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The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder

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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 2000 participants or meta-analyses from five or more studies or 2000 or more participants. We excluded meta-analyses that did not assess publication bias, except for meta-

Outcome
Genetics
Brain

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 80 authors from 27 countries and 6 continents. The contents of the manuscript are endorsed by 366 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.

1. 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.

2. 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 2000 participants. We required meta-analyses to report data from five or more studies or 2000 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.

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

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.

3. 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 80 authors from 27 countries and 6 continents (Supplemental Figure 2). It has been endorsed by 366 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.

4. 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, b, 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.

5. 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 et al., 2018; Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher and Hawkridge, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018a, b; 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 5700 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)

6. 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 U.S. 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 5300 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 youths is consistent with a meta-analysis of 21 studies with over 1600 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 %. 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., 2021).

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).

7. 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.

7.1. 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 et al., 2019a,b).

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, 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 sub-threshold 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 8000+ children with autism spectrum disorder (ASD) and/or ADHD and 5000 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., 2019a,b) (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).

7.2. 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 9300 youths) and hyperactivity-impulsivity symptoms (23 studies, over 7800 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 2500 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 4700 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., 2018a) (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., 2021).

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 2246 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 1139 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 two 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 geo-linking 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 25 % 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 7200 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 4826 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)

7.3. 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 2100 participants) (Wang et al., 2017). Another pair of meta-analyses likewise found no difference in serum iron levels (six studies, over 1700 participants) but small-to-moderate

reductions in serum ferritin (12 studies, over 6000 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 1067 patients with ADHD born between 1998 and 1999 with 1067 matched controls. Lower maternal vitamin D levels were associated with a roughly 50 % greater likelihood of ADHD in their children (Sucksdorff et al., 2021).

7.4. Environmental correlates of ADHD: events during pregnancy and birth

49 A meta-analysis of twelve studies with over 6000 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).

7.5. 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 4122 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).

8. 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.

8.1. Performance deficits in psychological processes

63 A meta-analysis of 137 studies with over 9400 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 1900 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, 1493 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 3900 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., 2021).

66 A meta-analysis of 37 studies with more than 2300 participants found a small-to-moderate association between ADHD and risky decision-making (Dekkers et al., 2016). Another meta-analysis, combining 22 studies with 3850 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 8200 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 3400 youths), inattention symptoms (26 studies, over 5900 youths), or hyperactivity-impulsivity symptoms (24 studies, over 4900 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 2000 participants) and small-to-moderate improvement in inhibitory control (26 studies, over 2200 participants) (Pauli-Pott et al., 2020).

8.2. 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 4100 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 3242 participants. The differences seen in children were not seen in adolescents or adults (Hoogman et al., 2017, 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 1870 participants (Norman et al., 2016) while medial frontal reductions were specific to ASD in 66 data sets with 3610 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 1870 participants (Norman et al., 2016), while the inferior frontal dysfunction was specific relative to autism in 3610 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/1161 participants, and 42 datasets/2005 participants, respectively (Lukito et al., 2020; Norman et al., 2016). Another meta-analysis including 130 fMRI studies with 1914 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 1250 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, 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).

9. 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.

9.1. 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).

9.2. 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).

9.3. 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 50–64 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., 2020). 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).

9.4. Other somatic disorders

87 A meta-analysis of 18 studies with more than 2500 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) and 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 1700 persons), moderately greater frequency of night awakenings and moderately lesser likelihood of being rested at wake-up (5 studies, over 1100 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 8000 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 6817 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 5671 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 18–64 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 allergic 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).

10. 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.

10.1. Quality of life

101 A meta-analysis of seven studies with over 5000 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 2300 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).

10.2. Emotional and social impairment

103 A study of over 8600 youths from the U.S. National Health Interview Survey found that those with ADHD were four times as likely to have a high level of emotional and conduct problems and three times as likely to have a high level of peer problems. It also found that they were eight to ten times as likely to manifest a high level of impairment 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 youths 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 1900 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 3750 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).

10.3. 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 40–50 % 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 8000 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).

10.4. 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., 2018b).

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).

10.5. 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 3900 individuals), which is much higher than the prevalence in the population (Beaudry et al., 2021).

122 A study using a nationally representative American sample of over 5000 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 youths 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).

10.6. 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 for 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, and 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).

10.7. Substance use disorders

128 A meta-analysis of twelve studies covering over 5400 people found that those with ADHD were almost three times more likely to be nicotine-dependent. Combining eleven studies with almost 2400 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 1800 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).

10.8. Other

131 Studies of 2.7 million girls from Denmark (Ostergaard et al., 2017), 380,000 from Sweden (Skoglund et al., 2019) and 7500 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 U.S. 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 2025 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 3685 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).

11. 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 €9860 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 7000 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 $2728 for non-ADHD family members of ADHD patients, almost double the $1440 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 €1500 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 €2800 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 5000 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 over a third of a million 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 €5500. With additional social transfers, the total rose to €8000 (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 2380 individuals first diagnosed with ADHD as adults. Their direct healthcare costs in the year following diagnosis averaged €4000. 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).

12. 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).

12.1. Effects of medications on symptoms: results from randomized, controlled clinical trials

148 Protocols for using medications for ADHD are well described in detailed guidelines prepared by professional health care associations (Alliance, 2011; Banaschewski et al., 2018; Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher and Hawkridge, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018a,b; 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 2000 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 1600 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 1500 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 1600 participants reported that atomoxetine moderately reduced ADHD symptoms. (Cheng et al., 2007).

154 A meta-analysis found that methylphenidate (13 studies, over 2200 adults) and lisdexamfetamine (five studies, over 2300 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 1300 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 2900 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 1300 participants found stimulants to be highly effective in reducing aggression, oppositional behavior, and conduct problems in youths 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).

12.2. 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 0–320); 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 6400 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 1463 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 4200 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 4557 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 9421 youths with ADHD and 2986 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 above an annual average cumulative defined daily dose of 84 halved the risk for traumatic brain injuries, after adjusting for confounders (Liao et al., 2018).

164 A nationwide study compared 7200 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 6200 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 5000 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 2300 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 1300 participants, nicotine (6 studies, 884 participants), cocaine (7 studies, 950 participants), or cannabis abuse or dependence (9 studies, over 1100 participants) (Humphreys et al., 2013).

173 A nationwide study of over 7500 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 those 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).

12.3. *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 youths 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 4180 ADHD patients in the ENIGMA-ADHD

Working Group set of 36 cohorts from around the world (Hoogman et al., 2017, 2019).

12.4. 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 4600 youths) and over three times more likely to experience decreases in appetite (52 studies, over 4800 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 3300 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 3000 youths), but about half as likely to cause nausea (8 studies, over 2750 youths) and vomiting (97 studies, over 2500 youths), and about a sixth as likely to cause drowsiness (9 studies, over 2800 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 2100 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 over 32,000 stimulant-treated ADHD children with over 11,000 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 3806 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 8300 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 women 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 1100 children) (Pozzi et al., 2018). Two others, one combining twenty studies with over 3000 participants, and another combining 37 studies with over 3800 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 3300 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 over 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 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).

12.5. 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 8300 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. 4304 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).

13. 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.

13.1. 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 four studies with 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 1200 youths), general behavior (8 studies, over 1000 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).

13.2. 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).

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 1300 participants) and visuospatial working memory (18 studies, over 1000 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).

13.3. 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 1408 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 1640 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 survey 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).

14. 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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Appendix A. Supplementary data

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