



King's Research Portal

DOI:

[10.1016/S2215-0366\(16\)30032-3](https://doi.org/10.1016/S2215-0366(16)30032-3)

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Asherson, P., Buitelaar, J., Faraone, S. V., & Rohde, L. A. (2016). Adult attention-deficit hyperactivity disorder: key conceptual issues. *The Lancet Psychiatry*, 3(6), 568-578. Advance online publication. [https://doi.org/10.1016/S2215-0366\(16\)30032-3](https://doi.org/10.1016/S2215-0366(16)30032-3)

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Attention-deficit hyperactivity disorder 2

Adult attention-deficit hyperactivity disorder: key conceptual issues

Philip Asherson, Jan Buitelaar, Stephen V Faraone, Luis A Rohde

Lancet Psychiatry 2016;
3: 568–78

Published Online
May 13, 2016

[http://dx.doi.org/10.1016/S2215-0366\(16\)30032-3](http://dx.doi.org/10.1016/S2215-0366(16)30032-3)

See *Series* page 555

This is the second in a *Series* of two papers about attention-deficit hyperactivity disorder

MRC Social Genetic and Developmental Psychiatry, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK (Prof P Asherson PhD); Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience and Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, Netherlands (J Buitelaar PhD); Department of Psychiatry and Department of Neuroscience and Physiology, State University of New York (SUNY) Upstate Medical University, Syracuse, NY, USA (S V Faraone PhD); K G Jebsen Centre for Neuropsychiatric Disorders, Department of Biomedicine, University of Bergen, Bergen, Norway (S V Faraone); Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (Prof L A Rohde); and National Institute for Developmental Psychiatry, Brazil (Prof L A Rohde)

Correspondence to: Prof Philip Asherson, MRC Social Genetic and Developmental Psychiatry, Institute of Psychiatry Psychology and Neuroscience, King's College London, SE5 8AF London, UK
philip.asherson@kcl.ac.uk

For many years, attention-deficit hyperactivity disorder (ADHD) was thought to be a childhood-onset disorder that has a limited effect on adult psychopathology. However, the symptoms and impairments that define ADHD often affect the adult population, with similar responses to drugs such as methylphenidate, dexamphetamine, and atomoxetine, and psychosocial interventions, to those seen in children and adolescents. As a result, awareness of ADHD in adults has rapidly increased and new clinical practice has emerged across the world. Despite this progress, treatment of adult ADHD in Europe and many other regions of the world is not yet common practice, and diagnostic services are often unavailable or restricted to a few specialist centres. This situation is remarkable given the strong evidence base for safe and effective treatments. Here we address some of the key conceptual issues surrounding the diagnosis of ADHD relevant to practising health-care professionals working with adult populations. We conclude that ADHD should be recognised in the same way as other common adult mental health disorders, and that failure to recognise and treat ADHD is detrimental to the wellbeing of many patients seeking help for common mental health problems.

Attention-deficit hyperactivity disorder (ADHD) as a lifespan disorder

ADHD is classified in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5) as a childhood-onset neurodevelopmental disorder, defined by the presence of developmentally inappropriate and impairing levels of inattention, hyperactivity, and impulsivity.¹ Epidemiological surveys find that 5–6% of children meet DSM-IV criteria for ADHD,^{2,3} with a slightly higher prevalence expected when DSM-5 criteria are applied.⁴ Meta-analysis of follow-up studies of children with ADHD found that 15% of children retained the full diagnostic criteria by the age of 25 years, with a further 50% of those meeting subthreshold criteria with persistence of ADHD symptoms causing continued impairments.⁵ Another study using a survey approach of 629 adults in ten countries found that 50% of children with ADHD continued to meet diagnostic criteria for ADHD as adults.⁶ More recently, two follow-up studies of children from child mental health clinics in southeast England and the Netherlands, meeting DSM-IV combined-type (inattention and hyperactivity-impulsivity) criteria for ADHD, found far higher persistence rates of ADHD in young adulthood, in the region of 80%.^{7,8} The increased prevalence of persistence in these studies might be related to the focus on combined-type cases, greater severity of ADHD in patients treated in European child mental health services, and the use of informant data when establishing the diagnosis at follow-up.^{7,9,10}

These findings are largely consistent with the estimated prevalence of ADHD in adults, which ranges from 2·5% to 3·4% in meta-analytic studies of population surveys.^{11,12} However, all adults meeting diagnostic criteria for ADHD did not necessarily meet full ADHD criteria during their

childhood. The present DSM-5 criteria allow for this possibility by stating that the criterion for age of onset is that “several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years”.¹ This criterion allows children with subthreshold levels of ADHD symptoms and no impairment to meet diagnostic criteria for ADHD later in life and raises the possibility that the full diagnosis of ADHD might emerge at different developmental stages. The traditional explanation for this is that children with high intelligence quotients (IQs) or well developed executive function skills, who are well supported by structured home and school settings, might make use of so-called external scaffolding that facilitates compensatory behavioural mechanisms. Once such external scaffolding is removed, when leaving home and school for example, the full syndrome could emerge. Interestingly, this account of later-onset ADHD shows the interdependence of the association between symptoms and impairments of the disorder. An alternative hypothesis suggests that ADHD symptom expression depends on the efficiency of executive control processes.¹³ Poor maturation of cortical control during the adolescent years might lead to later-emerging ADHD in some cases. Findings suggest that a late-onset ADHD-like syndrome might emerge, even in the absence of substantial childhood symptoms, perhaps reflecting an acquired syndrome with a different set of causal risk factors.^{10,14}

Nevertheless, for the vast majority of patients diagnosed with ADHD in clinical settings during adulthood, there is a clear account of ADHD from childhood. Therefore, to provide an understanding of the developmental trajectory of the disorder, the way it presents in adults, and its effect on adult mental health is of considerable interest. Across many regions of the world, ADHD is only just emerging as

a disorder that is diagnosed and treated by adult mental health services, despite the high prevalence of adult ADHD and established links to psychosocial, functional, and mental health problems. Even more striking are the very high rates of undiagnosed or untreated ADHD within adult clinical and forensic services. Several studies point to high rates of undiagnosed ADHD in prisons (roughly 26%),¹⁵ addiction units (roughly 12%),^{16,17} and general adult mental health services (roughly 16%).¹⁸ Rates of adult ADHD in primary care are less well established, but it is clear that a substantial group of patients presenting with non-psychotic long-term mental health problems meet diagnostic criteria for ADHD.¹⁹

The diagnostic construct of ADHD

For many years, researchers have argued that most mental health disorders reflect the extreme and impairing tail of one or more continuously distributed traits. Present research strategies, such as the Research Domain Criteria (RDoC), increasingly focus on delineating the underlying neurobiological substrates that underpin dimensions of psychopathology.²⁰ Among these, ADHD is one of the best examples in which no point of rarity can be found in the distribution of ADHD symptoms and impairments seen throughout the population.²¹ Symptoms of ADHD cluster together into two key dimensions of inattention and hyperactivity-impulsivity, are reliably measured, and are strong predictors of functional impairments, but they reflect continuous traits rather than a categorical disorder.^{22,23} Of particular relevance to adult ADHD is the relative persistence of inattention and improvements in hyperactive-impulsive symptoms during development, so that many patients who had the combined type presentation of ADHD as children present with predominantly inattentive symptoms as adults.^{7,23,24}

Many studies support the continuous nature of ADHD symptoms, although most of this work has been done in children rather than in adults.^{21,25–27} These studies report the following: estimates of heritability are similar for continuous ratings of ADHD symptoms in the general population and the categorical disorder (around 70–80%);²⁸ group heritability estimates show that genetic risk for the disorder is shared with genetic risk for the continuous trait;^{26,29} polygenic risk scores for ADHD predict ADHD trait scores in general population samples;³⁰ the association of ADHD with cognitive performance deficits is similar for the clinical disorder and ADHD symptom scores in general population samples;³¹ and risk of impairment shows a linear relationship with severity of ADHD symptoms in population samples.^{27,32} As a result, the boundary between patients with and without a clinically significant disorder is defined by the presence of clinically significant impairment. Although the presence of impairment is a defining characteristic of many adult mental health disorders, such as anxiety and depression, the inclusion of impairment criteria is particularly

important for trait-like disorders such as ADHD and personality disorders, where the symptoms do not reflect a change from the premorbid state. Thus, the diagnosis of ADHD is to some extent dependent on perceptions of what amounts to clinically significant impairment. However, the symptoms of inattention and hyperactivity-impulsivity are known to reflect individual differences in brain structure and function that largely derive from genetic influences,³³ and the associated impairments are often severe.³⁴

In clinical practice, the continuous nature of ADHD should not present diagnostic difficulties in moderate-to-severe cases, but might cause difficulties in mild cases with more subtle forms of impairment. Careful attention is needed to assess the effect of ADHD symptoms on impairment and quality of life, including an understanding of the broader range of problems linked to ADHD (eg, executive function [self-regulation] impairments, sleep problems, irritability, and internal restlessness), in addition to functional impairments such as traffic accidents and occupational underachievement. Therefore, some individuals, who seem to function well, might nevertheless suffer from a substantial mental health problem related to ADHD. When assessing impairments, it is important to take into account that even minor levels of symptoms can cause considerable distress to individuals because of the chronic and persistent nature of ADHD symptoms, which are experienced by people with ADHD on a daily basis.

Rater effects and measurement of ADHD symptoms

One factor complicating the assessment of ADHD is the change in informant during development. Throughout most of childhood and early adolescence, the primary informants for diagnostic information are parents and teachers, who report mainly on the basis of observed behaviours. For this reason, the ADHD symptoms listed in DSM-IV/5 and International Classification of Diseases (10th edition; ICD-10) are largely descriptions of observed behaviours rather than subjective reports of mental state changes. Rater effects turn out to be important in the assessment of ADHD.^{9,35} Several pieces of evidence indicate that informant report (eg, parents) is more accurate than self-report, with adults tending to under-rate their symptoms. Quantitative genetic studies using ADHD self-report scales in general population twin samples find far higher heritability for parent report (around 70–80%) than for self-report (around 35–50%).³⁶ Although these figures might be related to rater bias in parents inflating heritability estimates, this seems unlikely when converging evidence is considered. For example, high heritability estimates based on diagnosed cases of adult ADHD (using multiple sources of information) are similar to those of childhood cases of ADHD.²⁸ Rater effects were also seen in a 6-year follow-up study of children with combined -type ADHD.

Panel 1: Age-appropriate attention-deficit hyperactivity disorder symptoms (DSM-5)

- Mind seems elsewhere, even in the absence of any obvious distraction
- Starts tasks, but quickly loses focus and is easily side-tracked
- Fails to finish tasks in the workplace
- Reporting unrelated thoughts
- Problems returning calls, paying bills, keeping appointments
- Difficulty in managing sequential tasks; difficulty in keeping materials and belongings in order; messy, disorganised work
- Poor time management
- Tends to fail to meet deadlines
- Feeling restless
- Unable or uncomfortable being still for an extended time, such as in restaurants or meetings
- Might be perceived by others as being restless and difficult to keep up with
- Butts into conversations or activities, might start using other people's belongings without permission, might intrude into or take over what others are doing

Higher prevalence of persistent ADHD was found when the diagnosis was based on parent report than on self-report. Moreover, parent-reported ADHD, but not self-reported ADHD was subsequently validated by the association with cognitive performance measures on sustained attention and inhibitory control tasks.³⁵

An attempt to improve the criteria by including more age-appropriate descriptions has been included in DSM-5 (panel 1). These descriptions of ADHD symptoms are nevertheless largely behavioural and might still be subject to rater effects. One alternative that could lead to more accurate self-ratings of ADHD is to focus on subjective accounts of mental state phenomena, in the same way as individuals might report feeling depressed, experiencing a panic attack, or hearing a voice. Surprisingly, there have been only limited attempts to pursue such a phenomenological approach in ADHD. Another option is to develop more objective cognitive or neuroimaging tests for ADHD. A further approach is to provide a more detailed account of the types of behavioural problems reported by adults with ADHD. As a result, providing alternative accounts of adult ADHD that might provide more objective measures of ADHD symptoms, or a better understanding of the mental state changes and behavioural problems experienced by adults is of considerable interest.

Cognitive and neuroimaging markers of ADHD

Cognitive performance measures of attention and impulsivity have been suggested in neurocognitive studies as markers of ADHD symptoms, with several companies marketing different versions of continuous performance tasks (sustained attention and inhibitory control tasks that measure errors of omission,

commission, and reaction time). The assumption made is that omission errors reflect behavioural inattention, commission errors reflect behavioural impulsivity, and reaction time variability reflects fluctuations in attention. An additional measure has been the use of actigraph data to capture overactivity during experimental tasks or in daily life. Of these measures, activity level rather than cognitive performance might provide the best prediction of adult ADHD.^{7,37,38} Preliminary studies show reasonable separation of cases from healthy controls when all parameters are combined (sensitivity and specificity around 85–90%), but poor separation of cases from clinical controls,^{37,38} due to heterogeneity and absence of specificity of the cognitive impairments to ADHD. Persistence of the disorder from childhood into adulthood might also be predicted by objectively measured activity level but not by cognitive performance measures.⁷

Cognitive performance measures have also been investigated in children as predictors of the clinical response to methylphenidate. Although drug effects on cognitive performance measures are observed, these do not seem to covary with the clinical response, suggesting that the test variables cannot be considered proxies for ADHD symptoms.^{39,40} Another approach has been the use of electroencephalography as a cost-effective measure of neuronal activity, in particular the use of the theta-beta ratio (TBR) as an aid to diagnosis. Unfortunately, available publications and meta-analyses were unable to find consistent case-control differences, indicating that TBR has limited value as a diagnostic tool.⁴¹

Further research is clearly needed to identify clinically useful cognitive and neural biomarkers of ADHD, although these approaches are hampered by the marked heterogeneity of the cognitive and neural deficits seen in adult ADHD. This obstacle complicates the identification of cognitive or neural measures, although it is feasible that such approaches will identify more homogeneous subtypes of ADHD. Nevertheless, promising findings are beginning to emerge from neuroimaging studies, showing the increased sensitivity of measures of neural activity compared with cognitive performance measures.³³ Examples include consistent evidence of reduced activation of the ventral striatum when anticipating a reward⁴² and deficits in deactivation of the default mode network when engaging in cognitive tasks.⁴³

One particularly interesting approach is to look for markers of clinical change which covary with the clinical disorder, either during the treatment response to drugs or during follow-up studies. An investigation of the covariation of ADHD symptoms with regional brain activation patterns during a functional MRI (fMRI) go/no-go paradigm (assessing inhibitory processes) during treatment with methylphenidate and atomoxetine found that ADHD symptom improvement was associated with reductions in bilateral motor cortex activation for both treatments. Symptom improvements were also

differentially related to gains in task-related activations for atomoxetine and reductions for methylphenidate in the right inferior frontal gyrus, left anterior cingulate, and bilateral posterior cingulate cortex.⁴⁴ Although these preliminary findings are proof-of-principle at this stage, they do show the value of outcome studies in identification of neural biomarkers for ADHD symptoms.

Characteristic features of ADHD that support the diagnosis

Focus on the mental state of adult patients with ADHD has been of more immediate clinical value than the use of cognitive or neuroimaging data. Symptoms such as feeling physically restless, emotional dysregulation, excessive mind wandering, and sleep-onset insomnia are all clinically relevant symptoms that are commonly seen in adult ADHD. Surprisingly, these symptoms are not well studied in ADHD despite their potential value in clinical practice.

Sleep problems

Disturbed sleep is reported by 70% or more of adults with ADHD. In particular, diurnal rhythm abnormalities have been identified that are associated with sleep-onset insomnia.⁴⁵ Although not formally a criterion for ADHD, the presence of sleep-onset problems associated with reports of ADHD symptoms can be used to support the diagnosis of ADHD. For example, many adults with ADHD complain that they are too physically and mentally restless to fall asleep. We should also be alert to the possibility that sleep apnoea might cause symptoms of ADHD.⁴⁶

Emotional dysregulation

Another associated feature of ADHD, recommended by DSM-5 as supporting the diagnosis, is emotional dysregulation including low frustration tolerance, irritability, and mood lability.¹ Several reports highlight the very high frequency of emotional dysregulation in adult ADHD with either rating scale measures^{47–49} or experience sampling of mood states throughout the day.⁵⁰ These studies show that emotional dysregulation is present in non-comorbid cases of adult ADHD and predicts impairment beyond that explained by inattention and hyperactivity-impulsivity.^{47,48,50} A common set of genes influence emotional dysregulation and core ADHD symptoms in children.⁵¹ Importantly, emotional dysregulation in adults with ADHD responds to stimulants and atomoxetine with a similar effect size as the core ADHD symptoms of inattention and hyperactivity-impulsivity.^{52–55} Although these findings suggest that symptoms of emotional dysregulation should be viewed as a core component of ADHD, because they frequently occur in other disorders (eg, anxiety, mood disorders, substance misuse, and personality disorders) they are not used as primary diagnostic criteria for the classification of ADHD.

Excessive mind-wandering

Another common feature of adult ADHD is excessive mind-wandering, also referred to as mental restlessness.^{56–58} In DSM-5, mind-wandering is briefly mentioned as the occurrence of unrelated thoughts. Mind-wandering occurs when a person's mind drifts away from a task and focuses on internal thoughts and images that are unrelated to the task or situation at hand. Although mind-wandering is a universal experience, some forms of mind-wandering are detrimental because they arise spontaneously and interfere with task performance. Interestingly, mind-wandering is associated with performance deficits overlapping with those seen in ADHD, including educational performance, driving accidents, and cognitive performance errors such as commission errors and reaction time variability on sustained attention and inhibition tasks.⁵⁹ Mind-wandering is also strongly correlated with neural activity within the brain's default mode network, which has consistently shown deficient deactivation during task conditions in ADHD.^{59,60} For these reasons, spontaneous mind-wandering, detrimental to performance, has been proposed as a mechanism explaining some of the symptoms and impairments of ADHD.⁵⁶

Several studies have reported increased spontaneous mind-wandering in adult ADHD.^{57,58} Adults with ADHD frequently report a distractible mental state with multiple unrelated thoughts that are constantly on the go and jump from one topic to another.⁶¹ Mind-wandering is also a feature of other mental health disorders such as depressive ruminations or obsessional thoughts and might therefore lack specificity. However in ADHD, mind-wandering is characterised by unfocused, short-lived distractible thoughts with no pattern of repeated thoughts or abnormality of content.⁶¹

Our research⁶² showed that excessive mind-wandering was strongly correlated with ADHD symptoms, was a strong predictor of the diagnosis (sensitivity and specificity around 90% for case-control differences), co-varied with ADHD symptoms over a 6-month period, and was a better predictor of ADHD-related impairments than the inattentive and hyperactive-impulsive symptoms of ADHD. Excessive mind-wandering has several potential advantages as a clinical measure because it reflects a characteristic feature of the mental state reported by adults with ADHD and can be measured with rating scales^{56,58} and experience sampling in daily life⁶³ or during sustained attention tasks.⁵⁷

Executive function

Another aspect of ADHD is behaviour reflecting difficulties with executive functions such as inhibition and working memory. Whether dysfunctions of executive control reflect primary causal processes in ADHD is hotly debated. For example, cognitive test measures of executive control do not seem to predict long-term outcome in ADHD,^{35,64} are not strong predictors of

ADHD symptoms and impairments,⁶⁵ and are neither necessary or sufficient to cause ADHD.⁶⁶ Furthermore, the results of neuropsychological tests of executive functions do not correlate highly with behavioural rating scale measures of executive dysfunction.⁶⁷ Nevertheless, at a behavioural level, ecologically valid descriptions of executive functions seem to show core behavioural problems that are strongly related to ADHD and respond well to drug treatments for ADHD.^{68–70} These clinically useful measures can be captured by the Brief Rating Inventory of Executive Function,⁷¹ which assesses organising, prioritising, and initiating work; focusing, sustaining, and shifting attention to tasks; regulating alertness, sustaining effort, and processing speed; managing frustration and regulating emotions; using working memory and accessing recall; and monitoring and self-regulation of behaviour.

Course and outcome

Reasons for the persistence and desistence of ADHD into adulthood are not well understood, but are of considerable interest because they identify potential targets for early prevention and treatment. Factors influencing course and outcome include general cognitive ability, severity of ADHD, causal factors (genes and environment), brain maturation and development, and the presence of co-occurring mental health and neurodevelopmental disorders.³³ Protective factors, such as exercise,⁷² might also have an important role. One study⁷³ using an adoption at birth design to control for genetic influences showed the possible role of hostile parenting using mothers' reports of their own hostile behaviour towards their child. In this study, hostile parenting was both evoked in parents by having an infant with high levels of impulsive and overactive behaviour, but also acted as a causal influence by increasing the later development of ADHD symptoms in children. Consistent with this finding, another study found that high levels of parental criticism were associated with persistence of hyperactive behaviour between the ages of 7 and 13 years, even after controlling for oppositional defiant behaviour.⁷⁴ Whether such parental effects have any effect on longer term outcomes in adults is not known.

The role of genetic influences on stability and change in ADHD during adolescence and young adulthood has been investigated in population twin studies.⁷⁵ The findings suggest a core set of genetic influences that explain stability of the syndrome. However, in addition, new genetic effects influence risk for the disorder at different developmental stages, which suggests that maturational or developmental processes come into play, altering the interplay of neurobiological processes that lead to ADHD symptoms and impairments at different ages. At the clinical level, persistence of ADHD is associated with the severity of ADHD during childhood,⁷⁶ and might be particularly high for people with high levels of both childhood inattentive and hyperactive-impulsive symptoms⁶ and for those with

psychiatric comorbidity, exposure to adversity, and a family history of the disorder.^{76,77}

There is also considerable interest in understanding the cognitive and neural deficits that mediate genetic risks on ADHD and might also be involved in persistence and remission of the disorder throughout development. One prominent hypothesis is that at the cognitive and neural level, measures of executive control and preparation-vigilance reflect interacting processes with different developmental courses that contribute to risk for ADHD. In a 6-year follow-up study using cognitive and electroencephalographic data of 110 young people with childhood DSM-IV combined type ADHD and 169 controls, ADHD persisters differed from remitters on preparation-vigilance measures but not on executive control measures.³⁵ This finding suggests that the preparation-vigilance measures might be markers of remission that improve alongside ADHD symptoms. As such, they might reflect malleable processes that can be targeted for prevention of long-term persistence of the disorder. High IQ also seemed to play a part in reducing risk for persistence of ADHD into young adulthood.

Adult-onset ADHD: a potential new trajectory for the disorder

ADHD has been traditionally conceptualised as a neurodevelopmental disorder and is included under this umbrella term in DSM-5.¹ Although some disorders known to have a neurodevelopmental trajectory, such as schizophrenia, do not necessarily begin in childhood, ICD-10 clearly defines that a neurodevelopmental disorder should have an onset during infancy or childhood. Thus, it is not surprising that age-of-onset during early childhood emerged as a key element in the definition of ADHD. However, in the past four decades, experts behind diagnostic manuals have struggled with the lack of evidence to define an accurate age of onset beyond which symptoms should no longer be considered part of the ADHD syndrome. The age of onset definitions applied were based solely on clinical wisdom; DSM-III introduced ADHD criterion B, requiring symptoms to be present before the age of 7 years, and DSM-IV-TR added that impairment must also be present by this same age. Under DSM-5 this definition has been changed to several symptoms (with or without impairment) before the age of 12 years.

A report by Moffitt and colleagues¹⁰ presented new data challenging the notion that ADHD always begins in childhood. In a representative birth cohort including 1037 subjects born in Dunedin, New Zealand, that were followed up to age 38 years with a retention rate of 95%, prevalence rates of childhood and adulthood disorder were in accordance with estimates from previously published work (6% in childhood and 3·1% in adulthood). However, one finding challenged the present conceptualisation of ADHD. The great majority of individuals qualifying for a diagnosis of adult ADHD

when the age-of-onset criterion was not applied (87%) did not have prior childhood ADHD. Importantly, the ADHD features in these adults did not seem to be accounted by their present comorbidities. Although both the child-onset and adult-onset groups showed similar levels of impairments in adulthood, they seemed to differ with regard to symptoms of ADHD in adulthood, genetic influences, and cognitive deficits.

Two other investigations in representative population samples from other regions (Brazil and the UK) found similar results. In the 1993 Pelotas Birth Cohort, 5249 individuals were followed up to age 18–19 years, with 81·3% retention. Only 12·6% of young adults meeting the symptom and impairment criteria for ADHD as adults had the disorder in childhood.⁷⁸ In the E-Risk Longitudinal Twin Study, a UK nationally representative birth cohort of 2232 twins born in England and Wales with 93% retention at age 18 years, ADHD diagnoses were assessed in childhood at ages 5, 7, 10, and 12 years and in young adulthood at age 18 years. In individuals meeting ADHD criteria as adults, 67·5% did not meet the criteria for ADHD at any assessment at or before age 12 years. Individuals with late-onset ADHD showed similar ADHD symptoms and impairment compared with the persistent group.⁷⁹

These findings suggest the existence of two phenotypically similar syndromes, with childhood onset and adulthood onset of ADHD symptoms and impairments reflecting distinct developmental trajectories, potentially linked to different causal influences and neural mechanisms. However, these are very recent findings and should be interpreted with caution. A third of the sample in the Dunedin study¹⁴ had conduct disorder as children and others showed signs of ADHD, so the adulthood-onset individuals were not free from earlier developmental problems during childhood. Attention also needs to be paid to measurement issues such as the use of self-ratings versus informant-ratings. In the Dunedin sample, both the childhood-onset and adulthood-onset groups had similar levels of adult ADHD symptoms according to informant reports, but not according to self-ratings, and similar levels of adult impairment.¹⁴ This finding is in line with the ADHD clinical follow-up studies that show greater diagnostic rates at follow-up when informant report, rather than self-report, is used as the primary source of information.³⁵ Further studies are therefore needed to clarify the proportion of adult cases that had subthreshold ADHD symptoms as children, as well as to provide an improved understanding of the clinical presentation of adults who had ADHD as children. As discussed previously, alternative measures such as sleep problems, excessive mind-wandering, emotional dysregulation, and executive function deficits could also be used to investigate the onset and developmental trajectory of ADHD. Because at present there are no clinical investigations of the adult-onset group, it is unknown whether they have

similar or different neural underpinnings, response to treatments, and prognosis to the child-onset group.

ADHD, treatment, and comorbidity

One reason for the under-diagnosis of ADHD by adult mental health services is the nature of the clinical syndrome, which shares characteristics with other common adult mental health disorders. These include clinical features associated with adult ADHD that do not form part of the present DSM-5 or ICD-10 diagnostic criteria. Examples include poor concentration, distractibility, restlessness, over-talkativeness, sleep problems, irritability, impulsiveness, and low self-esteem. However, in this regard, adult ADHD is no different from other common mental health disorders, many of which also share a similar set of overlapping symptoms. One clear distinction from most adult-onset disorders is the typical early onset and trait-like persistence of ADHD symptoms, which show what someone is usually like, rather than a change in premorbid mental state and episodic course. Because diagnostic symptom overlap is common for adult mental health disorders, this is unlikely to provide a full explanation for under-diagnosis of ADHD. A far more likely explanation is the present absence of awareness and training in the diagnosis and clinical management of ADHD in adults. Understanding of the similarities and differences between adult ADHD and common mental health disorders such as anxiety, depression, bipolar disorder, personality disorder, substance misuse, and antisocial behaviour is therefore of great importance to clinical practice. Such disorders occur at increased rates in adult ADHD, when they could have a further effect on long-term negative outcomes. Comorbid medical

Panel 2: Symptoms and impairments of ADHD that can mimic other mental health disorders

Anxiety

- Worrying about performance deficits, excessive mind-wandering, feeling overwhelmed, feeling restless, avoidance of situations due to ADHD symptoms, such as difficulty waiting in queues or social situations requiring focused attention, and sleep problems linked to mental restlessness

Depression

- Unstable moods, impatience, irritability, poor concentration, sleep disturbance, low self-esteem
- Personality disorder (eg, borderline and antisocial)
- Chronic trait-like psychopathology linked to behavioural problems, emotional instability, impulsive behaviour, and poor social relationships

Bipolar disorder

- Restlessness, sleep disturbance, mood instability, ceaseless unfocused mental activity, and distractibility

Panel 3: Key points and conclusions

Main findings

- Adult ADHD is a common mental health problem affecting 2.5–3.4% of the adult population
- Undiagnosed ADHD is found in 10% or more of non-psychotic patients attending general adult, addiction, and prison mental health services
- Beyond the core symptoms of inattention and hyperactivity-impulsivity, ADHD is characterised by a wide range of mental health symptoms and impairments including initial sleep insomnia, excessive mind-wandering, restlessness, emotional instability, and behaviour showing difficulty with executive functions
- ADHD symptoms and impairments can mimic other common mental health disorders, leading to incorrect diagnoses and targeting of treatments
- The treatment response of adult ADHD symptoms and impairments to stimulants and atomoxetine shows these drugs to be among the most effective pharmacological treatments for any mental health disorder
- Pharmacoepidemiological studies show reductions in criminal convictions, accidental injuries, substance misuse, and suicides after treatment of ADHD

Research recommendations

- Investigate the prevalence of undiagnosed ADHD in patients receiving treatments for mental health problems in primary care
- Investigate objective measures of ADHD symptoms, characterisation of the mental state and behavioural problems experienced by adults to improve recognition of ADHD in clinical practice
- Identify cognitive, neural, and genetic biomarkers to aid in diagnosis, clinical subtyping, and targeting or selection of treatments
- Investigate the effectiveness of ADHD drug treatments on ADHD symptoms and impairments in the context of co-occurring personality, anxiety, and mood disorders
- Investigate the effects of ADHD drug treatments on a wider range of outcomes including emotional instability, aggression, dysthymia, and sleep problems
- Investigate the effectiveness of psychosocial treatments (including cognitive psychological education, cognitive behaviour therapy, and mindfulness-based interventions) on longer term outcomes in ADHD
- Investigate ADHD trajectories comparing clinical and population samples with special attention to potential adulthood-onset ADHD

disorders are also a concern, with substantial evidence associating adult ADHD with obesity,^{80–82} and data linking the disorder to increased mortality, with the strongest single predictor being accident rates.⁸³

Treatment

The high rate of undiagnosed ADHD in individuals with mental health problems is also a concern, given the availability of effective drug and behavioural treatments for ADHD. Short-term, randomised, placebo-controlled trials of methylphenidate, d-amphetamine, and atomoxetine all show marked clinical effects on ADHD symptoms, with standardised mean differences between drug and placebo groups in the range of 0.4 to 0.7 in adult ADHD.^{84–87} These moderate-to-large clinical effects compare favourably with the effects of antidepressants on depression or antipsychotics on psychosis, for example, demonstrating the importance of appropriate targeting of ADHD treatments. Although both stimulant

and non-stimulant drugs show clinically significant evidence for efficacy, the stimulants are more effective for the short durations of treatment which are characteristic of placebo-controlled studies.⁸⁸ Evidence from controlled trials for the longer term benefits of pharmacological treatments is largely absent, although a systematic review identified five randomised controlled trials and ten open-label extension studies with total follow-up of at least 24 weeks. All of the randomised trials reported that drug treatment was significantly better than placebo for treating ADHD in adults; the extension studies all reported that the favourable effect of drugs seen in short-term trials was maintained during open-label follow-up.⁸⁹ Pharmacoepidemiological studies using national registry data highlight the potential for very substantial long-term benefits of treatment, not only on core ADHD symptoms, but also on serious co-occurring problems. By comparison of periods of patients on and off ADHD drug treatments, reductions in criminal convictions,⁹⁰ transport accidents,⁹¹ substance misuse,⁹² and suicidal behaviour have been shown during periods on ADHD drug treatments.⁹³

Psychosocial treatments including psychoeducation, cognitive behaviour therapy, and use of support groups, skills training, and coaching are thought to provide additional benefits in the clinical management of ADHD,^{94,95} although studies are generally small and not well designed. Whether such approaches reduce the core symptoms of ADHD or rather improve secondary outcomes such as psychosocial and functional impairments is uncertain. A study of 419 adult patients with ADHD randomised to drug or placebo, with and without group psychotherapy, provides some clarification.⁹⁶ Short-term and 1-year effects of drug treatment, but not psychotherapy, were seen on ADHD symptoms. Group psychotherapy was, however, associated with better 1-year outcome on a measure of overall clinical improvement (clinical global impression) when combined with the trial drug than when combined with placebo. This finding is consistent with present guidelines that recommend psychological therapies are used as an adjunct to drug treatment in adult ADHD.⁹⁷

Comorbidity

Despite the obvious contribution that ADHD makes to adult psychopathology and mental health problems, the similarities and differences from other common mental health disorders and the effects on treatment in comorbid cases are poorly understood. Three main groups should be considered. In the first group, ADHD might mimic other disorders, either because of overlap with core ADHD symptoms such as restlessness and poor concentration, or because of characteristic associated features of ADHD such as emotional instability, low self-esteem, and sleep problems (panel 2). This group of individuals is important to identify because they are likely to respond to appropriate drug treatment for ADHD.

In the second group, neurodevelopmental traits and disorders are often seen to develop alongside ADHD. These include features of autism spectrum disorder, specific reading difficulties (dyslexia), and developmental coordination disorder (dyspraxia). Such neurodevelopmental comorbidities have a marked effect on functional impairment but, unlike ADHD symptoms, do not respond to drug treatments for ADHD.

In the third group, co-occurring disorders might develop as a complication of ADHD. For example, children with ADHD are at greater risk for the development of substance misuse disorders, anxiety, depression, personality disorders (including antisocial and borderline), and criminal behaviour. The effects of treating ADHD in this third group are not yet well researched and the present advice is based mainly on the experience of individual expert clinicians. For example, although we know that emotional dysregulation often improves when treating adult ADHD, there is little information on the effect of treating ADHD in comorbid ADHD patients with borderline or antisocial personality disorders. Nevertheless, pharmacoepidemiological studies^{90–93} suggest that treating ADHD can reduce associated criminal behavior, substance misuse, and suicide.

Another question is the part that ADHD plays in the maintenance of anxiety and depression and the effects of treating ADHD in comorbid cases. The ubiquitous nature of emotional symptoms in adult mental health means that all individuals with a non-episodic form of emotional instability should be screened for ADHD, including those with chronic dysthymia, cyclothymia, and personality disorders. At present, such patients are often mistakenly diagnosed as having bipolar disorder, cyclothymia, or borderline personality disorder, even in cases where there are moderate-to-severe levels of ADHD symptoms and impairments.⁹⁸

Conclusions

We conclude that ADHD should be recognised in the same way as other common adult mental health conditions, and that failure to recognise and treat ADHD is detrimental to the wellbeing of many patients seeking help for mental health problems. Although further research is needed to assess the effects of ADHD drug treatments in ADHD complicated by comorbidities, effective clinical

management of ADHD should be an essential component of adult mental health care. A list of key points and research recommendations is provided in panel 3.

Contributors

The first draft of the report was written by PA and LAR. All authors contributed to the Review and writing of the report.

Declaration of interests

In the past 3 years, JB has been a consultant or member of advisory board or speaker for Janssen-Cilag BV, Eli Lilly, Lundbeck, Roche, Shire, and Servier. He has received no other financial or material support, including expert testimony, patents, and royalties, or been an employee of any of these companies, and is not a stock shareholder of any of these companies. In the past year, SVF received income, potential income, travel expenses, or research support from Arbor, Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, and NeuroLifeSciences. With his institution, SVF has a USA patent (US20130217707 A1) for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, SVF received income or research support from Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. SVFaraone receives royalties from books. LAR reports grants and personal fees from Eli Lilly, grants and personal fees from Novartis Biocencias, grants and personal published by Guilford Press (Straight talk about your child's mental health), Oxford University Press (Schizophrenia: the facts), and Elsevier (ADHD: non-pharmacologic interventions), fees from Janssen-Cilag, grants and personal fees from Shire, other from Oxford Press, and other from Artmed, outside the submitted work. PA reports grants from Vifor Pharma and GW Pharma, other (non-personal pecuniary) from Shire, grants and other (non-personal pecuniary) from Janssen, other (non-personal pecuniary) from Eli Lilly, other (non-personal pecuniary) from Novartis, grants from QbTech, and other (non-personal pecuniary) from Alcobra outside the submitted work.

Acknowledgments

PA is supported by NIHR Biomedical Research Centre for mental health, NIHR/MRC (14/23/17), Action Medical Research (GN 2315), and European Union (643051, 602805, 667303). SVF is supported by the K G Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway, and the European Union's Seventh Framework Programme for research, technological development, and demonstration under grant agreement no 602805 and NIMH grant R01MH094469. LAR is supported by a grant from National Counsel of Technological and Scientific Development (CNPq; grant number 304678/2010-4). JB is supported by grants from the Netherlands Organization for Health Research and Development (ZonMw 60-60600-97-193), the Netherlands Organization for Scientific Research (NWO; grants 1750102007010, 433-09-242, and 056-13-015), and by the European Commission's Seventh Framework programme (FP7/2007-2013) under grant agreement 278948 (TACTICS), 602450 (IMAGEMEND), 602805 (AGGRESSOTYPE), and 603016 (MATRICS), and Horizon 2020 research programme (grant agreement 643051 [MiND] and 642996 [BRAINVIEW]). His research also receives funding from the US NIH Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centers of Excellence.

References

- 1 APA. Diagnostic and Statistical Manual of Mental Disorders DSM 5—5th edn. Washington, DC: American Psychiatric Publishing, 2013.
- 2 Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry* 2007; **164**: 942–48.
- 3 Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics* 2012; **9**: 490–99.
- 4 Tannock R. Rethinking ADHD and LD in DSM-5: proposed changes in diagnostic criteria. *J Learn Disabil* 2013; **46**: 5–25.
- 5 Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006; **36**: 159–65.

Search strategy and selection criteria

Two approaches were taken. First, to cite the most established findings that have been replicated or demonstrated in systematic reviews and meta-analyses. Second, to highlight new emerging findings that require further research to confirm or refute initial findings. The text clarifies which of the newly emerging findings require further research.

- 6 Lara C, Fayyad J, de Graaf R, et al. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. *Biol Psychiatry* 2009; **65**: 46–54.
- 7 Cheung CH, Rijdsdijk F, McLoughlin G, Faraone SV, Asherson P, Kuntsi J. Childhood predictors of adolescent and young adult outcome in ADHD. *J Psychiatr Res* 2015; **62**: 92–100.
- 8 van Lieshout M, Luman M, Twisk JWR, et al. A 6-year follow-up of a large European cohort of children with attention-deficit/hyperactivity disorder-combined subtype: outcomes in late adolescence and young adulthood. *Eur Child Adolesc Psychiatry* 2016; published online Feb 2. DOI: 10.1007/s00787-016-0820-y.
- 9 Barkley R, Murphy KR, Fischer M. ADHD in adults: what the science says. New York: Guilford Press, 2007.
- 10 Moffitt TE, Houts R, Asherson P, et al. Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study. *Am J Psychiatry* 2015; **172**: 967–77.
- 11 Fayyad J, De Graaf R, Kessler R, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry* 2007; **190**: 402–09.
- 12 Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009; **194**: 204–11.
- 13 Johnson MH. Executive function and developmental disorders: the flip side of the coin. *Trends Cogn Sci* 2012; **16**: 454–57.
- 14 Castellanos FX. Is adult onset ADHD a distinct entity? *Am J Psychiatry* 2015; **172**: 929–31.
- 15 Young S, Moss D, Sedgwick O, Fridman M, Hodgkins P. A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations. *Psychol Med* 2015; **45**: 247–58.
- 16 Huntley Z, Maltezos S, Williams C, et al. Rates of undiagnosed attention deficit hyperactivity disorder in London drug and alcohol detoxification units. *BMC Psychiatry* 2012; **12**: 223.
- 17 van de Glind G, Konstenius M, Koeter MW, et al, and the IASP Research Group. Variability in the prevalence of adult ADHD in treatment seeking substance use disorder patients: results from an international multi-center study exploring DSM-IV and DSM-5 criteria. *Drug Alcohol Depend* 2014; **134**: 158–66.
- 18 Deberdt W, Thome J, Lebecq J, et al. Prevalence of ADHD in nonpsychotic adult psychiatric care (ADPSYC): A multinational cross-sectional study in Europe. *BMC Psychiatry* 2015; **15**: 242.
- 19 Faraone SV, Spencer TJ, Montano CB, Biederman J. Attention-deficit/hyperactivity disorder in adults: a survey of current practice in psychiatry and primary care. *Arch Intern Med* 2004; **164**: 1221–26.
- 20 Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010; **167**: 748–51.
- 21 Chen W, Zhou K, Sham P, et al. DSM-IV combined type ADHD shows familial association with sibling trait scores: a sampling strategy for QTL linkage. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 1450–60.
- 22 Shah PJ, Morton MJ. Adults with attention-deficit hyperactivity disorder—diagnosis or normality? *Br J Psychiatry* 2013; **203**: 317–19.
- 23 Larsson H, Dilshad R, Lichtenstein P, Barker ED. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. *J Child Psychol Psychiatry* 2011; **52**: 954–63.
- 24 Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry* 2000; **157**: 816–18.
- 25 Kuntsi J, Pinto R, Price TS, van der Meere JJ, Frazier-Wood AC, Asherson P. The separation of ADHD inattention and hyperactivity-impulsivity symptoms: pathways from genetic effects to cognitive impairments and symptoms. *J Abnorm Child Psychol* 2014; **42**: 127–36.
- 26 Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 737–44.
- 27 Moffitt TE, Arseneault L, Belsky D, et al. A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci USA* 2011; **108**: 2693–98.
- 28 Larsson H, Chang Z, D'Onofrio BM, Lichtenstein P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. *Psychol Med* 2014; **44**: 2223–29.
- 29 Larsson H, Anckarsater H, Råstam M, Chang Z, Lichtenstein P. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8 500 twin pairs. *J Child Psychol Psychiatry* 2012; **53**: 73–80.
- 30 Stergiakouli E, Martin J, Hamshere ML, et al. Shared genetic influences between attention-deficit/hyperactivity disorder (ADHD) traits in children and clinical ADHD. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 322–27.
- 31 Kuntsi J, Wood AC, Rijdsdijk F, et al. Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Arch Gen Psychiatry* 2010; **67**: 1159–67.
- 32 Kooij JJ, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CA, Houdiamont PP. Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. *Psychol Med* 2005; **35**: 817–27.
- 33 Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nature Rev Dis Primers* 2015; published online Aug 6, 2015. DOI:10.1038/nrdp.2015.20.
- 34 Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BMC Psychiatry* 2010; **10**: 67.
- 35 Cheung CH, Rijdsdijk F, McLoughlin G, et al. Cognitive and neurophysiological markers of ADHD persistence and remission. *Br J Psychiatry* 2015; published online Aug 6. DOI:10.1192/bjp.bp.114.145185.
- 36 Merwood A, Greven CU, Price TS, et al. Different heritabilities but shared etiological influences for parent, teacher and self-ratings of ADHD symptoms: an adolescent twin study. *Psychol Med* 2013; **43**: 1973–84.
- 37 Edebol H, Helldin L, Norlander T. Measuring adult Attention Deficit Hyperactivity Disorder using the Quantified Behavior Test Plus. *PsyCh journal* 2013; **2**(1): 48–62.
- 38 Edebol H, Helldin L, Norlander T. Objective Measures of Behavior Manifestations in Adult ADHD and Differentiation from Participants with Bipolar II Disorder, Borderline Personality Disorder, Participants with Disconfirmed ADHD as Well as Normative Participants. *Clin Pract Epidemiol Ment Health* 2012; **8**: 134–43.
- 39 Bedard AC, Stein MA, Halperin JM, Krone B, Rajwan E, Newcorn JH. Differential impact of methylphenidate and atomoxetine on sustained attention in youth with attention-deficit/hyperactivity disorder. *J Child Psychol Psychiatry* 2015; **56**: 40–48.
- 40 Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naïve boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007; **62**: 954–62.
- 41 Arns M, Loo SK, Sterman MB, et al. Editorial Perspective: How should child psychologists and psychiatrists interpret FDA device approval? Caveat emptor. *J Child Psychol Psychiatry* (in press).
- 42 Plichta MM, Scheres A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. *Neurosci Biobehav Rev* 2014; **38**: 125–34.
- 43 Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. *Neuropsychol Rev* 2014; **24**: 3–15.
- 44 Schulz KP, Fan J, Bédard AC, et al. Common and unique therapeutic mechanisms of stimulant and nonstimulant treatments for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2012; **69**: 952–61.
- 45 Van Veen MM, Kooij JJ, Boonstra AM, Gordijn MC, Van Someren EJ. Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. *Biol Psychiatry* 2010; **67**: 1091–96.
- 46 Youssef NA, Ege M, Angly SS, Strauss JL, Marx CE. Is obstructive sleep apnea associated with ADHD? *Ann Clin Psychiatry* 2011; **23**: 213–24.
- 47 Skirrow C, Asherson P. Emotional lability, comorbidity and impairment in adults with attention-deficit hyperactivity disorder. *J Affect Disord* 2013; **147**: 80–86.
- 48 Barkley RA, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. *J Am Acad Child Adolesc Psychiatry* 2010; **49**: 503–13.

- 49 Surman CB, Biederman J, Spencer T, Miller CA, McDermott KM, Faraone SV. Understanding deficient emotional self-regulation in adults with attention deficit hyperactivity disorder: a controlled study. *Atten Defic Hyperact Disord* 2013; **5**: 273–81.
- 50 Skirrow C, Ebner-Priemer U, Reinhard I, Malliaris Y, Kuntsi J, Asherson P. Everyday emotional experience of adults with attention deficit hyperactivity disorder: evidence for reactive and endogenous emotional lability. *Psychol Med* 2014; **44**: 3571–83.
- 51 Merwood A, Chen W, Rijdsdijk F, et al. Genetic associations between the symptoms of attention-deficit/hyperactivity disorder and emotional lability in child and adolescent twins. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 209–20 e4.
- 52 Rosler M, Retz W, Fischer R, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. *World J Biol Psychiatry* 2010; **11**: 709–18.
- 53 Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. *Biol Psychiatry* 2005; **58**: 125–31.
- 54 Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *J Clin Psychiatry* 2007; **68**: 93–101.
- 55 McCarthy J, Chaplin E, Underwood L, et al. Characteristics of prisoners with neurodevelopmental disorders and difficulties. *J Intellect Disabil Res* 2016; **60**: 201–06.
- 56 Seli P, Smallwood J, Cheyne JA, Smilek D. On the relation of mind wandering and ADHD symptomatology. *Psychon Bull Rev* 2015; **22**: 629–36.
- 57 Shaw GA, Giambra L. Task-unrelated thoughts of college students diagnosed as hyperactive in childhood. *Dev Neuropsychol* 1993; **9**: 17–30.
- 58 Weyandt LL, Iwaszuk W, Fulton K, et al. The internal restlessness scale: performance of college students with and without ADHD. *J Learn Disabil* 2003; **36**: 382–89.
- 59 Smallwood J, Schooler JW. The science of mind wandering: empirically navigating the stream of consciousness. *Annu Rev Psychol* 2015; **66**: 487–518.
- 60 Skirrow C, McLoughlin G, Banaschewski T, Brandeis D, Kuntsi J, Asherson P. Normalisation of frontal theta activity following methylphenidate treatment in adult attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol* 2015; **25**: 85–94.
- 61 Asherson P. Clinical assessment and treatment of attention deficit hyperactivity disorder in adults. *Expert Rev Neurother* 2005; **5**: 525–39.
- 62 Mowlem F, Skirrow C, Reid P, et al. Validation of the Mind Excessively Wandering Scale (MEWS) and the relationship of mind-wandering to impairment in adult ADHD. *J Affect Disord* (in press).
- 63 Killingsworth MA, Gilbert DT. A wandering mind is an unhappy mind. *Science* 2010; **330**: 932.
- 64 Coghill DR, Hayward D, Rhodes SM, Grimmer C, Matthews K. A longitudinal examination of neuropsychological and clinical functioning in boys with attention deficit hyperactivity disorder (ADHD): improvements in executive functioning do not explain clinical improvement. *Psychol Med* 2014; **44**: 1087–99.
- 65 Barkley RA, Murphy KR. Impairment in occupational functioning and adult ADHD: the predictive utility of executive function (EF) ratings versus EF tests. *Arch Clin Neuropsychol* 2010; **25**: 157–73.
- 66 Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry* 2005; **57**: 1336–46.
- 67 Biederman J, Petty CR, Fried R, et al. Discordance between psychometric testing and questionnaire-based definitions of executive function deficits in individuals with ADHD. *J Atten Disord* 2008; **12**: 92–102.
- 68 Adler LA, Dirks B, Deas P, et al. Self-reported quality of life in adults with attention-deficit/hyperactivity disorder and executive function impairment treated with lisdexamfetamine dimesylate: a randomized, double-blind, multicenter, placebo-controlled, parallel-group study. *BMC Psychiatry* 2013; **13**: 253.
- 69 Adler LA, Dirks B, Deas PF, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2013; **74**: 694–702.
- 70 Yang L, Cao Q, Shuai L, Li H, Chan RC, Wang Y. Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: a randomized controlled trial. *Int J Neuropsychopharmacol* 2012; **15**: 15–26.
- 71 Roth RM, Isquith PK, Gioia G. Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) Professional Manual. Lutz, FL, 2005.
- 72 Rommel AS, Halperin JM, Mill J, Asherson P, Kuntsi J. Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 900–10.
- 73 Harold GT, Leve LD, Barrett D, et al. Biological and rearing mother influences on child ADHD symptoms: revisiting the developmental interface between nature and nurture. *J Child Psychol Psychiatry* 2013; **54**: 1038–46.
- 74 Musser ED, Karalunas SL, Dieckmann N, Peris TS, Nigg JT. Attention-deficit/hyperactivity disorder developmental trajectories related to parental expressed emotion. *J Abnorm Psychol* 2016; **125**: 182–95.
- 75 Chang Z, Lichtenstein P, Asherson PJ, Larsson H. Developmental twin study of attention problems: high heritabilities throughout development. *JAMA Psychiatry* 2013; **70**: 311–18.
- 76 Biederman J, Petty CR, O'Connor KB, Hyder LL, Faraone SV. Predictors of persistence in girls with attention deficit hyperactivity disorder: results from an 11-year controlled follow-up study. *Acta Psychiatr Scand* 2012; **125**: 147–56.
- 77 Biederman J, Faraone S, Milberger S, et al. Predictors of persistence and remission of ADHD into adolescence: results from a four-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 343–51.
- 78 Caye A, Rocha TM, Anselmi L, et al. ADHD does not always begin in childhood: Evidence from a large birth cohort. *JAMA Psychiatry* (in press).
- 79 Agnew-Blais JC, Polanczyk GV, Danese A, et al. Persistence, remission and emergence of ADHD in young adulthood: results from a longitudinal, prospective population-based cohort. *JAMA Psychiatry* (in press).
- 80 Cortese S, Castellanos FX. The relationship between ADHD and obesity: implications for therapy. *Expert Rev Neurother* 2014; **14**: 473–79.
- 81 Cortese S, Moreira-Maia CR, St Fleur D, Morcillo-Penalver C, Rohde LA, Faraone SV. Association between ADHD and obesity: a systematic review and meta-analysis. *Am J Psychiatry* 2015; **173**: 34–43.
- 82 Cortese S, Faraone SV, Bernardi S, Wang S, Blanco C. Adult attention-deficit hyperactivity disorder and obesity: epidemiological study. *Br J Psychiatry* 2013; **203**: 24–34.
- 83 Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet* 2015; **385**: 2190–96.
- 84 Cunill R, Castells X, Tobias A, Capellà D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. *Pharmacoevidenciol Drug Saf* 2013; **22**: 961–69.
- 85 Koesters M, Becker T, Kilian R, Fegert JM, Weinmann S. Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. *J Psychopharmacol* 2009; **23**: 733–44.
- 86 Castells X, Ramos-Quiroga JA, Rigau D, et al. Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: a meta-regression analysis. *CNS Drugs* 2011; **25**: 157–69.
- 87 Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. *Cochrane Database Syst Rev* 2011; **6**: CD007813.
- 88 Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry* 2010; **71**: 754–63.
- 89 Fredriksen M, Halmøy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: a review of controlled and naturalistic studies. *Eur Neuropsychopharmacol* 2013; **23**: 508–27.
- 90 Lichtenstein P, Larsson H. Medication for attention deficit-hyperactivity disorder and criminality. *N Engl J Med* 2013; **368**: 776.

- 91 Chang Z, Lichtenstein P, D'Onofrio BM, Sjölander A, Larsson H. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. *JAMA Psychiatry* 2014; **71**: 319–25.
- 92 Chang Z, Lichtenstein P, Halldner L, et al. Stimulant ADHD medication and risk for substance abuse. *J Child Psychol Psychiatry* 2014; **55**: 878–85.
- 93 Chen Q, Sjölander A, Runeson B, D'Onofrio BM, Lichtenstein P, Larsson H. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. *BMJ* 2014; **348**: g3769.
- 94 Philipsen A. Psychotherapy in adult attention deficit hyperactivity disorder: implications for treatment and research. *Expert Rev Neurother* 2012; **12**: 1217–25.
- 95 Young S, Amarasinghe JM. Practitioner review: non-pharmacological treatments for ADHD: a lifespan approach. *J Child Psychol Psychiatry* 2010; **51**: 116–33.
- 96 Philipsen A, Jans T, Graf E, et al, and the Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study (COMPAS) Consortium. Effects of group psychotherapy, individual counseling, methylphenidate, and placebo in the treatment of adult attention-deficit/hyperactivity disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; **72**: 1199–210.
- 97 NICE. Attention Deficit Hyperactivity Disorder: The NICE guideline on diagnosis and management of ADHD in children, young people and adults: The British Psychological Society and The Royal College of Psychiatrists; 2008.
- 98 Asherson P, Young AH, Eich-Höchli D, Moran P, Porsdal V, Deberdt W. Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. *Curr Med Res Opin* 2014; **30**: 1657–72.