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Commentary: ADHD lifetime trajectories and the relevance of the developmental perspective to Psychiatry: reflections on Asherson and Agnew-Blais, (2019)

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Attention-deficit/hyperactivity disorder (ADHD) is, by definition, an early-onset disorder and its status as such has been reified by diagnostic systems for almost 40 years. Nevertheless, not until recently has there been an empirical test, using population-based, prospective data, of whether the majority of ADHD cases emerge in childhood. The first study to address this question showed, astonishingly, that 90% of the adults who were diagnosed with ADHD had no history of the disorder during childhood. Perhaps even more astonishingly, this finding was soon replicated in a series of studies reviewed by Asherson and Agnew-Blais (2019) that reported that anywhere from <1% to 10% of ADHD cases emerge in adolescence and adulthood.

The new evidence that ADHD can emerge later than childhood comes with several questions (Castellanos, 2015; Caye, Sibley, Swanson, & Rohde, 2017; Faraone & Biederman, 2016; Shaw & Polanczyk, 2017). The review by Asherson and Agnew-Blais (2019) is timely in providing a detailed description of the data on which the findings are based and a thoughtful discussion of whether late-onset ADHD is likely to be a real phenomenon as opposed to a methodological artifact.

As discussed by Asherson and Agnew-Blais (2019), a number of pieces of evidence have accumulated that call into question the special status of childhood-onset ADHD and suggest the existence of an adult-onset group. For example, initial clinical accounts failed to show clinically meaningful differences between individuals reporting an early versus a later onset of disorder. Moreover, estimates of disorder persistence rates from childhood to adulthood did not match the estimates of prevalence in children and adults, indicating that new cases were emerging after the age limit determined by diagnostic systems. DSM-5 reflected these findings by raising the onset of ADHD symptoms criterion from 7 to age 12, but did not recognize individuals reporting an onset of ADHD beyond 12 years.

Moffitt et al. (2015) were the first to address directly the issue of late-onset ADHD in the community using data from the Dunedin Multidisciplinary Health and Development Study, which is a population-based longitudinal study. Very soon after this initial report, data from another seven studies appeared, five of which used prospective, longitudinal data from population-based cohorts in the United Kingdom (E-Risk Longitudinal Twin Study and ALSPAC), Brazil (1993 Pelotas Birth Cohort and the Brazilian High- Risk Study), and Sweden (Swedish National Register) and two of which used data from clinical cohorts in the United States (New York Longitudinal Study and MTA Study). The capacity of these studies to address questions of global public health significance demonstrates the tremendous value they have accrued from years of investment from funding agencies and researchers.

In summary, these population-based cohorts followed individuals from childhood into their mid-20s (with the Dunedin Study extending to age 38) and estimated the prevalence of late-onset ADHD from 0.4% to 10.3%. Women were represented at higher rates in the adult ADHD group than in the childhood ADHD group. Individuals with late-onset ADHD were significantly impaired and presented objective negative outcomes (e.g. in the Dunedin Study, administrative records demonstrated lower credit ratings, longer duration of social welfare benefit receipt, and more injury-related insurance claims). Co-informants (when available) supported the presence of symptoms. In general, the late-onset group did not present cognitive impairments that are characteristics of ADHD, such as low IQ and basic processing deficits, but had significant complaints about their cognitive functioning. Comorbidity at follow-up was common, especially substance use disorders, but 34%–57% of participants had no comorbid disorder. As children, late-onset cases had higher rates of oppositional defiant disorder and conduct disorder than individuals with no ADHD. Dimensional assessment showed elevated externalizing symptoms and elevated scores on general and

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externalizing factors of psychopathology. Polygenic scores for ADHD calculated in the Dunedin Study, ALSPAC and Brazilian High Risk Cohort were not increased for individuals with late-onset ADHD, although the restricted size of this group limits this analysis. In the E-Risk Study, a co-twin with childhood ADHD did not confer increased risk for late-onset ADHD.

The key question that Asherson and Agnew-Blais address is whether the existence of the late-onset group is likely to be real. They conclude that a subset of cases can be better explained by measurement noise (e.g. different informants at different time points), comorbid disorders, and by failure to identify symptoms that were present earlier or that would have been identified if assessments had been conducted more often. That still leaves another group who have no ADHD symptoms in childhood, but who present with ADHD symptoms and impairment as young adults.

Who are these individuals with emergent ADHD in late adolescence or young adulthood? One possibility is that childhood and late-onset ADHD share similar early-emerging neurobiological vulnerabilities, but among those with late-onset ADHD, 'protective' factors in childhood – such as parental support – suppress early symptom expression. This is in keeping with concepts of ADHD as a multifactorial entity, in which environmental factors can counteract genetic risk, keeping symptom expression below a clinical threshold (Shaw & Polanczyk, 2017).

A second possibility is that the emergence of ADHD in late adolescence or adulthood reflects heterotypic continuity in a general liability to psychopathology that is present from childhood. The relationships among diverse forms of disorder were powerfully demonstrated by a recent study, also from a population-based sample. In this case, data came from the Danish health register, which tracked a cohort of almost six million people for up to 17 years, starting at a mean age of 32 (IQR 7.4–52.9) years (Plana-Ripoll et al., 2019). Researchers investigated the risk of developing any comorbid disorder given any primary diagnosis. Disorders were categorized into groups, with ADHD clustered alongside conduct disorder and childhood emotional disorders in a behavioral disorders group. Results were compelling: given the diagnosis of any index group of disorders, there was an increased risk of developing any and all types of comorbid disorder groups. This increased risk was bidirectional: behavioral disorders increased risk for the emergence of other disorders (e.g. mood or substance-related disorders) and all other disorders increased risk for the emergence of behavioral disorders (Plana-Ripoll et al., 2019). These findings are consistent with the notion that different mental disorders, including ADHD, may arise from a common liability (Hyman, 2019).

Genome-wide association studies (GWAS) point in the same direction. In a GWAS meta-analysis, Demontis et al. (2019) identified risk variants for ADHD in 12 independent loci and detected significant genetic overlap between ADHD and 43 phenotypes, including major depressive disorder, educational attainment, obesity-related phenotypes, smoking, insomnia, and others (Demontis et al., 2019). These results were recently replicated and extended in the population of Denmark, where extensive genetic sharing across ADHD, autism spectrum disorder, major depressive disorder, eating disorders, bipolar disorder, and schizophrenia was demonstrated. Genes identified as conferring risk were those related to neurodevelopment, increasing the risk for mental disorders in general early in life (Schork et al., 2019). Thus, it is possible to hypothesize that individuals with late-onset ADHD may have a strong liability to psychopathology that either fails to meet a clinical threshold for ADHD earlier in life or that is manifest as other symptoms at that time. ADHD may emerge in adolescence or adulthood, however, with the expression of new genes, neurobiological changes related to puberty, or new environments.

With so many new and controversial data and hypotheses challenging conventional wisdom about ADHD, Asherson and Agnew-Blais (2019) brilliantly illuminate key methodological and conceptual concerns, recommend future directions for research, and provide a thoughtful discussion of the implications for treatment. Importantly, they suggest that clinicians should consider the presence of symptoms and impairment criteria (rather than strict diagnostic thresholds) as guides to whether adults need treatment, not forgetting to consider exacerbating factors such as drug abuse and other disorders. The potential presence of a late-onset ADHD group also has important implications for researchers, who must rise to the challenge of describing whether the genetic, cognitive, or neural architecture of late-onset ADHD differs from that of childhood-onset ADHD. The new evidence also highlights the importance of not constraining research questions to current diagnostic criteria, but rather to testing the criteria and revising them in an iterative fashion. We expect that innovative approaches will provide robust data about the nature of mental disorders and about ADHD in particular, informing future classification systems that may ultimately improve the care of children and adolescents

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