Life-Span Studies of ADHD - Conceptual Challenges and Predictors of Persistence and Outcome

Arthur Caye[1], James Swanson[2], Anita Thapar[3], Margaret Sibley[4], Louise Arseneault[5], Lily Hechtman[6], L. Eugene Arnold[7], Janni Niclasen[8,9], Terrie Moffitt[10] and Luis Augusto Rohde[1,11]

1. ADHD Outpatient Program, Hospital de Clínicas de Porto Alegre, Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
2. Department of Pediatrics, University of California, Irvine.
3. MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK.
4. Department of Psychiatry & Behavioral Health at the Florida International University, Herbert Wertheim College of Medicine.
5. MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London.
6. Department of Psychiatry, McGill University, Montreal, Quebec.
7. Department of Psychiatry, Nisonger Center, Ohio State University, Columbus, Ohio
8. Department of Psychology, University of Copenhagen, Copenhagen, Denmark
9. Centre for Collaborative Health, Aarhus University, Aarhus, Denmark
10. Department of Psychology and Neuroscience, Duke University, Durham, North Carolina
11. National Institute of Developmental Psychiatry for Children and Adolescents, Brazil

Corresponding author: Luis Augusto Rohde, Serviço de Psiquiatria da Infância e Adolescência, Hospital de Clinicas de Porto Alegre, 4o andar, Rua Ramiro Barcelos 2350, Porto Alegre, Brazil, 90035-003. Phone: 555133598094. Email: lrohde@terra.com.br

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ABSTRACT:

There is a renewed interest in better conceptualizing trajectories of Attention-Deficit/Hyperactivity Disorder (ADHD) from childhood to adulthood, driven by an increased recognition of long-term impairment and potential persistence beyond childhood and adolescence. This review addresses the following major issues relevant to the course of ADHD in light of current evidence from longitudinal studies: 1) conceptual and methodological issues related to measurement of persistence of ADHD; 2) estimates of persistence rate from childhood to adulthood and its predictors; 3) long-term negative outcomes of childhood ADHD and their early predictors, and 4) the recently proposed new adult-onset ADHD. Estimates of persistence vary widely in the literature, and diagnostic criteria, sample characteristics and information source are the most important factors explaining variability among studies. Evidence indicates that ADHD severity, comorbid conduct disorder and major depressive disorder, and treatment for ADHD are the main predictors of ADHD persistence from childhood to adulthood. Comorbid conduct disorder and ADHD severity in childhood are the most important predictors of adverse outcomes in adulthood among children with ADHD. Three recent population studies suggested the existence of a significant proportion of individuals who report onset of ADHD symptoms and impairments after childhood. Finally, we highlight areas for improvement to increase our understanding of ADHD across the life span.

KEYWORDS: ADHD; persistence; outcomes; predictors; course; longitudinal investigations

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurobiological disorder characterized by a persistent and impairing pattern of inattentive, hyperactive, and/or impulsive symptoms [1]. Meta-analyses suggest prevalence rates around 5 to 7.1% in childhood and 2.5 to 5% in adulthood [2-4]. The disorder is associated with adverse outcomes for affected individuals, their families and society in general [5].

There is recent interest in better conceptualized adult ADHD [6] and its trajectories from childhood to adulthood [5]. A previous meta-analysis found that only 15% of diagnosed children continued presenting full ADHD diagnosis in adulthood, although 65% presented with a subsyndromal phenotype [7]. This figure would suggest a much lower adult ADHD prevalence rate (15% of 5-7% = 0.8-1.1%) than what has been detected both in meta-analyses (2.5%-5%) [3, 4] and in a multi-national study on ADHD prevalence in adults (3.4%) [8]. There is a current debate about reasons for this discrepancy. Some investigators suggest that the 15% persistence rate is a clear underestimation due to change of informants between adult and child assessments and inadequacy of the ADHD diagnostic criteria for adults. Major aspects of both the ADHD phenotype and its impairments might be different in adults, and other approaches to define persistence, like cognitive and social dysfunction, are lacking in the literature.[6] In addition, controversies also exist surrounding new findings suggesting an unexpected ADHD trajectory. Three recent population studies found a substantial number of individuals with onset of clinically significant ADHD symptoms and impairments after childhood, challenging the established notion of ADHD as exclusively a childhood-onset neurodevelopmental disorder. [9-11]

This narrative review of the literature addresses the following topics that might increase our understanding about these discrepant findings: a) conceptual and methodological issues inherent to the study of ADHD trajectories; b) data on persistence rates from longitudinal ADHD studies; c) predictors of ADHD persistence from childhood to adulthood; d) child and adolescent predictors of adult ADHD negative outcome; e) new adult-onset cases and their predictors.

CONCEPTUAL AND METHODOLOGICAL ISSUES INHERENT TO THE STUDY OF ADHD TRAJECTORIES

a) ADHD Diagnosis

In the last 50 years, the diagnostic criteria for ADHD from DSM-II to DSM-5 have been modified [1, 12, 13]. Previous work has demonstrated that use of different diagnostic criteria is one of the major factors influencing variability in ADHD prevalence rates worldwide over the last three decades [2, 14]. ADHD persistence is the proportion affected by the diagnostic definitions in childhood (denominator) who also meet the definition in adult life (numerator) [6,9]. A birth cohort study with assessments of the disorder from childhood to adulthood (15) provided different ADHD persistence rates depending on the diagnostic system used on multiple follow-up waves [15]. An adult norm-based diagnostic approach yielded the highest persistence rate compared to any other approaches (29.3% against 11.2% to 13.8% for strict criteria definitions). While some studies assessed individuals at baseline in childhood for ADHD using previous classifications (DSM-II, DSM-III) [16-21], others used more contemporary systems such as DSM-IV [11, 22, 23]. Assessments at follow up are likewise a source of heterogeneity in persistence estimates: studies have used DSM-III [17, 24], DSM-IV [15, 20, 21, 25], and DSM-5 [9, 11] criteria to determine ADHD diagnosis in adulthood. Differences of criteria may occur even in a same study in longitudinal assessments.

One study evaluated how differences in case definition might impact persistence estimates in the 16-year clinical follow-up of the Multimodal Treatment Study of ADHD (MTA) [26]. Persistence estimates varied widely from 1.9% (requiring DSM-IV criteria, combining parent and self-report in the Diagnostic Interview Schedule for Children (DISC) with an item-level AND rule) to 61.4% (requiring norm-based symptom count, combining parent and self-report in the DISC with an item-level OR rule). Based on findings from a ROC analysis of impairment, the authors concluded that the best combination of sensitivity and specificity was achieved using a norm-based threshold of four symptoms from either list (more than two standard deviations above the mean of the local normative comparison group) assessed with rating scales and

combining parental and self-report information with an item-level OR rule. This approach yielded a persistence rate of 60% for symptoms and 41% for symptoms with impairment.

Although the presence of impairment has been required by the successive revisions of diagnostic criteria for ADHD, the level of impairment required is not unanimous. The level of impairment substantially affects variability in ADHD prevalence rates worldwide and across the last three decades [2, 14]. Using full DSM-5 criteria, a recent population study assessing ADHD prevalence in adults [27] found a rate of 3.55% (95%CI 2.98–4.12%) for at least moderate impairment, but only 1.4% for severe clinical impairment. Thus, diagnostic rates vary substantially from one study to another depending on the level of impairment required for diagnosing the disorder at baseline and endpoint, [28].

Another conceptual issue is the source of impairment, which has varied across studies. Some studies used general measures of impairment, such as the Clinical Global Assessment Scale [29], Clinical Global Impression Scale [30], or the Global Assessment of Functioning [31], while others used measures that specifically assess impairment derived from ADHD symptoms, such as questions included in ADHD modules of structured or semi-structured diagnostic instruments [11, 20, 21]. Instruments created to assess impairment specifically related to ADHD, as the Barkley Functional Impairment Scale (BFIS) were also used [22]. Two paramount clinical follow-ups, the multimodal treatment Study of children with ADHD (MTA) [26] and the Pittsburgh ADHD Longitudinal Study (PALS) [32], used the Impairment Rating Scale (IRS) proposed by Fabiano et al for children with ADHD. [33] Although it is questionable whether the source of impairment can be clearly specified when comorbidity is the rule, persistence rates ascertained by different instruments, even for the same level of impairment, may be substantially different.

b) Sample characteristics

The origin of the sample (community or clinical) affects prevalence rates and clinical correlates of psychiatric disorders [34]. Clinical samples of individuals with ADHD in general include more severe cases than population samples and

thus, report increased comorbidity [35]. Part of this increased morbidity is expected according to the “Berkson’s Bias”, a mathematical bias due to restricting the sample to those individuals seeking clinical treatment and showing greater levels of severity and comorbidity [34, 36]. Thus, it is not surprising that ADHD persistence rates appear to be higher in clinical samples [18, 22, 23, 28] than in population-based samples [9-11]. Barriers to health services across countries also affect persistence rates. It is expected that clinical samples will select more severe and socially deprived cases in countries with accessible health care like the UK or Scandinavian countries. [37]

Additionally, retention rate is related to selection bias [38] affecting the representativeness of the sample, especially in population-based samples. A population-based sample with a substantial amount of participants lost to follow-up might underestimate persistence rates, since severe cases may have a higher risk of persistence and a higher risk of not attending several longitudinal assessments. [39].

c) Demographic aspects

Longitudinal ADHD studies assess individuals at different ages both at baseline in childhood and end point during adulthood [11, 40]. Considering the general trend that prevalence rates of ADHD decrease across the life cycle, regardless of the criteria used (see Faraone, Biederman, and Mick, [7]), age at assessment might be another factor influencing persistence rates. The literature shows that ADHD prevalence in adolescence is about half of that in childhood [2], and prevalence estimates continue to decrease in adulthood. This has been illustrated most clearly by a long ADHD follow-up study that assessed participants with childhood-onset ADHD at different time points in adulthood. The prevalence of ADHD declined to 43% at 18 years of age and 22% at 41 years (Mannuzza et al. [17]; Klein et al. [41]). In addition to attrition, these studies used different informants and diagnostic criteria classifications at different assessment points in adulthood, making it unclear whether the decrease in rate was mainly due to age or methodology. Regardless, age at entry into the study and age at endpoint clearly affect reported persistence rates.

The literature in general also suggests that females might have a higher persistence rate than males, as well as more negative outcomes in adulthood [42], although this could not be confirmed in the MTA sample. This sex difference might be responsible in part for the lower, in some studies absent, male/female preponderance during adulthood (see Matte et al. [27]; Vitola et al., personal communication). Thus, the proportion of females in the study may affect the observed persistence rate. This might be even more important in studies reporting persistence rates based on samples composed exclusively of males or females [17, 20, 21]. However, these differences might also be due to higher severity, comorbidity or adverse social background of girls diagnosed with ADHD compared to boys, instead of being only determined by gender.

d) Informants

Who is reporting the information is a major factor explaining heterogeneity in worldwide ADHD prevalence in childhood and adolescence [2]. The agreement between parents and teachers on ADHD symptoms is low in childhood, and the literature indicates that children tend to underreport their ADHD symptoms [5]. Consequently, the choice of the informant in childhood impacts the estimate of prevalence, and changing sources may impact estimates of persistence. As a complication, this informant effect may differentially influence various aspects of ADHD diagnostic criteria (e.g., either symptoms or impairment).

Although some reports suggest good inter-rater reliability between adult self-report and parent reports of childhood and adulthood symptoms [43], others documented that neither are reliable for retrospectively reporting ADHD symptoms in childhood [9, 44]. In adult clinical studies, parents or relatives that knew the individual during childhood tend to report retrospectively fewer childhood ADHD symptoms than adult retrospective self-reports [32, 45], the opposite of adult current report on symptoms and impairments [26, 42].

Thus, persistence rates will depend heavily on which information source was selected during childhood and adulthood. This is especially important because some studies change information source from the parent source in childhood to

affected individual (self) source in adulthood, potentially artificially deflating persistence rates [9-11].

DATA ON PERSISTENCE RATES FROM LONGITUDINAL ADHD STUDIES FROM CHILDHOOD TO ADULTHOOD

Based on the issues discussed above, it is not surprising that ADHD persistence rates from childhood to adulthood vary substantially among studies (Figure 1). The figure shows estimates of full ADHD diagnostic persistence reported by longitudinal studies that followed children to a mean age of at least 18 years. A comparison of the extremes is informative. The lowest rate detected was 4% in a clinical study in the US [17]. This study followed referred boys diagnosed with DSM-II hyperkinetic disorder at ages 5 to 11 years and reassessed their ADHD status 17 years later with DSM-III-R criteria. Potential factors responsible for this low rate include: 1) The sample was composed exclusively of males (see below); 2) Patients with comorbid conduct disorder at baseline were excluded; 3) Change of diagnostic system and assessment approach: DSM-II with clinical interview at baseline and DSM-III-R with structured interview at follow up; 4) Requirement of endorsement of childhood ADHD symptoms and impairment at follow up to diagnose adult ADHD; 5) The strict use of a DSM threshold instead of a norm-based approach. The authors emphasize that recall bias might have constrained the persistence rate (see Klein et al. [41]). The highest ADHD persistence rate found was 76% in the UK study by Cheung and colleagues [22]. Authors followed children and adolescents (mean age 11.8, 87% males) with ADHD combined type (DSM-IV) criteria for 6.6 years. Factors that might be responsible for this very high rate include: 1) A short follow-up time; 2) Similarity of assessment in the two time points, using DSM-IV and a structured interview and no change of information source (parent report); 3) A clinical sample composed of only ADHD combined type (see below); 4) relatively young age at follow up .

PREDICTORS OF ADHD PERSISTENCE FROM CHILDHOOD TO ADULTHOOD

The comprehensive review of persistence rates found few studies that report factors in childhood related to the course of symptoms into adulthood. A recent systematic review and meta-analysis summarizing the findings thus far concluded that available reports are heterogeneous and hard to combine [46]. However, a meta-analysis of predictors assessed and reported by at least three studies is summarized in Table 1.

Characteristics of the clinical syndrome were the most consistent risk factor for persistence: comorbid conditions like Conduct Disorder (CD) and Major Depressive Disorder (MDD), severe ADHD, and treatment for ADHD are associated with ADHD persistence. The finding that ADHD treatment is a risk factor for persistence is not surprising, since the most severe cases are selected for treatment. Barriers to health care may influence this finding; lack of access to treatment might be a marker of environmental or socioeconomic risk factors (e.g, ethnic minorities or living in an area with limited resources [47, 48]. Importantly the two studies that found the effect of ADHD treatment adjusted their findings for disorder severity, but possibly the treatment-severity relationship was not fully captured by the instruments used. A clinical study that followed individuals for 5 years after a 12-month randomized clinical trial found that medication adherence was related to greater improvement but higher end-point symptoms, while symptom severity at baseline was the most important single predictor of persistent symptoms at follow-up [49]. Disentangling this bias adequately would require a randomized clinical trial with good adherence and retention for several years comparing outcome between allocated groups at baseline. However, maintaining adherence to assigned treatment over long periods may not be possible.

An analysis of the MTA evaluated childhood factors influencing persistence of ADHD into adulthood at a mean age of 24.7 years [50]. ADHD symptom severity, comorbidities, and parental mental health problems were the most important risk factors for persistence, while childhood IQ, socioeconomic status, parental education and parent-child relationships showed no association with persistence. These findings are, in general, similar to what was reported in the meta-analysis (see Table 1). However, treatment assignment was not evaluated

as a risk factor, having been found in previous reports to have lost significant association with symptom severity by 3 years [51, 52].

EVALUATION AND PREDICTION OF TRAJECTORIES OF ADHD SYMPTOMS

Another possible approach to evaluate persistence and remission is to investigate trajectories of symptoms rather than categorical diagnosis. Since few studies using this approach followed subjects from childhood to adulthood, we also included studies where the last assessment was in late adolescence in this section.

One study evaluated baseline differences between trajectories of ADHD symptoms (persistently high compared to declining) through grades 3 to 12, when participants are expected to be 17 or 18 years old [53]. Participants with a more chronic trajectory were more aggressive and more hyperactive at school, and more emotionally dysregulated at home than their peers with a declining trajectory of ADHD symptoms. The investigators also reported a more stable pattern of inattentive symptoms compared to hyperactive symptoms, a finding that was reported in previous studies [54]. In a different study, 8395 twin pairs were assessed for ADHD at ages 8, 12, 14 and 16 with a DSM-IV ADHD symptom subscale. [55] Consistent with population-based and clinical studies, there was a general decline of symptoms across ages, and inattentive symptoms persisted more than hyperactive/impulsive symptoms. Authors reported important inter-individual differences in the developmental course of symptoms, mostly explained by genetic influences independently of baseline severity. Another study (Howard et al, 2016) showed protective effects related to parenting and attendance in college that were manifested in the transition from adolescence to adulthood [56]. In the adult assessment of the MTA, a dimensional outcome based on symptom-severity showed a large difference between the overall ADHD group and comparison group. However, neither initial random allocation to treatment with medication nor self-selected, extended use of medication significantly predicted adult outcomes on this variable within the ADHD group (Swanson et al., personal communication).

The Avon Longitudinal Study of Parents and Children, a large birth cohort in the UK, analyzed factors associated with latent-class trajectories of ADHD symptoms age 4 to 17 years. The persistent class (3.9% of the sample and 40.2% of participants with high childhood scores) had mostly males (72.9%) and higher conduct problems, language impairments, and social-communication problems and lower IQs. Also, the persistent group had higher ADHD genetic liability as indexed by ADHD polygenic risk scores, whereas other psychiatric genetic risk scores (schizophrenia, bipolar disorder and depression) were not associated with trajectories (Riglin et al, personal communication).

PREDICTORS OF ADULT ADHD DELETERIOUS OUTCOMES THAT CAN BE DETECTED IN CHILDHOOD AND ADOLESCENCE

There is substantial evidence documenting adverse outcomes for those affected by ADHD compared to those without the disorder [5, 6]. ADHD affects a wide range of functional domains including academic, social, and occupational contexts. Studies have documented lower academic achievement [57, 58], higher unemployment, and lower income for probands with ADHD followed into adulthood [28, 59, 60]. The risk of substance use disorders (SUD) and antisocial personality disorder is higher in patients with ADHD than in non-affected individuals [61-65]. Individuals with ADHD are more likely to have traffic accidents than the general population [66-68]. Other documented outcomes include obesity [69, 70], dysfunctional family relationships [28, 71] and emotional dysregulation [72]. These functional impairments may result in reduced perception of well-being [73] and be related to adverse outcomes like higher overall mortality rates in individuals with current or past ADHD diagnosis [74]. A comprehensive meta-analysis has confirmed a longitudinal association of childhood ADHD with adverse outcomes, the most relevant being mental disorders and substance abuse, academic and professional underachievement, criminality, and risky driving behaviors [75]. The 16-year follow-up of the MTA showed that adverse outcomes in education, work, and risky sexual behavior were associated with ADHD and symptom persistence; the risk increases in a progressive fashion: the local normative comparison group (LNCG) had the lowest risk, symptom-persistent ADHD the highest, with symptom-desistent

ADHD in between. For emotional outcomes, like anxiety and depression, there difference was not significant between those whose symptoms remitted and the LNCG, while both were doing better than ADHD persisters. Alcohol use and jail time did not differ significantly across any of the groups assessed, probably because alcohol use was so common and jail time so rare [76].

Although these adverse adult outcomes associated with ADHD are unquestionable, much less clear are their childhood predictors. Several factors have been suggested as influencing the outcome in ADHD subjects, like the clinical profile (ADHD severity and comorbidities), pre-natal factors [77], genetic and family loading, gene-environment interactions, and protective factors like exercise and cognitive ability [5, 78].

A recent systematic review and meta-analysis on ADHD and criminality consistently identified these risk factors for arrests, convictions and incarcerations [79]: male sex, low intelligence quotient, severe ADHD, and comorbid conduct disorder. Low socioeconomic status was associated in univariate analysis but the effect faded in multivariate analysis. A study of unimodal (medication only) and multimodal treatments initiated in the 1970s evaluated long-term effects and showed an initial protective effect in the multimodal treatment group that dissipated in the adult follow up [80, 81].

ADHD severity, comorbid conduct disorder and oppositional defiant disorder, sexual abuse, school suspension, family history of SUD or ADHD and male gender were associated with SUD development in ADHD, whereas ADHD inattentive subtype and a fearful temperament were inversely associated [82]. One study found that the development of SUD in adulthood was predicted by age of treatment initiation in childhood (the later, the higher the risk for SUD) and that the relation was moderated by antisocial personality disorder [83]. The MTA found no residual effect of initial assignment to 14 months' treatment with medication and no effect of current treatment with medication in the development of SUD in adolescence [84]. The PALS, a clinical follow-up, found medication to be a risk factor that lost significance when controlling for other factors at baseline [85].

A cross-sectional analysis of data from nationwide registers found the overall mortality rate higher among ADHD patients than in the general population, and the risk was especially higher in females, and with comorbid oppositional defiant disorder, conduct disorder, and SUD. The mortality rate ratio was 4.25 (95% confidence interval: 3.05-5.78) for individuals diagnosed with ADHD at ages 18 or older, compared to 1.86 for 5 or younger and 1.58 for those diagnosed between 6 and 17 years of age [74].

In the Milkauwee follow-up study, higher ADHD scores in childhood predicted a wide range of worse outcomes like educational, occupational, financial and driving problems, whereas lower IQ was associated only with worse educational and occupational outcomes [28].

NEW ADULT-ONSET CASES AND THEIR PREDICTORS

Historically, ADHD has been conceptualized as a child-onset neurodevelopmental disorder [86]. The last DSM version (DSM-5) launched in 2013 [1] included the disorder in the neurodevelopmental disorders section. Three recent population studies from diverse cultures challenged the notion that ADHD has its onset only in childhood by suggesting the existence of a significant large proportion of individuals who report onset of ADHD symptoms and impairments after childhood [9-11]. The most surprising finding among the three studies is the similarity in the rates of these new adult-onset cases in the three studies: 87% of the adults with ADHD presented new adult-onset in the New-Zealand study [9], 87.4% in the Brazilian study [10], and 67.5% in the UK investigation [11]. However, issues have been raised about the meaning of these findings. One hypothesis is that the new onset cases are the result of the false positive paradox. Another explanation is that in all three samples there was a shift from parent-report or teacher report in childhood to self-report in adulthood. However, the British study has controlled for this potential bias in secondary analyses[11]. A recent analysis in the ALSPAC cohort relying on the same source information for assessments, and using a screening instrument for ADHD (hyperactive SDQ scale) at ages 7 and 17 years old (parental assessment), found that 54% of the adult cases were new-onset cases. In addition, the persistence rate was only 22%. (Riglin et al, personal communication).

In an analysis of predictors in childhood for the adult-onset ADHD cases, the British study [11] found that higher IQ, and lower externalizing and internalizing scores differentiated the adult-onset individuals from the ADHD persistent group. One possible explanation for this would be that high intelligence and lack of comorbidity allow the disorder to go undetected during childhood and adolescence. In the Dunedin study, the following childhood factors differentiate the adult ADHD group from non-ADHD adult group: higher ADHD scores by teachers' report, conduct disorder and lower reading ability scores [9]. Future investigations need to clarify which factors predict adult-onset cases compared to individuals without ADHD. An international effort comparing data sets from different cultures on this question is ongoing.

CONCLUSIONS

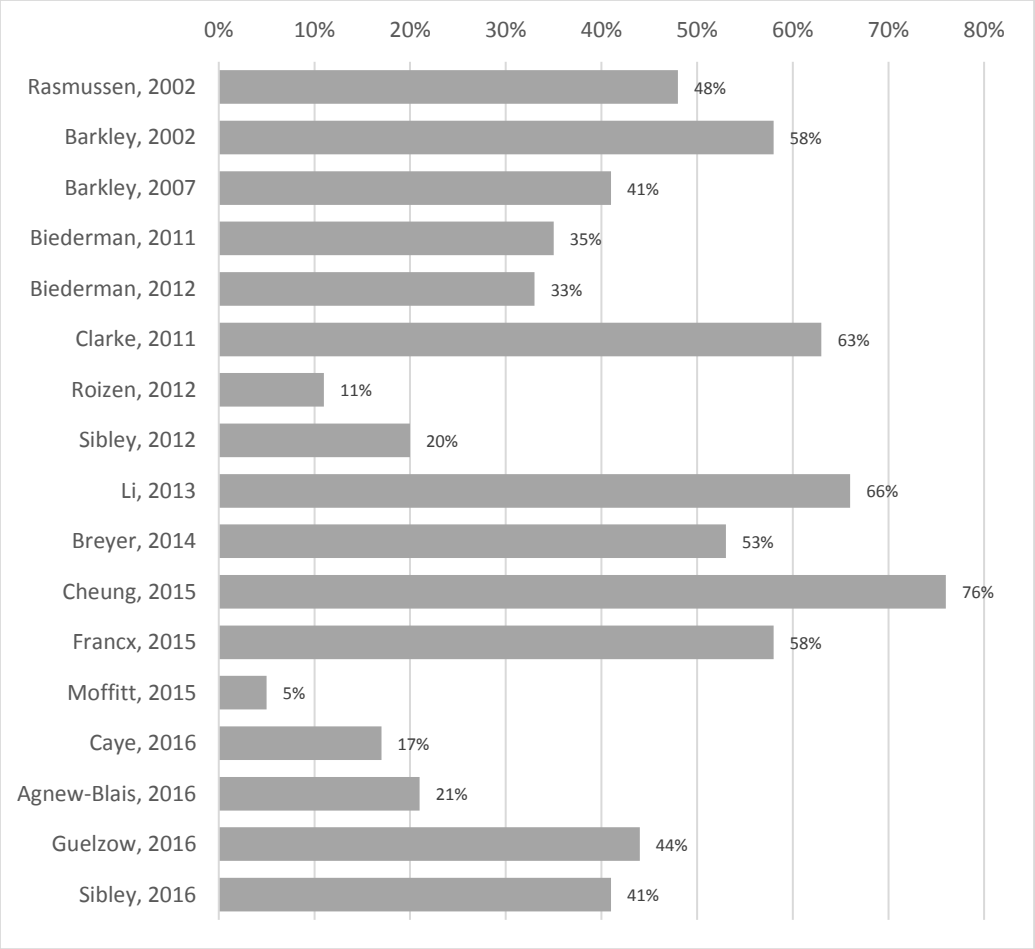
Several methodological factors intrinsically related to the ADHD diagnosis (e.g., diagnostic criteria), demographic and sample characteristics (e.g., clinical or population origin and age), and information source (self or other) seem to be responsible for different persistence rates from childhood to adulthood among studies. Since evidence from longitudinal studies on ADHD is scarce and extremely heterogeneous in methodology, it is difficult to disentangle with statistical methods the role of each of these factors in explaining the heterogeneity of ADHD persistence rate. This scenario results in a wide range of observed persistence rates among studies, from as low as 4% [17] to as high as 76% [22].

The available literature indicates that ADHD severity, comorbid conduct disorder and major depressive disorder and treatment for ADHD are the main predictors of ADHD persistence from childhood to adulthood [46]. Comorbid conduct disorder in childhood is ubiquitous as a predictor of multiple adverse outcomes like premature mortality, SUD, and criminality, whereas other factors have controversial effects depending on the study. Male sex is a risk factor for SUD and criminality but is protective in terms of the overall mortality rate. Stimulant medication use may protect against the development of SUD (although the MTA, the largest prospective study, failed to find such an effect).

Severity of ADHD appears to be positively associated with criminality and SUD, but its relationship with mortality could not be assessed due to lack of data.

Finally, innovative investigations like those suggesting the possibility of an adult-onset ADHD trajectory predicted by higher cognitive reserve and lower symptomatology in childhood are important to expand our knowledge about ADHD trajectories across the life cycle.

Figure 1. Estimates of ADHD persistence rates into adulthood in longitudinal studies.



All reported studies are longitudinal studies with mean age at follow up of at least 18 years old and a full diagnosis (syndromatic) definition of persistence.

Table 1. Summary of risk factors reported in the systematic review and meta-analysis by Caye and colleagues (2016).

Factors meta-analyzed and significantly associated with persistence

PREDICTOR	ODDS RATIO	95% CONFIDENCE INTERVAL	P-VALUE
Severe ADHD	2.33	1.6 – 3.39	< 0.001
Treatment for ADHD	2.09	1.04 – 4.18	0.037
Comorbid Major Depressive Disorder	1.80	1.1 – 2.95	0.019
Comorbid Conduct Disorder	1.85	1.06 – 3.24	0.03

Factors meta-analyzed nonsignificantly associated with persistence[a]

PREDICTOR	ODDS RATIO	95% CONFIDENCE INTERVAL	P-VALUE
Female gender	1.23	0.84 – 1.81	0.295
Comorbid ODD	1.65	0.75 – 3.65	0.213

Factors meta-analyzed and consistently not associated with persistence

PREDICTOR	ODDS RATIO	95% CONFIDENCE INTERVAL	P-VALUE
Single parent family	1.08	0.25 – 1.29	0.179

PREDICTOR	SMD[b]	95% CONFIDENCE INTERVAL	P-VALUE
Intelligence quotient	0.03	-0.18 - -0.23	0.8

Factors not meta-analyzed but associated with persistence in individual studies

Combined ADHD Subtype • Comorbid Bipolar Disorder • Parental ASPD[c]

a. Authors note that sensitive analysis or the adoption of less conservative meta-analysis techniques (fixed-effects models) would result in a positive and significant association for Comorbid ODD and female gender, whereas single parent family and intelligence quotient have consistent small and not significant effects on persistence across included studies.
b. Standardized Mean Difference
c. Antisocial Personality Disorder

REFERENCES OF IMPORTANCE

Reference	How it adds to the literature
REFERENCES OF MAJOR IMPORTANCE	
● ● Hechtman et al (2016)	A report on long-term outcomes of ADHD children and controls within the larger clinical trial on the field and its relationship with symptom persistence and desistance.
● ● Caye et al (2016)	First systematic review of childhood predictors of ADHD persistence. Provides summarized estimates of risk with meta-analytic techniques.
● ● Moffitt et al (2015)	The first time that the late-onset ADHD was reported in an analysis of a four-decade longitudinal cohort.
● ● Dalsgaard et al (2015)	An analysis of health records found a significant association between ADHD and overall mortality.
● ● Erskine et al (2016)	A comprehensive systematic review of long-term outcomes of ADHD and conduct disorder. Provides summarized estimates of risk with meta-analytic techniques.
REFERENCES OF IMPORTANCE	
● Sibley et al (2016)	This was the first study to analyze a wide range of ADHD persistence definitions and test for the accuracy of those definitions within one clinical sample.
● Agnew-Blais et al (2016)	An UK longitudinal cohort found similar results in regard to the late-onset ADHD and reported factors from childhood related to this trajectory.
● Caye et al (2016)	A Brazilian longitudinal cohort found similar results in regard to the late-onset ADHD and tested for multiple confounding factors in secondary analyses.

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