric/duodenal ulcers and gastroesophageal reflux disease), then cardiovascular system medications (primarily for hypertension and arrhythmias) (Zhang et al., 2020a).

What is the Impact of ADHD on Patients and Families?

ADHD is a disorder associated with serious distress and/or impairments in living. Although, as documented below, many severe adverse outcomes have been associated with ADHD, the typical patient does not experience all, or even most, of these problems. Many patients live enjoyable and productive lives, especially if they receive treatment.

Quality of Life

101. A meta-analysis of seven studies with over 5,000 youths and their parents reported large impairments in the quality of life of youths with ADHD relative to typically developing peers, regardless of whether evaluated by the youths themselves or by their parents. Physical functioning was only moderately impaired, but emotional functioning and social functioning was strongly impaired. School functioning was strongly impaired. As youths with

ADHD grew older, their quality of life compared with typically developing peers grew worse in physical, emotional, and school domains. (Lee et al., 2016).

102. A meta-analysis of 17 studies encompassing 647 families (over 2,300 participants) evaluated the quality of life of parents whose children had ADHD relative to parents with typically developing children. Parents of the former reported a moderate deficit in quality of life relative to parents of the latter (Dey et al., 2019).

Emotional and Social Impairment

103. A study of over 8,600 youths from the US National Health Interview Survey found that those with ADHD were six times as likely to have a high level of emotional, conduct, and peer problems, and nine times as likely to manifest a high level of impairment including interference with home life, friendships, classroom learning, and leisure activities (Strine et al., 2006).

104. A meta-analysis of 22 studies with over 21,000 participants found that youth with ADHD were strongly impaired in the ability to modulate their reactivity to novel or stressful events (Graziano and Garcia, 2016). Another meta-analysis, combining twelve studies with over 1,900 participants, found that adults with ADHD had very elevated levels of emotional dysregulation compared with normally developing controls (Beheshti et al., 2020).

105. A meta-analysis found that children with ADHD had medium-to-large impairments in socializing with peers as measured by rejection/likability, popularity, and friendships (61 studies, over 24,000 children). They also had moderate impairments in social skills such as sharing, cooperating, turn-taking, reciprocity (68 studies, over 148,000 children), and social-

information processing, such as recognizing social cues, identifying problems, generating solutions, and avoiding biases (23 studies, over 3,750 children) (Ros and Graziano, 2018).

106. A study of over 53,000 U.S. children from the National Survey of Children's Health found that those with ADHD were 2.4 times as likely to engage in bullying (Montes and Halterman, 2007). A more recent study of some 64,000 children using the same database confirmed this finding, reporting that those with ADHD were 2.8 times more likely to engage in bullying (Benedict et al., 2015).

Accidental Injuries

107. A nationwide cohort study of over 50,000 youths with ADHD and an equal number of age-, sex-, and comorbidity-matched controls drawn from Taiwan's National Health Insurance Research Database reported that having ADHD was associated with a more than three-quarters greater likelihood of burn injury. For those under six years old, the risk was doubled. For youths between six and seventeen years old, the increase in risk was about 70 percent. There were no significant differences between boys and girls (Yeh et al., 2020).

108. A meta-analysis of 32 studies covering more than four million people found that those with ADHD had a 40 to 50% greater risk of accidental physical injuries (Ruiz-Goikoetxea et al., 2018a).

109. A Swedish national registers study followed 17,408 individuals with ADHD from 2006 to 2009 and found that patients with ADHD had an almost 50% greater risk of serious transport accidents (Chang et al., 2014b).

110. A U.S. study of over 8,000 high school and collegiate athletes (predominantly male football players) found that those with ADHD were three times as likely to have had three or more reported concussions (Nelson et al., 2016).

111. A meta-analysis of 16 studies encompassing over 175,000 people estimated that controlling for mileage driven, those with ADHD were 23% more likely to be involved in vehicular crashes (Vaa, 2014).

112. A retrospective cohort study of over 18,000 New Jersey drivers found that the crash risk for those with ADHD was a third greater than for those without (Curry et al., 2017).

113. A meta-analysis of five studies, comprising over three thousand patients with minor traumatic brain injury (mTBI) and over nine thousand controls found that those with mTBI were twice as likely to have ADHD than those without mTBI (Adeyemo et al., 2014).

Premature Death and Suicide

114. A Danish study of almost two million people found ADHD is associated with a small risk for premature death, mostly due to accidents. When ADHD was accompanied by other psychiatric and substance use disorder, the chances of premature death increased (Dalsgaard et al., 2015b).

115. A cohort study of more than 2.2 million Taiwanese found no increased risk of death from natural-causes associated with ADHD. But people with ADHD had twice the rate of suicide, twice the rate of death by homicide, and a 30% greater rate of death from unintentional injury (Chen et al., 2019c).

116. Using nationwide registers in Denmark, a cohort study of 2.9 million people reported a fourfold higher rate of suicide attempts and deaths in patients with ADHD. The risk was over tenfold in those with ADHD plus another psychiatric diagnosis (Fitzgerald et al., 2019).

117. A meta-analysis found that persons with ADHD attempted suicide at twice the rate of typically developing people (six studies, over 65,000 persons), had over three times the rate of suicidal ideation (23 studies, over 70,000 persons), and over six times the rate of completed suicide (four studies, over 130,000 persons) (Septier et al., 2019).

118. A Taiwanese study of over 20,000 adolescents and young adults with ADHD and over 61,000 age- and sex-matched non-ADHD individuals found that those with ADHD were almost four times as likely to attempt suicide, and over six times as likely to repeat suicide attempts. Methylphenidate or atomoxetine treatment did not increase the risk of suicide attempts or repeated suicide attempts. Long-term methylphenidate treatment was associated with a lower risk for repeated suicide attempts among men (Huang et al., 2018).

119. In a prospective cohort study of more than 2.6 million Swedes, adults with ADHD had a small increase in premature death, mostly due to accidents and suicide. There was no significant association for children with ADHD (Sun et al., 2019b).

Crime and Delinquency

120. A study of the Danish population using nationwide registers found that, compared with other youth, those diagnosed with ADHD were more than twice as likely to be convicted of criminal offenses and were three times as likely to be incarcerated. After adjusting for other

risk factors, those with ADHD were 60% more likely to have been convicted of a crime, and 70% more likely to have been incarcerated (Mohr-Jensen et al., 2019).

121. A meta-analysis comprising 21 studies and over 19,500 prison inmates found that the prevalence of ADHD in prisons based on interview diagnoses was 20.5% with no differences observed between males and females or adolescents and adults (Young et al., 2015). Another meta-analysis reported the prevalence of ADHD among adolescents in juvenile detention to be just over 17%, both for males (24 studies, over 24,000 individuals) and females (13 studies, over 3,900 individuals), which is much higher than the prevalence in the population (Beaudry et al., 2020).

122. A study using a nationally representative American sample of over 5,000 adults found that those with ADHD were over twice as likely to be perpetrators of physical dating violence, and 65% more likely to be victims of such violence (McCauley et al., 2015).

123. In a nationwide study of over 21,000 Icelandic adolescents and young adults, 14% reported having been interrogated at a police station. Of these, 15% reported making a false confession. Those with ADHD were twice as likely to make a false confession (Gudjonsson et al., 2016).

124. A study using the Danish national registries looked at violent crimes against youth aged 7-18 years, among a total of 678,000 individuals. Children with ADHD were 2.7 times more likely to be victims of violent crimes than their typically developing peers, after adjusting for confounding risk factors (Christoffersen, 2019).

Educational Underachievement

125. A study of a U.S. sample of almost 30,000 adults found that those with ADHD were twice as likely not to have graduated from high school on time, after adjusting other psychiatric disorders (Breslau et al., 2011).

126. A nationwide cohort study of over 750,000 Scottish school children using linked national registers identified those who had been prescribed medicine for ADHD. Even while receiving medication, these children were more than three times as likely as typically developing peers to have low educational achievement, more than twice as likely to drop out of school before age 16, more than eight times as likely to have a record of special educational needs, 50% more likely to get injured, 40% more likely to be unemployed. These results were adjusted for socioeconomic confounders and other psychiatric conditions (Fleming et al., 2017).

127. A meta-analysis of ten studies and 830 youths found that ADHD was strongly associated with poorer performance on measures of overall, expressive, receptive, and pragmatic language (Korrel et al., 2017).

Substance Use Disorders

128. A meta-analysis of twelve studies covering over 5,400 people found that those with ADHD were almost three times more likely to be nicotine-dependent. Combining eleven studies with almost 2,400 participants, those with ADHD were 50% more likely to develop a drug or alcohol use disorder than those without ADHD (Lee et al., 2011).

129. A meta-analysis found that ADHD was associated with a more than twofold greater odds of alcohol-use disorders (13 studies, over 20,000 participants) and nicotine-related disorder (14 studies, over 1,800 participants) (Groenman et al., 2017).

130. A Swedish study of over half a million people found a more than threefold association between ADHD and subsequent drug use disorders after adjusting for sex and parental education (Sundquist et al., 2015).

Other

131. Studies of 2.7 million girls from Denmark (Ostergaard et al., 2017), 380,000 from Sweden (Skoglund et al., 2019) and 7,500 from Taiwan (Hua et al., 2020) found that those with ADHD were more likely to have teen pregnancies than those without ADHD. Consistent with these results, large studies from Sweden (Chang et al., 2014a), Finland (Chudal et al., 2015) and a consortium of eight European countries (Pohlabeln et al., 2017) each found ADHD to be more likely among children of teenage mothers than among children of older mothers.

132. A study of over 36,000 people from the US reported that ADHD increased the risks for problem gambling, spending too much money, reckless driving, and quitting a job without a plan for what to do next (Bernardi et al., 2012).

133. A nationwide study using Taiwan's National Health Insurance Research Database compared 675 adults with ADHD and 2,025 without ADHD, matched by age and sex. After adjusting for other psychiatric disorders, urbanization level of residence, and monthly income, those with ADHD had 3.4 times the risk of developing dementia (Tzeng et al., 2019).

134. A meta-analysis of nine studies encompassing almost a million and a half people found that ADHD is associated with a threefold greater risk of poisoning in children (Ruiz-Goikoetxea et al., 2018b). In a study from Taiwan comparing 3,685 children with ADHD with 36,000 controls, those with ADHD had a more than fourfold greater risk of deliberate self-poisoning (Chou et al., 2014).

135. A longitudinal study of some 15,000 U.S. adolescents reported that those with ADHD had a 12% reduction in employment and a 34% reduction in earnings relative to non-ADHD siblings (Fletcher, 2014).

136. Using Danish registers, a nationwide population study of over 675,000 youths between the ages of 7 and 18 found that youths with ADHD were 3.7 times as likely to be reported as victims of sexual crimes than normally developing controls. After adjusting for covariates, such as parental violence, parental inpatient mental illness, parental suicidal behavior or alcohol abuse, parental long-term unemployment, family separation, and child in public care outside the family, youths with ADHD remained almost twice as likely to be reported as victims of sexual crimes (Christoffersen, 2020).

What is the Economic Burden of ADHD?

Given the many adverse outcomes associated with ADHD, it will come as no surprise to readers that these effects have a substantial economic cost to individual patients, families, and society.

137. A systematic review of seven European studies of hundreds of thousands of participants estimated total ADHD-related costs in the Netherlands as €9,860 to €14,483 per patient per year, with annual national costs more than €1 billion (Le et al., 2014).

138. A review of the costs of child, youth and adult ADHD in Australia estimated the total annual costs to be over $20 billion Australian dollars, or $25,000 per person with ADHD. This includes financial costs of $12.8 billion, well-being losses of $7.6 billion, and productivity losses of $10.2 billion (Australian ADHD Professionals Association, 2019).

139. A systematic review of 19 U.S. studies of hundreds of thousands of people found that ADHD was associated with overall national annual costs from $143 to $266 billion, mostly associated with adults ($105 to $194 billion). Costs borne by family members of people with ADHD ranged from $33 - $43 billion (Doshi et al., 2012).

140. A study with over 7,000 workers in ten nations found that those with ADHD had an average of 22 annual days of lost role performance compared with those without ADHD (de Graaf et al., 2008).

141. A study of a U.S. national Fortune 100 company's database of over 100,000 beneficiaries compared healthcare costs for youths with ADHD with matched controls without ADHD. The annual average cost per family member was $2,728 for non-ADHD family members of ADHD patients, almost double the $1,440 for family members of matched controls (Swensen et al., 2003).

142. German health insurance records, including over 25,000 patients with ADHD, indicate that patients with ADHD cost roughly €1,500 more annually than those without ADHD. Main cost drivers were inpatient care, psychiatrists, and psychotherapists. Mood, anxiety, substance use disorders, and obesity were significantly more frequent in patients with

ADHD. The additional costs resulting from these conditions added as much as €2,800 per patient (Libutzki et al., 2019).

143. Using the National Health Insurance Service claims data for the population aged 19 years or younger in South Korea (69,353 diagnosed with ADHD), the total annual economic burden due to ADHD was estimated to be $47.55 million (Hong et al., 2020).

144. Using the Danish national registers, over 5,000 adults with a diagnosis of ADHD in adulthood who had not received a diagnosis in childhood were identified. Excluding cases with missing data, other psychiatric diagnoses, and cases without a same-sex sibling free of any diagnosed psychiatric diagnoses, a final cohort was formed consisting of 460 sibling pairs. On average, adults with ADHD had an annual economic burden of just over €20,000 compared with their normally developing siblings (Daley et al., 2019).

145. A nationwide cohort study of over 445,000 people in the Swedish national registers compared healthcare costs for three groups: those with childhood ADHD that persisted into adulthood, those whose ADHD remitted in adulthood, and those who never had ADHD. Those who never had ADHD had average annual healthcare costs of €304. Those in remission had double the cost, and those with persistent ADHD over triple the cost (Du Rietz et al., 2020).

146. A nationwide population study of over 83,000 persons with ADHD and 334,446 non-ADHD controls matched by age and sex used Danish national registries to calculate the net socioeconomic cost of ADHD. Relative to controls, and summing net direct health costs and net losses from lower income and employment, the yearly average cost per individual with

ADHD came to just over €16,000. Including additional social transfers, the total rose to just over €23,000. For partners of persons with ADHD, the additional yearly average cost per individual was almost €5,500. With additional social transfers, the total rose to €8,000 (Jennum et al., 2020).

147. Using a database that tracks more than sixty German nationwide health insurance programs, a study of five million member records identified 2,380 individuals first diagnosed with ADHD as adults. Their direct healthcare costs in the year following diagnosis averaged €4,000. Despite explicit German guidelines recommending ADHD medication, only a third were prescribed medication, dropping to one eighth four years later. Two-thirds received psychotherapy. The authors concluded that "guideline recommendations are not yet comprehensively implemented in everyday routine care" (Libutzki et al., 2020).

Which Medications are Safe and Effective for Treating ADHD?

As determined by governmental regulatory agencies around the world, several medications are safe and effective for treating ADHD symptoms as determined by randomized controlled clinical trials that typically study patients for several weeks. These medications, which are as efficacious, or more efficacious, than many medications used for non-psychiatric disorders (Leucht et al., 2012), are classified as either stimulants (methylphenidate and amphetamine) or non-stimulants (atomoxetine, extended release guanfacine, and extended release clonidine).

<u>Effects of Medications on Symptoms: Results from Randomized, Controlled Clinical Trials</u>

148. Protocols for using medications for ADHD are well described in detailed guidelines prepared by professional health care associations (Alliance, 2011; Banaschewski T, 2018;

Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018; Pliszka, 2007; Schoeman and Liebenberg, 2017; Seixas et al., 2012; Taylor et al., 2004; Wolraich et al., 2011).

149. A network meta-analysis found stimulants to be highly effective in reducing the symptoms of ADHD. Compared with placebo, as rated by clinicians, amphetamines were associated with large improvements in all age groups (youths 6 studies with 2179 participants, adults 5 studies with 1521 participants), methylphenidate with large improvements in youths (9 studies, 2677 participants) and moderate ones in adults (11 studies, 2909 participants). Extended release guanfacine (7 studies, 1930 participants) led to moderate improvements in children. Atomoxetine led to moderate improvements in all age groups (youths 21 studies with 3812 participants, adults 11 studies with 3377 participants). Taking side effects into account, the medications with the best benefit-to-risk ratios were methylphenidate for children and adolescents, and amphetamines for adults (Cortese et al., 2018a).

150. A meta-analysis of 18 studies with over 2,000 adults with ADHD found three amphetamine derivatives (dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts) to be associated with moderate reductions in ADHD symptoms (Castells et al., 2011). Another meta-analysis, combining four studies with 216 youths, found mixed amphetamine salts to be slightly more effective at reducing ADHD symptoms than methylphenidate (Faraone et al., 2002).

151. A meta-analysis of 19 parallel group trials with over 1,600 participants, found methylphenidate produced moderate to large improvements in teacher-rated ADHD symptoms, teacher-rated behavior and parent-rated quality of life. There was no evidence of serious adverse events, and just a slightly elevated risk of non-serious side effects (Storebø et al., 2015).

152. A meta-analysis found dexmethylphenidate strongly reduced youth ADHD symptoms relative to placebo (seven studies, almost 1,500 participants), and had three times the clinical response rate (four studies, over 600 participants) (Maneeton et al., 2015). Another meta-analysis, covering six RCTs with 253 participants, reported that methylphenidate strongly reduced adult ADHD symptoms, with higher doses resulting in greater improvement (Faraone et al., 2004).

153. A meta-analysis of seven studies with over 1,600 participants reported that atomoxetine moderately reduced ADHD symptoms. (Cheng et al., 2007).

154. A meta-analysis found that methylphenidate (13 studies, over 2,200 adults) and lisdexamfetamine (five studies, over 2,300 adults) led to small-to-moderate reductions in symptoms of emotional dysregulation; for atomoxetine (three studies, 237 adults) the reductions were small (Lenzi et al., 2018). Another meta-analysis covering nine studies with over 1,300 youths reported atomoxetine to be associated with small reductions in emotional symptoms (Schwartz and Correll, 2014).

155. A meta-analysis reported moderate-to-strong improvements in ADHD symptoms with methylphenidate in ADHD patients with borderline intellectual functioning or intellectual disability (8 studies, 423 children). (Sun et al., 2019a).

156. A meta-analysis of 23 studies with over 2,900 children with ADHD reported that stimulant medications reduced anxiety by 14% relative to placebo (Coughlin et al., 2015).

157. A meta-analysis of nine studies with over 1,300 participants found stimulants to be highly effective in reducing aggression, oppositional behavior, and conduct problems in youth with ADHD (with and without oppositional defiant disorder) and conduct disorder, as measured by teachers, and moderately effective as measured by parents (Pringsheim et al., 2015).

Effects of Medications on Impairments Associated with ADHD: Results from Naturalistic Studies

158. A Swedish registry study of over 650,000 students found that treatment with ADHD medication for three months resulted in a more than nine-point gain in grade point sum (on a scale of 0 to 320); treatment was associated with an increase in the probability of completing upper secondary school by two-thirds (Jangmo et al., 2019).

159. A Swedish national register study of over 61,000 youths with ADHD found that their test scores were higher during periods they were taking medication vs non-medicated periods (Lu et al., 2017). A Danish study of over half a million children (over 6,400 with ADHD) found that discontinuation of ADHD medication was associated with a small but significant decline in grade point averages (Keilow et al., 2018). A meta-analysis of nine RCTs comprising 1,463

patients found that discontinuing medications led to a worsening in quality of life for children and adolescents but not adults. (Tsujii et al., 2020)

160. A Swedish cohort study of over 25,000 ADHD patients found a one-third reduction in criminality among men receiving ADHD medication, and a 40% reduction for women (Lichtenstein et al., 2012). A Danish national registry study of over 4,200 individuals with childhood ADHD found that crime rates in adulthood were 30-40% lower during periods of taking ADHD medication (Mohr-Jensen et al., 2019).

161. A Danish cohort study of over 700,000 people, including 4,557 with ADHD, found that among teenagers with ADHD, stimulant treatment was associated with a decrease in rates of injuries (30% for ten-year olds and 40% for twelve-year olds) (Dalsgaard et al., 2015a).

162. Using the Swedish national registries, a study followed 9,421 youths with ADHD and 2,986 youths with both ADHD and other psychiatric diagnoses from 2006 to 2013. It compared periods when they were taking ADHD medication with periods when they were not. During medicated periods both groups had a greater than 10% reduction in unintended injuries, and a greater than 70% reduction in traumatic brain injuries (Ghirardi et al., 2020).

163. A Taiwanese study of over 124,000 youths with ADHD found that methylphenidate treatment decreased the risk for traumatic brain injuries, after adjusting for confounders (Liao et al., 2018).

164. A nationwide study compared 7,200 Taiwanese youths with ADHD with 36,000 children without ADHD. After adjusting by age, sex, urbanization level, and geographic region, boys with ADHD were almost 40% more likely and girls with ADHD 60% more likely to suffer bone

fractures (Guo et al., 2016). Another study from Taiwan identified over 6,200 youths newly diagnosed with ADHD and assessed the effect of methylphenidate treatment. The risk of bone fractures was 20% lower in those who had over half a year of methylphenidate treatment (Chen et al., 2017b).

165. A population-based, electronic medical records database in Hong Kong identified over 17,000 individuals aged 6-19 years who had been prescribed methylphenidate. Of these, almost 5,000 had at least one trauma-related emergency room admission. Researchers found a 9% reduction in such admissions during periods covered by a methylphenidate prescription compared with periods with no active prescription (Man et al., 2015).

166. A meta-analysis of five studies with over 13,000 participants found that ADHD medications (primarily stimulants) were associated with a greater than 10% reduction in unintentional injuries (Ruiz-Goikoetxea et al., 2018a).

167. Using Swedish national registers, a study of over 17,000 people with ADHD found that medication for ADHD was associated with a greater than 50% reduction in the risk of serious transport accidents among males but not females. Over 40% of crashes by male patients would have been avoided if they had been receiving treatment during the entire period (Chang et al., 2014b). A U.S. national cohort study of 2.3 million people with ADHD examined emergency room visits for motor vehicle crashes over ten years. Males with ADHD had a 38% lower risk of crashes in months when receiving ADHD medication compared with months when not receiving medication, and females a 42% lower risk in months when receiving ADHD medication. About a fifth of crashes would have been

avoided if they had been on medication throughout the period of the study (Chang et al., 2017).

168. A longitudinal study using the Taiwan Health Insurance Research Database compared almost 18,000 adolescent and young adults with ADHD with over 70,000 age- and sex-matched controls. Short-term use of ADHD medications was associated with a 30% reduction in sexually transmitted infections, and long-term use with a 40% reduction, though these reductions were only among males (Chen et al., 2018a).

169. A nationwide longitudinal cohort study using the Swedish national registers found that among more than 38,000 individuals with ADHD, ADHD medication was associated with a greater than 40% reduction in the risk for depression three years later. The risk decreased with the duration of ADHD medication use. Depression was 20% less common when patients received ADHD medication compared with periods when they did not (Chang et al., 2016).

170. A Swedish population-based study of 38,000 people with ADHD found a 20% decline in suicide related events among those prescribed stimulants during periods when they were under treatment as opposed to during periods when they were not under treatment. No such benefit was found for non-stimulant medications (Chen et al., 2014).

171. A Taiwanese study identified 85,000 youths with ADHD using National Health Insurance data to examine whether methylphenidate use affected suicide attempts. After adjusting for relevant variables, it found a 60% lower risk of suicide in those using methylphenidate

for 3 months to half a year, and a 70% reduction among those using methylphenidate for more than half a year (Liang et al., 2018b).

172. A study using the Swedish national registers investigated the association between prescription stimulant medication for ADHD in 2006 and substance abuse during 2009 among all 38,753 people born between 1960 and 1998 and diagnosed with ADHD. After controlling for relevant variables, it found a greater than 30% reduction in indicators of substance abuse among those prescribed stimulants. The longer the duration of medication, the lower the rate of substance abuse (Chang et al., 2014c). A meta-analysis of 14 studies with over 2,300 participants found that people with ADHD were about half as likely to smoke cigarettes when regularly treated with stimulant medications (Schoenfelder et al., 2014). A meta-analysis found that stimulants did not increase the risk for alcohol (11 studies, over 1,300 participants, nicotine (6 studies, 884 participants), cocaine (7 studies, 950 participants), or cannabis abuse or dependence (9 studies, over 1,100 participants) (Humphreys et al., 2013).

173. A nationwide study of over 7,500 Taiwanese adolescents with ADHD and over 30,000 matched controls found that long-term use of ADHD medication use was associated with a 30% decrease in teenage pregnancy (Hua et al., 2020).

174. A nationwide population-based cohort using Taiwan's National Health Insurance Research Database identified over 68,000 children and adolescents with a diagnosis of ADHD and who were prescribed methylphenidate and compared them with an identical number of controls matched on age, gender and year of first ADHD diagnosis. After

controlling for potential confounders, ADHD individuals prescribed methylphenidate had a one-fifth lower rate of all-cause mortality than ADHD individuals not prescribed methylphenidate. Delayed use of methylphenidate, on the other hand, was associated with slightly higher (5%) mortality. Long-term methylphenidate use was associated with a one-sixth lower rate of all-cause mortality. The authors caution, however, that "information lacking in the database precluded the measurement of other possible confounders, such as family history, psychosocial stressors, effect of behavioural therapy or severity of comorbidities," and thus unmeasured confounding cannot be excluded (Chen et al., 2020a).

175. A nationwide population-based cohort using Taiwan's National Health Insurance Research Database identified over 90,000 individuals younger than 18 years with a diagnosis of ADHD, and compared risk of burn injury between those not on methylphenidate, those on methylphenidate for less than 90 days, and this on methylphenidate for more than 90 days. The data suggested that fully half the incidence of burn injuries could have been prevented by taking methylphenidate. Compared with patients not taking methylphenidate, those taking it for less than 90 days had a 30% lesser risk of burn injuries, and those taking it for 90 days or more a 57% reduction in risk, after adjusting for confounders (Chen et al., 2020b).

Effects of Medications for ADHD on the Brain

176. A meta-analysis of methylphenidate treatment for ADHD found moderate improvements in response inhibition (25 studies, 787 participants) and sustained attention

(29 studies, 956 participants), but no significant effect on working memory (13 studies, 559 participants) (Tamminga et al., 2016).

177. A meta-analysis of 14 fMRI studies with 212 participants reported that medication treatment for ADHD made the brains of youth with ADHD function in a way that was more like the brains of people without ADHD in brain areas involved in the control of cognition, which is typically disrupted in ADHD (Rubia et al., 2014). Medication treatment for ADHD had no effect on brain structure in studies of 4,180 ADHD patients in the ENIGMA-ADHD Working Group set of 36 cohorts from around the world (Hoogman et al., 2017; Hoogman et al., 2019).

Adverse Effects of ADHD Medications

178. A meta-analysis found that stimulants moderately reduced total sleep time (7 studies, 223 children), delayed the onset of sleep (7 studies, 171 children), and slightly-to-moderately decreased sleep efficiency (7 studies, 155 children) (Kidwell et al., 2015). A meta-analysis found that children and adolescents on methylphenidate were 50% more likely to report abdominal pain (46 studies, over 4,600 youths) and over three times more likely to experience decreases in appetite (52 studies, over 4,800 youths) and weight (7 studies, over 850 youths) (Holmskov et al., 2017). An umbrella review of network meta-analyses and meta-analyses of RCTs and cohort studies examined 78 adverse events across 19 categories of 80 psychotropic medications in children and adolescents with mental disorders including data from nine network meta-analyses, 39 meta-analyses, 90 individual RCTs, and eight cohort studies with a total of 337,686 children and adolescents included

(Solmi et al., 2020). Five medications for ADHD were associated with significantly worse anorexia (atomoxetine, d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), four with insomnia (d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), three with weight loss (atomoxetine, methylphenidate, modafinil), two each with abdominal pain (methylphenidate, guanfacine), discontinuation due to adverse event (lisdexamphetamine, guanfacine), hypertension (atomoxetine, lisdexamphetamine), and sedation (clonidine, guanfacine), and one with QT prolongation (guanfacine)..

179. A meta-analysis of twelve studies with over 3,300 adults found that those taking atomoxetine were about 40% more likely to discontinue treatment due to adverse events than those on placebo (Cunill et al., 2013). A meta-analysis found that methylphenidate was more than twice as likely to induce insomnia as atomoxetine (10 studies, over 3,000 youths), but about half as likely to cause nausea (8 studies, over 2,750 youths) and vomiting 97 studies, over 2,500 youths), and about a sixth as likely to cause drowsiness (9 studies, over 2,800 youths) (Liu et al., 2017a). A meta-analysis of methylphenidate treatment studies reported a 55% increase in adverse events relative to placebo, none life-threatening (11 studies, over 2,100 youths), but a fivefold increase in anorexia (3 studies, 613 youths), and more than fourfold increase in insomnia (4 studies, 749 youths) (Ching et al., 2019).

180. Children treated with stimulants may show delays in expected height gains averaging two centimeters over one or two years. These sometimes attenuate over time and often reverse when treatment is stopped (Faraone et al., 2008). A medical records study from the USA comparing 32,999 stimulant-treated ADHD children with 11,515 controls found continuing declines in expected height over a four-year period. A study from Germany,

however, specifically addressed whether stimulants predicted patients being very short (i.e., being less than or equal to the third percentile of the population). After comparing 3,806 boys not treated with methylphenidate with 118 treated boys, the results did not indicate that methylphenidate increased the probability of this adverse outcome (McCarthy et al., 2018).

181. A study using Danish national registers followed over 700,000 individuals for an average period of almost a decade. Looking at 8,300 people with ADHD, stimulant users had more than twice the rate of cardiovascular events (primarily hypertension) than nonusers. These events were rare (Dalsgaard et al., 2014).

182. A meta-analysis of five studies with over 43,000 children and adolescents found no significant difference in adverse cardiac events between methylphenidate and atomoxetine, and a meta-analysis of three studies with 775 adults found no significant difference in adverse cardiac events between methylphenidate and placebo (Liang et al., 2018a).

183. A meta-analysis covering people of all ages reported methylphenidate was not associated with a higher risk of all-cause death (3 studies, over 1.4 million people), heart attack or stroke (3 studies, over half a million people) (Liu et al., 2019a).

184. A cohort study of over 1.8 million pregnancies in the United States and over 2.5 million pregnancies in the health registries of Denmark, Finland, Sweden, Norway, and Iceland reported that use of methylphenidate (but not amphetamines) by pregnant woman was associated with a higher risk for cardiac malformations from 12.9 per thousand infants to 16.5 per thousand infants (Huybrechts et al., 2018). A meta-analysis of four studies of three

million women also found that intrauterine exposure to methylphenidate was associated with a higher risk of cardiac malformations (Koren et al., 2020).

185. A meta-analysis examining the safety of atomoxetine found no significant increase in risk of irritability (3 studies, over 1,100 children) (Pozzi et al., 2018). Two others, one combining twenty studies with over 3,000 participants, and another combining 37 studies with over 3,800 participants, found no increase in risk of all-cause treatment discontinuation in youths (Catala-Lopez et al., 2017; Schwartz and Correll, 2014). However, a meta-analysis of twelve studies with over 3,300 adults found 40% greater rate of all-cause treatment discontinuation, leading to a conclusion that "atomoxetine has a poor benefit–risk balance for the treatment of adults with ADHD" (Cunill et al., 2013).

186. The Hong Kong Clinical Data Analysis & Reporting System, a population-based, electronic medical records database, was used to examine over 25,000 people receiving methylphenidate for ADHD. During the 90-day period prior to initiation of treatment, individuals with ADHD were greater than six times more likely to attempt suicide than after treatment. After ongoing treatment, the risk for attempted suicide was no longer elevated among patients with ADHD (Man et al., 2017).

187. Using the same Hong Kong database, the risk for psychosis did not differ between periods when patients were on and off methylphenidate treatment (Man et al., 2016).

188. A Swedish registry study of over 23,000 adolescents and young adults treated with methylphenidate for ADHD found no evidence for an association between psychosis and methylphenidate treatment. A year after initiation of methylphenidate treatment, the

incidence of psychotic events was 36% lower in in those with a history of psychosis and 18% lower in those without a history of psychosis relative to the period immediately before the beginning of treatment (Hollis et al., 2019).

Misuse and Diversion of Stimulant Medications

189. A systematic review of 109 studies concluded that the non-medical use of prescribed stimulants is a significant public health problem, especially in college students. Most non-medical use is associated with zero or minor medical effects, but adverse medical outcomes, including death, occur in some individuals, particularly when administered by non-oral routes. Academic and occupational performance enhancement were the most commonly cited motivations for non-medical use of stimulants, but there is little evidence that academic performance is improved by non-medical use in individuals without ADHD (Faraone et al., 2020).

190. The non-medical use of prescribed stimulants in individuals without ADHD is associated with lower educational attainment. A U.S. prospective study followed a nationally representative sample of over 8,300 high school seniors from age 18 to age 35. Those who used prescription stimulants non-medically were 17% less likely to earn a bachelor's degree than those who had neither medical or non-medical use (McCabe et al., 2017).

191. A retrospective study compared 4.4 million people dispensed ADHD medications with 6.1 million people dispensed asthma medications. Obtaining prescriptions from multiple prescribers or filling prescriptions at multiple pharmacies was highly correlated with abuse, misuse, and diversion. These "shopping" behaviors were four times more frequent in the

ADHD group than in the asthma group. Those dispensed stimulant medications were more than eight times as likely to engage in shopping behavior than those dispensed nonstimulants, but only one in 250 people with stimulant prescriptions engaged in shopping behavior (Cepeda et al., 2014).

192. A U.S. study of over 440,000 respondents found that use of illegal drugs or other non-medical use of prescription drugs preceded non-medical use of ADHD medication in more than three out of four cases (Sweeney et al., 2013).

193. A study examined Swedish national pharmacy dispensing data for all 56,922 individuals who filled a methylphenidate prescription between 2010 and 2011. 4,304 of the methylphenidate users (7.6%) overused medication as measured by dispensed prescriptions. Overuse was 17 times more frequent for ages 46-65 compared with ages 6-12 year. It was also twice as frequent among those with previous alcohol and drug misuse (Bjerkeli et al., 2018).

194. Large studies of calls to U.S. poison control centers related to ADHD medications find that intentional exposures, including suspected suicide and medication abuse and/or misuse is associated with admission to critical care units and, rarely, death especially when snorted or injected (Faraone et al., 2019a; King et al., 2018).

Which Non-Medication Treatments are Safe and Effective for ADHD?

Many non-medical treatments have been proposed for ADHD. Most of those offered on the Internet have not been tested or have been shown not to be effective. In this section, we distinguish between the effects of a treatment for ADHD symptoms and other benefits it may

confer. Due to the way these therapies are implemented and recorded in the medical record, large scale naturalistic studies of longer-term outcomes are not possible.

Behavioral and Cognitive-Behavioral Therapies

Behavioral treatments for ADHD are diverse in nature and have a different content and focus depending on the age of the patient. For preschoolers and grade-school children, parents are trained to improve their method of disciplining and interacting with their children. For adolescents and adults, therapy helps patients improve their organizational skills. For some patients, teachers contribute to a program aimed at improving the child's behavior. Some of these therapies focus on improving social behaviors and developing practical skills. In this section, however, we focus only on the ability of such treatments to improve ADHD symptoms. Readers should keep in mind that the failure of a treatment to substantially improve ADHD symptoms does not mean it is not useful for other purposes.

195. A meta-analysis found parent training for preschool children with ADHD to be associated with a moderate reduction in parent-reported ADHD symptoms (15 studies, few with active controls, over a thousand participants) and conduct problems (14 studies, few with active controls, over a thousand participants), but no significant results for independently assessed ADHD symptoms (6 studies, 403 participants) and conduct problems (6 studies, 311 participants). Independent assessments reported a small reduction in negative parenting (10 studies, 771 participants) (Rimestad et al., 2019).

196. A meta-analysis of 19 studies of cognitive behavior therapy (CBT) for adults with ADHD included 896 participants. It found associations with moderate improvements in self-

reported ADHD symptoms and self-reported functioning. But when limited to the two studies with active controls and blind assessors (N = 244 participants), it found only small improvements (Knouse et al., 2017). In another meta-analysis of 160 patients with adult ADHD, CBT led to large to moderate improvements compared with waiting list controls. In three studies of 191 patients CBT led to small to moderate improvements compared with active controls (Young et al., 2020).

197. A meta-analysis of 32 studies with over two thousand participants found that cognitive training resulted in small to moderate improvements in executive functioning in preschoolers with ADHD (Scionti et al., 2019).

198. A meta-analysis explored the effectiveness of meditation-based therapy. It found moderate reductions in ADHD symptoms in both children and adolescents (6 RCTs, 240 participants) and adults (6 RCTs, 339 participants), but half the studies did not use active controls. Removing studies with waiting list controls made results nonsignificant. The authors concluded "there is insufficient methodologically sound evidence to support the recommendation of meditation-based therapies as an intervention aimed to target ADHD core symptoms or related neuropsychological dysfunctions in children/adolescents or adults with ADHD" (Zhang et al., 2018).

199. A meta-analysis found that social skills training for youth with ADHD did not improve teacher-assessed social skills (11 studies, over 1,200 youths), general behavior (8 studies,

over 1,000 youths), or school performance and grades (5 studies, over 600 youths) (Storebo et al., 2019).

200. A meta-analysis of ten studies with 893 youths reported that organizational skills interventions led to moderate reductions in parent-reported inattention symptoms (Bikic et al., 2017).

Computer-based Cognitive Training and Neurofeedback

201. A meta-analysis of five randomized controlled trials (RCTs) with 263 participants exploring the efficacy of neurofeedback found a small reduction in inattention, but no significant reduction in hyperactivity-impulsivity or overall ADHD symptoms with ratings by probably blinded evaluators (researchers measuring outcomes did not know if patients were receiving the active or control treatment) (Micoulaud-Franchi et al., 2014). A more recent meta-analysis of ten RCTs with 256 participants found no effect on inattention symptoms, but a small-to-medium reduction in hyperactivity-impulsivity symptoms (Van Doren et al., 2019).

202. The European ADHD Guidelines Group published meta-analyses of cognitive training and neurofeedback for youth. Probably blinded cognitive training studies with active controls (6 studies, 287 youths) reported no significant reduction in ADHD symptoms. But they did find moderate improvements in verbal working memory (5 studies, 263 youths). There were no significant effects on academic outcomes in math and reading (95 studies, 290 youths) (Cortese et al., 2015). Blinded neurofeedback studies with active/sham controls (6 studies, 251 participants) found no significant reduction in ADHD symptoms (Cortese et al., 2016a).

203. A meta-analysis found that working memory training led to short-term improvements in both verbal working memory (21 studies, over 1,300 participants) and visuospatial working memory (18 studies, over 1,000 participants), with "no convincing evidence that even such near-transfer effects are durable." Moreover, most of the studies lacked active controls (Melby-Lervag and Hulme, 2013).

Supplements, Diet, and Exercise

204. Omega-3 fatty acid supplementation was associated with small-to-medium improvements in ADHD symptoms in three meta-analyses (ten studies with 699 participants, 16 studies with 1,408 participants, 7 studies with 534 participants) (Bloch and Qawasmi, 2011; Chang et al., 2018; Hawkey and Nigg, 2014). Another meta-analysis, with 18 studies and 1,640 participants, found tiny improvements (Puri and Martins, 2014).

205. A meta-analysis found no evidence of any effect of omega-3 fatty acid supplements on parent-rated (5 studies, 650 children) or teacher-rated (3 studies, 598 children) emotional lability symptoms, or parent-rated (8 studies, 875 children) or teacher-rated (6 studies, 805 children) oppositional symptoms in children with ADHD (Cooper et al., 2016).

206. A meta-analysis of five double-blind crossover studies with 164 participants found that restricting synthetic food colors from children's diets was associated with a small reduction in ADHD symptoms (Nigg et al., 2012).

207. A meta-analysis of ten studies (300 children) found exercise was associated with a moderate reduction in ADHD symptoms, but had no significant effect after adjusting for publication bias (Vysniauske et al., 2020). Another meta-analysis found no significant effect

of exercise on either hyperactivity/impulsivity (4 studies, 227 participants) or inattention symptoms (6 studies, 277 participants), but significant reductions in anxiety and depression (5 studies, 164 participants) (Zang, 2019).

208. A nationwide population study using the Swedish Twin Register identified almost 18,000 twins who completed a web-based examining the relationship between inattention and hyperactivity/impulsivity subtypes and dietary habits. The two subtypes of ADHD exhibited very similar associations. Both had significant associations with unhealthy diets. Both were more likely to be eating foods high in added sugar and neglecting fruits and vegetables while eating more meat and fats. After adjusting for degree of relatedness of twins (whether monozygotic or dizygotic) and controlling for the other ADHD subtype, the associations remained statistically significant for inattention, but diminished to negligible levels or became statistically nonsignificant for hyperactivity/impulsivity. Even for persons with inattention symptoms, adjusted correlations were small (never exceeding r = 0.10), with the strongest associations being for overall unhealthy eating habits and eating foods high in added sugar. Among over 700 pairs of monozygotic ("identical") twins, it found small but robust associations between inattention symptoms and unhealthy eating habits, and especially with consumption of foods high in added sugar. For hyperactivity/impulsivity symptoms, the association with unhealthy eating habits was weaker, and the association with consumption of foods high in added sugar became statistically insignificant (Li et al., 2020).

Discussion

This work has curated evidence-based statements about ADHD which paint a picture of the disorder that we summarize as follows:

> ADHD is a chronic disorder in which developmentally inappropriate symptoms of inattention and/or hyperactivity/impulsivity lead to impairments in many aspects of living. The disorder, which starts in childhood or early adolescence and is more common in boys than girls, affects 5.9% of youth and 2.8% of adults worldwide. There are multiple genetic and environmental risk factors that accumulate in various combinations to cause ADHD. These risk factors lead to subtle changes in multiple brain networks and in the cognitive, motivational, and emotional processes they control. People diagnosed with ADHD have an elevated risk for school failure, antisocial behavior, other psychiatric problems, somatic disorders, drug and alcohol abuse, accidental injuries, and premature death, including attempted and completed suicide. As a result, ADHD costs society hundreds of billions of dollars each year. Several medications are safe and effective for treating ADHD and for preventing many adverse outcomes. Non-medication treatments are available but, compared with medications, are less effective for reducing inattention, hyperactivity, and impulsivity.

Despite this large body of evidence, we have much more to learn about the disorder and its various manifestations. Epidemiologic studies have taught us that ADHD occurs around the world, but we know little about how culture affects the expression of ADHD symptoms or the response to treatment. Because most research about ADHD is based on Caucasian and East

Asian samples, we must be cautious in generalizing our assertions to other groups. In addition, far more research pertains to males than females. We also need to learn more about ADHD in older adults. Future research into ADHD should examine more diverse samples from a wider range of cultural contexts.

We have learned much about the causes of ADHD but are only beginning to understand how genes and environment combine to cause the disorder and affect the brain to produce symptoms and impairments. Some of these causes may be shared with ADHD's somatic comorbidities. Examples include oxidative stress, inflammation, and insulin resistance. Future work should focus on biological and psychological causal mechanisms to find points of intervention that will improve the effectiveness of medical and non-medical treatments and, eventually, prevent onset of the disorder. Although the medications that treat ADHD are highly effective, we need better methods to prevent the misuse and diversion of these medications, especially among adolescents and young adults (Faraone et al., 2020).

Many decades of research have led to a method of diagnosing ADHD that is highly valid as a predictor of treatment response, family history of ADHD, many clinical features, measures of brain structure and function, and adverse outcomes. Nevertheless, there are several new directions for diagnosis. One is to better understand the nature and causes of emotional symptoms in ADHD and whether these should be incorporated into diagnostic criteria (Faraone et al., 2019b). Another is to determine if and how mild or sub-threshold cases of ADHD should be diagnosed and treated (Kirova et al., 2019). Different trajectories of ADHD across the life-cycle need to be further investigated.

Many researchers are trying to develop computerized or biological tests using information about the patient's behavior, brain and/or genetic makeup. The hope is that such tests will one day diagnose the disorder, predict a personalized approach to treatment or assist clinicians in these areas. Others are working on methods that use the vast data available from medical records to predict which patients with ADHD are at greatest risk for adverse outcomes later in life. Such work may someday allow healthcare systems to allocate resources to the highest risk patients.

Although we have good treatments for ADHD, even the best treatments are only partially effective. The future of treatment for ADHD will include new medications currently in development and a stronger evidence base for novel non-medication treatments for treating ADHD symptoms or associated impairments, such as trigeminal nerve stimulation (McGough et al., 2019) and game-based treatments (Craven and Groom, 2015; Dovis et al., 2015). And more data are needed to improve existing non-medication treatments and to test the efficacy of traditional therapies such as acupuncture, yoga, and Ayurvedic therapies. Also, little is known about how the somatic disorders that co-occur with ADHD interact with treatments for ADHD and how the symptoms of the disorder affect somatic outcomes. We need to learn more about how duration of treatment affects outcomes over longer periods of time.

We also know little about stigma and ADHD. Stigmatizing attitudes toward ADHD are common and may play a role in socially and clinically important outcomes. These negative attitudes affect patients at all stages of their life. Such attitudes have been documented among

individuals at all ages and in all groups, including family, peers, teachers, clinicians, and even individuals with ADHD themselves (Lebowitz, 2016).

Despite these and other gaps in our knowledge about ADHD, nearly two and a half centuries after the first textbook description of an ADHD-like syndrome, the statements about ADHD which we have curated, make us confident that the contemporary diagnosis of the disorder is a valid and useful category that can be used around the world to improve the lives of the many people who suffer from the disorder and its complications.

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