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Doctoral Thesis

THE DEVELOPMENTAL COURSE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PERSISTENCE, REMISSION AND EMERGENCE OF SYMPTOMS FROM CHILDHOOD TO ADULTHOOD

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This thesis is part of the Tripartite Graduate Program on Developmental and Translational Neuroscience. This program is run by Brazilian Graduate Programs in Psychiatry and Mental Health regarded as of international level by the Brazilian Ministry of Education from three Universities (Universidade Federal de São Paulo, Universidade de São Paulo, e Universidade Federal do Rio Grande do Sul). The Tripartite program aims to train the top researchers in the country with advanced knowledge on innovative field methodologies in strategic areas such as population neuroscience, evidence-based phenomenology, clinical neuroscience, integrative neuroscience and evidence-based prevention of mental disorders.

ABSTRACT

Attention-deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that affects children, adolescents and adults. Several adverse outcomes have been consistently associated with a diagnosis of ADHD at any point in life. In this thesis, we were dedicated to the study of the course of ADHD from childhood to adulthood focusing on three perspectives. First, we discuss the age at onset of ADHD. Historically, ADHD has first been identified and described in children. Prospective clinical studies of children with ADHD found that the disorder might persist throughout adulthood, and the concept of adult ADHD remained tied to a childhood-onset disorder. Diagnostic manuals included age at onset in childhood as a core criterion for a valid ADHD diagnosis in adolescence and adulthood. However, recent studies challenged the validity of this criterion, suggesting that many ADHD cases in adulthood might have had a late onset. In this thesis, we present our contribution to the field with original data from a longitudinal birth cohort in Brazil and a theoretical discussion on the evidence so far available on the matter. Second, our research tried to parse out children who are at high risk for either persisting with ADHD throughout adolescence (for those already affected) or developing ADHD during their development into young adulthood. While many risk factors are already known, the literature is heterogeneous, findings are sometimes contradictory, and there is little clinical translation from the evidence. We reviewed and meta-analyzed the evidence available on risk factors for ADHD persistence, providing summary estimates for several known risk factors. We then developed and validated a multivariable risk calculator that aggregated several of these risk factors into one accurate individualized risk prediction. This tool is intended for research and clinical use, and available on-line. Third, we investigated the relative immaturity effect, by which children who are born later in the school calendar year present are more frequently diagnosed with ADHD. We did so by reviewing and meta-analyzing the evidence available, and by analyzing data from three large community-based cohorts placed in Brazil. The effect of relative immaturity is a conceptual demonstration of the importance of developmental adaptations in the genesis or worsening of ADHD symptoms, which might influence its emergence along childhood, adolescence and adulthood.

RESUMO

O Transtorno de Déficit de Atenção/Hiperatividade (TDAH) é um transtorno comum do neurodesenvolvimento que afeta crianças, adolescentes e adultos. O diagnóstico de TDAH estão consistentemente associados com desfechos adversos em qualquer idade. Nesta tese, nós nos dedicamos ao estudo do curso do TDAH da infância até a idade adulta, focando em três perspectivas. Primeiro, discutimos a idade de início do TDAH. Historicamente, o TDAH foi identificado e descrito pela primeira vez em crianças. Estudos clínicos prospectivos de crianças com TDAH descobriram que o transtorno pode persistir até a idade adulta, e o conceito de TDAH adulto permaneceu conectado a um transtorno de início na infância. Manuais diagnósticos incluíram idade de início na infância como um critério central para um diagnóstico válido de TDAH na adolescência e idade adulta. Entretanto, estudos recentes desafiaram a validade empírica deste critério, sugerindo que muitos casos de TDAH na idade adulta podem ter um início tardio. Nesta tese, apresentamos nossa contribuição nesta área com dados originais de uma coorte de nascimento no Brasil, e uma discussão teórica a respeito da evidência disponível sobre o assunto. Na segunda perspectiva, nossa pesquisa tentou identificar crianças que estão em risco para persistir com TDAH ao longo da adolescência (para aquelas já afetadas pelo transtorno) ou desenvolver TDAH ao longo do seu desenvolvimento até o início da idade adulta. Embora diversos fatores de risco sejam conhecidos, a literatura é heterogênea, os achados são por vezes contraditórios, e existe pouca tradução da evidência para a clínica. Nós revisamos e meta-analisamos a evidência disponível em fatores de risco para a persistência de TDAH, produzindo assim estimativas sumarizadas de risco para diversos fatores conhecidos. Em um segundo estudo, desenvolvemos e validamos uma calculadora de risco multivariada que agrega vários destes fatores em uma predição de risco individualizada e acurada. Esta ferramenta está disponível gratuitamente *on-line*, e pode ser usada em contextos clínicos e de pesquisa. Na terceira perspectiva, investigamos o efeito da imaturidade relativa, pelo qual crianças que nasceram mais tarde no ano letivo são mais frequentemente diagnosticadas com TDAH. Nós revisamos e meta-analisamos a evidência disponível, e analisando dados de três grandes coortes comunitárias no Brasil. O efeito da imaturidade relativa é uma demonstração conceitual da importância de adaptações desenvolvimentais na gênese de sintomas de TDAH, que podem influenciar sua emergência ao longo da infância, adolescência ou idade adulta.

Theoretical framework

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental syndrome characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity[1]. ADHD commonly affects children, adolescents and adults[2,3]. Evidence from clinical, epidemiological and longitudinal studies have consistently documented strong associations between ADHD and adverse life outcomes[4-6]. Children with ADHD show an increased risk of accidental injuries[7], poor relationship with peers[8] and parents[9], worse quality of life[10], and impaired school performance[11]. Adolescents with ADHD show more school refusal and grade retention[11], earlier and more frequent use of marijuana, tobacco and other illicit drugs[12,13], earlier sexual engagement[14] and more frequent teenage pregnancy[15,16]. Adults with ADHD have lower education attainment, reduced job performance, and increased emotional problems[17-19]. At all ages, there is increased mortality by external and accidental causes[20]. Overall, the estimated incremental economic burden imposed by ADHD ranges from $143 to $266 billion dollars in the United States alone, most of which is a consequence of lost productivity[21].

The evidence supporting the scientific knowledge behind the epidemiology, diagnosis, neurobiology and treatment has been growing rapidly in the last decades (Figure 1). Despite the wealth of data, several unanswered questions remain on all these areas pertaining to ADHD and its correlates. One critical area relates to how and when ADHD might emerge throughout development, and the factors by which it persists as a chronic life condition in some individuals: the developmental course of ADHD.

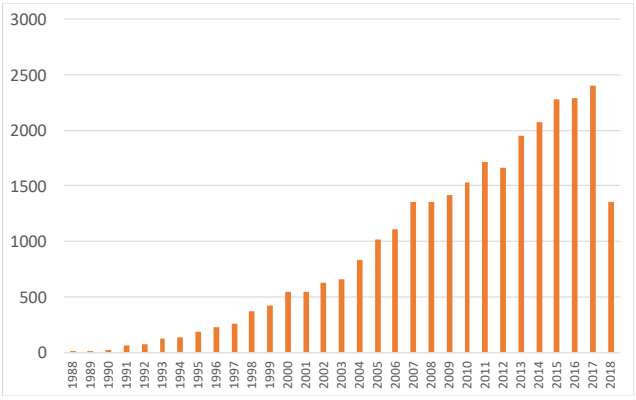

Figure 1. Number of publications by year containing the words ADHD or "hyperkinectic disorder" indexed in the Web of Science from 1980 to 2018 (as in August, 15th)

A historical perspective on the developmental course of ADHD

The ADHD syndrome was first described scientifically in the eighteenth century in children[22]. A Scottish physician named Alexandre Crichton wrote a book series entitled "An inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects''[23]. One of its chapters was focused on disorders of attention, in which he described a syndrome very much alike to what is nowadays known as the inattentive subtype of ADHD. Already at that time, Dr. Chrichton clearly indicated the idea that affected individuals were born with this syndrome and that it manifests very early in life: "When born with a person it becomes evident at a very early period of life". Another concept that was reintroduced later in the field is the tendency to remission. The author stated that this syndrome of distractibility "generally diminished with age". Both of these historical cornerstones on the developmental course of ADHD, the age at onset and the persistence/remission dichotomy, will be central in this thesis.

The first systematic case reports of an ADHD-like syndrome in the literature came over a century later with the lectures of Sir George Still to the Royal College of Physicians of London entitled "On Some Abnormal Psychical Conditions in Children''[24]. In these lectures, a specific group of children were described with features that resembled ADHD closely. Seven out of nine cases had an onset before age 7 – a cut-off which would be adopted decades later by the third version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). Similarly, Drs. Franz Kramer and Hans Pollnow, in a series of case reports entitled "On a hyperkinetic disease of infancy", observed that the peak onset of this disorder akin to ADHD was at age 6[25].

While the case reports accumulated, and leaned towards a more homogeneous syndrome, researchers started to link the early age at onset with presumed mild neurological deficits to convey an etiological-based nomenclature for the syndrome. Among the first terms was "minimal brain damage", later updated to "minimal brain dysfunction", based on the idea that the hyperactivity and inattention derived from abnormalities in the frontal lobes[26]. According to this view, the damage or dysfunction were a result of prenatal and perinatal

insults, thus the early presentation. This nomenclature was soon abandoned, however, due to its broadness and lack of specificity.

Therefore, the DSM-II incorporated ADHD into a more descriptive model, labeling it as "Hyperkinetic Reaction of Childhood"[27]. There were no specific criteria for age at onset, but the manual stated that the disorder was found especially in young children and tended to remit during adolescence. Years later, the DSM-III was the first diagnostic manual to specific require age at onset of symptoms before age 7, based solely on clinical experience[28].

Why does the course of ADHD matter?

Precise, evidence-based knowledge on the course of ADHD has several implications for research and clinical practice. These implications affect every other related field on ADHD, from diagnosis and classification to neurobiology and clinical management. Current assumptions on the course of ADHD might be overstated and lacking the support of evidence, as we will see further in the current thesis. These assumptions have nevertheless been shaping the way science and healthcare in ADHD goes forward in some key areas.

First, there is the issue of diagnosis and classification. Currently, the *Diagnosis and Statistical Manual for Mental Disorders, 5th edition* (DSM-5) classifies mental disorders according to their predominant occurrence along the lifetime [1]. ADHD is grouped among other neurodevelopmental disorders that occur in childhood. Not only the classification is important, but the diagnostic criteria as well. The DSM-5 requires the onset of many ADHD symptoms to be present in childhood (before age 12) for the diagnosis of the syndrome in an individual of any age. The assumption that ADHD is always a childhood-onset disorder, which is endorsed by the main diagnostic manuals, implicates that: a) individuals who report a later onset of symptoms are excluded from epidemiological, clinical and etiological studies on ADHD; b) adult and adolescent patients who do not confirm the required childhood-onset are deprived of treatment; c) ADHD is usually grouped with other childhood-onset neurodevelopmental disorders such as autism or dyslexia, despite different clinical presentation and underlying biology.

The understanding of the neurobiology of ADHD is affected by the understanding of the course of ADHD, not only by the way patients are selected or grouped, but also by the intricate conclusions that follow from the assumptions that prevail regarding the longitudinal pathways of symptoms across development. For instance, a childhood-onset centered framework for ADHD implies that the genetic vulnerability of individuals with ADHD should be mostly expressed as a phenotype when these are children – therefore, case-control studies in childhood were the most frequent design in the quest for ADHD genes in the last decades[29]. Likewise, longitudinal neuroimaging studies have usually departed from ADHD children who outgrow or not their ADHD throughout development assessing which structural and functional changes occur in the brain related to these symptom trajectories[30-32]. However, emergence of symptoms after childhood is never considered in these studies.

A paramount feature of the clinical management of medical conditions, including mental disorders, is the ascertainment of a correct prognosis. Meanwhile, the current understanding of ADHD is that of a chronic condition[1,30]. The available treatments, however, have only short-term effects that tend to disappear after discontinuation[33]. Long-term adherence is usually low [34,35]. Regardless of treatment, many children will get better and remit spontaneously during development. Many others will continue to experience lifelong impairing symptoms [36]. In the case of ADHD, parsing out children whose ADHD will remit from those whose ADHD will persist for many more years could inform clinicians in advance about who will benefit from intensive strategies to improve adherence, and who will benefit from a scheduled gradual strategy of testing tapering off treatment.

What is known on the course of ADHD?

Since the first reports on the nineteenth century to the first clinical trials, ADHD has always been conceptualized as a disorder of childhood, and most of the evidence on ADHD comes from studies conducted in school-aged children. Unsurprisingly, the first seminal studies to investigate the course of ADHD in a long-term basis departed from clinical samples of children with ADHD and their unaffected peers[37]. These studies were the first to unveil the deleterious long-term effects of having ADHD as a kid, a finding that was extensively replicated in further studies in the following decades[38]. Children with ADHD had, years

afterwards as adolescents and young adults, lower educational attainment, worse professional and financial achievements, and poorer satisfaction with their relationships. They also exhibited a range of other psychiatric disorders in young adulthood, such as depression and anxiety, more frequently than controls (Table 1).

However, a surprising finding at that time was that many of those young adults with a history of childhood ADHD still exhibited impairing symptoms of inattention, hyperactivity and impulsivity that were indistinguishable from those that they presented as children. Gradually, the field started to recognize the entity of adult ADHD, and epidemiological, etiological and clinical studies were conducted in this population. Currently, adult ADHD is widely recognized as a valid disorder with impairing features and proper response to treatment [6]. However, perhaps by the course of these findings, among the scientific community, adult ADHD remained tied to the idea of childhood ADHD.

Although these studies leveraged on a sound longitudinal design, there were marked methodological differences both within each study (in their multiple follow-up assessments) and among the studies. Some of these methodological differences could potentially have an impact on the estimation of persistence rates and frequency of adverse outcomes[39]. For instance, the ADHD diagnostic criteria have changed in the last decades. Several clinical studies included at baseline children with ADHD as per DSM-II or DSM-III[40,41], which had stringent criteria. At follow-up, they assessed adults with the more flexible DSM-IV criteria – such studies are likely to estimate higher persistence rates than those who had not changed the criteria during follow-up. A study by Margaret Sibley and colleagues investigated this specific issue in the 16-year clinical follow-up of the MTA [42]. In that study, 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).

While the relevance of the diagnostic criteria is evident, much less attention has been given to the information source needed for meeting these criteria. Even though it is good practice to inquire about

Table 1. Main studies reporting on longitudinal long-term outcomes of childhood ADHD.

Studies	**Sex**	**Baseline age (years old)**	**Follow-up (years)**	**Number included**	**Sample type**	**Case definition (baseline)**	**Main findings in young adulthood (Cases compared to Controls)**
Barkley, 2004/2006[43,44]	Both	4-12	14	220/225	Clinical	DSM-II	More criminal acts and drug abuse Lower educational achievement More social and work problems Higher rates of sexually transmitted diseases and early parenthood
Biederman, 2006/2012[19,45]	Males	6-17	10/16	169/217	Clinical	DSM-III-R	Higher rates of psychopathology Lower educational achievement Lower occupational status More substance addiction
Biederman, 2010[46]	Females	6-17	11	187	Clinical	DSM-III-R	Higher rates of psychopathology More substance addiction
Dalsgaard, 2015[20]	Both	No restriction	32	1922248	Community	ICD-9/10	Higher rates of mortality due to external causes
Galera, 2009/2012[11,47]	Both	4-18	8/18	1264/1103	Community	DSM-IV	More socioeconomic disadvantage Lower academic performance and educational achievement More grade retention
Mannuzza, 1989/1991, 1993/1997/1998/2008; Klein, 2012[18,41,48-50]	Both	6-12	9-33	104-189	Clinical	DSM-II	Higher rates of psychopathology Lower educational and occupational achievement Higher rates of arrests, convictions and incarceration Worse social outcomes More psychiatric hospitalizations
Swanson, 2017[34]; Hechtman, 2017[17]; Molina, 2018[13];	Both	7-10	12-16	717	Clinical	DSM-IV	Lower educational achievement Worse occupational outcomes More neuroticism and emotional liability More substance abuse

ADHD symptoms from all available sources (for instance, the patient, close relatives, and teachers), it is relatively clear that the main source of information changes across development from the main caregivers (usually the parents) to the own patient[51]. In the context of research, structured and semi-structured interviews usually consider only one report – either the parent report for children and the self-report for older adolescents and adults. Almost all longitudinal studies that span several developmental stages are affected by the change in the source of information[39]. This change might impact persistence estimates by adding external confounders, that is, the inter-rater agreement, which is known to be low to moderate between patients and their informants [51-53].

The nature of these samples also has the potential to impact the study of the ADHD course. The first longitudinal reports were clinically based. On one hand, they benefited from a thorough and careful clinical assessment; these samples were, in general, very well described and resembled the clinical scenario encountered by clinicians in their day-to-day practice. However, clinically referred samples often select more severe and impaired cases that might not speak to the entire population of ADHD patients. There is a tendency, therefore, that clinical samples would overestimate persistence and adverse outcomes compared to what are the true rates in the population, and that population-based samples underestimate these rates compared to what is actually seen in clinical practice[39].

The accumulation of longitudinal follow-up studies of children with ADHD revealed that persistence of symptoms throughout adulthood was a frequent outcome, but other possible developmental courses were observed. A seminal systematic review and meta-analysis on the subject determined that 15% of children with ADHD would still persist with a full syndrome (including symptom threshold, impairment and pervasiveness) by adulthood[36]. Another 35% would have remitted completely, regardless of treatment, in a course that could be called the “benign ADHD of childhood”. The remaining 50% would be partial remitters, still presenting with abnormal levels of symptoms that do not fulfill criteria for a formal diagnosis. Notably, the gradual persistence of the syndrome is associated with a gradient of functional outcomes: controls have better outcomes than remitters, who in turn have better outcomes than persisters[17].

In accordance with a neurodevelopmental perspective, longitudinal studies with neuroimaging data of children with ADHD and their peers have found that the differential trajectories of childhood ADHD are linked to the brain development. One of the first longitudinal neuroimaging studies with ADHD children was conducted by Professor Castellanos and his colleagues at the National Institute of Mental Health[54]. In this case-control study, 152 children and adolescents with ADHD had, at baseline, smaller volumes across all regions of the brain compared to 139 age- and sex-matched controls. In follow-up visits, differences persisted across development in most regions. The studies by Philip Shaw and colleagues investigated the developmental trajectories of ADHD cases and controls with longitudinal brain imaging [32,55,56]. They observed significant developmental abnormalities in cortical thinning, especially in the medial and dorsolateral prefrontal cortex – brain regions that are central to attention and cognitive control. Along development throughout adolescence, there was a general tendency of normalization of the cortex to a point where cases and controls were fairly equal in terms of brain development. Those findings matched the idea that ADHD frequently remits throughout adolescence. Furthermore, the analyses showed that when ADHD persisted, brain normalization did not occur, and the more ADHD symptoms in adulthood, the lesser the rate of cortical development in a continuous fashion. In general, the literature suggests that the remitted brain has similar functioning than the never affected brain in some – prefrontal cortex, default mode network – but not all – posterior cortex, thalamus, striatum – structures and networks[57]. Furthermore, well-powered case-control studies with a wide range age of participants found brain differences between patients and controls to be more pronounced in children and adolescents than in adults[58]. A case control study spanning participants from 8 to 30 years of age found smaller brain volumes to be consistent and developmentally stable from childhood to early adulthood[31]. However, the caudate and putamen volumes were found to increase in young adulthood in cases, while in controls it had a tendency to decrease. Authors hypothesize that overcompensatory mechanisms could be at play in such brain regions.

Another evidence that ADHD is a disorder strongly related to normal development comes from observations that equal demands for children of slightly different age (and therefore, assumed development) generate symptoms of ADHD. The current school system provides an opportunity for such a conclusion. During clinical assessments, children are frequently

compared to their classmates, who are usually grouped within a one-year range at school. Psychiatrists and pediatricians will, most of the times, rely on this comparison in order to set the threshold between clinically relevant ADHD symptoms and typical development[59]. Nevertheless, children are not of the exact same age within one classroom: because they were born on a 12-month range, there might be up to a 15% difference (at first grade, when they are 6 years old) of age between two classmates.

Accordingly, epidemiological and clinical studies found higher rates of ADHD among children who are relatively young compared to their classmates (i.e., were born in the last months of the school year)[60-67]. These reports leverage on three types of data: epidemiological samples using official records of ADHD diagnosis; epidemiological samples using official records of ADHD medication; and clinical samples assessing relative immaturity within diagnosed children and adolescents. Regardless of methodological differences, almost all those studies agree that being relative immature within the school year is a risk factor for receiving an ADHD diagnosis and/or medication. The estimates, however, are variable, with relative risks ranging from 1.12 to 2.43 considering only positive and significant associations.

Clearly, there is no plausible reason to assume that these children have a stronger biological load for ADHD, either genetic or environmentally. However, their relative immaturity along development, paired with untailored demands from school, might “produce” a syndrome much alike ADHD. There are two pieces of evidence that further support this notion. First, because of different school calendar years over the world, effects based on seasonality can be discarded – the effect is always set off along the birthdate for beginning school. Second, some studies suggest that the effect of relative immaturity reduces with age[60,61,65]. This is consistent with the idea that the older the children, the less the importance of month of birth on total age.

The sum of the evidence presented here provides strong support for the perspective of ADHD as a neurodevelopmental, childhood-onset disorder that has a natural tendency to ameliorate during development. In this perspective, adult ADHD is always a consequence of a failure during an individual’s brain development in recovering to normative levels, resulting in a long-lasting presentation. Nevertheless, there are still gaps on the literature that

warrant further studies for either endorsing this prevailing perspective or revealing its weaknesses, inciting a necessary debate in the scientific community.

What are the gaps on the evidence-based knowledge about the course of ADHD?

i. The age at onset of ADHD

The age at onset of ADHD is a concept in evolution. The DSM-III and the DSM-IV required that the maximum age for a valid diagnosis of ADHD was 7 years based on clinical experience together with plausible assumptions derived from a neurodevelopmental perspective of the disorder[28,68]. However, at least at the time when these manuals were conceptualized, there was no evidence to support the validity of any proposed cut-offs. Gradually, researchers began to underline the implications of setting a threshold that is not evidence-based. Professors Joseph Biederman and Russel Burkley were the first to question the validity of the age ate onset criterion proposed in the diagnostic manuals at their time[69]. They reviewed the evidence available, concluding that while there was empirical support for the idea that ADHD begins early in life, there was no empirical support for selecting the age of 7. They recommend further studies, calling attention to the relevance of this topic. If the proposed criterion was not operating towards more validity of the disorder, many patients with valid symptoms and impairment would have been prevented to receive proper diagnosis and treatment.

In fact, many years later, a systematic review by Kieling and colleagues identified several clinical and epidemiological studies that failed to find differences between individuals affected with ADHD who reported onset of symptoms before compared to those whose onset was after 7 years of age[70]. In the DSM-IV field trials, age at onset depended on the subtype of ADHD, with the inattentive subtype showing a later onset than the hyperactive-impulsive and combined subtypes[71]. Furthermore, the trials also showed that requiring age at onset for impairment – a novel criterion of the DSM-IV – reduced the agreement between clinical judgment and operationalized diagnosis. The rates of false negative diagnosis were high – clinicians would validate 75% of cases that had all criteria but age at onset for symptoms and impairment. Another important series of studies identified in the systematic

review evaluated children with ADHD with and without age at onset criteria on clinical settings. Those studies demonstrated that the groups were very similar in a broad range of features, such as levels of impairment, patterns of comorbidity, and neuropsychological measures[72-76]. Not only later onsets had the same clinical presentation, but they also responded to treatment with stimulant medication with similar effectiveness[77,78]. Kieling and colleagues did not identify any studies documenting significant differences between children with ADHD meeting or not the age at onset criterion.

The review also underlines that the concerns with the validity of the age onset criterion increase as the patient in question gets older: there is poor accuracy of the retrospective recall documented in prospective studies[79]. Nearly a half of children with ADHD denied having symptoms in childhood when asked retrospectively years afterwards. However, selecting a broader definition or even eliminating the age at onset criterion might have led to a hasty rise in prevalence, with potential undesired reactions of public opinion.

Considering the bulk of evidence in their review, Kieling and colleagues suggested that the next version of the DSM should revise the age at onset criterion. Authors' recommendation was to increase the threshold from 7 to 12 years old – at the same time, maintaining the childhood-onset nature of the disorder while reducing false negative rates of the later onset cases. Russel Barkley and Joseph Biederman recommended abolishing the age at onset criterion until enough evidence could support a specific threshold[69]. However, other researchers opposed the change, arguing that entrance in school is an environmental factor for an increase in symptoms from age 7 onwards, and that such increase should not be considered a true disorder[80]. Furthermore, they were concerned with the possibility of a massive increase in the prevalence of ADHD.

Polanczyk and colleagues went on to evaluate the clinical and epidemiological impact of raising the age at onset criterion to 12 years of age[80]. In the Environmental Risk (E-Risk) Longitudinal Study, which tracked 2,232 twins from England and Wales from birth to age 12, DSM-IV ADHD assessments were conducted at ages 5, 7, 10 and 12. With this longitudinal design, they could observe that a very small minority of children would fulfill full criteria between the ages of 7 and 12, resulting in a 0.1% increase in prevalence. Considering

evidence that 95% of individuals with adult ADHD from a population survey recalled onset before age 12, and that the expected increase in prevalence would be negligible, the DSM-5 committee opted to maintain the age at onset criterion at the broader level of 12 years of age.

After the revision of the DSM-5, new studies tested the impact of the modified criterion in prevalence and disorder validity. Contradicting the previous findings of Polanczyk and colleagues, these studies identified important rises in the prevalence of ADHD of up to 50% in adolescents and adults[81,82]. Another study on adults failed to find differences in quality of life and overall impairment between earlier and later onset of ADHD[83]. Nevertheless, all these studies were based on retrospective recall of age at onset, likely being subject to recall bias. In summary, as is the case in any change to less stringent diagnostic criteria, prevalence rates are expected to rise. Temporal trends are still lacking to inform on the actual magnitude of this increase.

The previous studies provided some insights on the nature and validity of later onset ADHD. However, long-term population-based longitudinal studies were at the time lacking to further clarify the question. A long follow-up was needed because further thresholds beyond adolescence, or even no threshold at all, should be carefully evaluated. Moreover, the long-term outcomes that conferred validity to the diagnosis of ADHD in childhood derived from analyses of children followed until at least young adulthood. To compare the validity of the traditional childhood-onset ADHD with later onset ADHD, such long-term outcomes needed to be measured. A population-based sample was needed because all the clinical samples so far conducted required the age at onset criterion for inclusion, and therefore no comparison group can be established. A prospective design was needed because the retrospective recall is inaccurate.

The first study to address these needs was derived from the Dunedin cohort, in New Zealand[84]. This study followed a representative cohort of 1037 individuals from birth to age 38. ADHD was assessed for the first time at ages 11 to 15, but requiring age at onset before 7. When participants were 38 years old, ADHD was again assessed, but this time without requiring age at onset as a retrospective recall. Surprisingly, the childhood ADHD cases and

adult ADHD cases consisted of essentially non-overlapping sets: almost 90% of adult cases lacked a prospectively collected childhood history of ADHD, and less than 10% of the childhood cases had persisted with ADHD. Those adults with ADHD, even if their onset was after the age of 15, reported more life impairment, less life satisfaction, more involvement in car accidents, worse savings behavior, and received government benefits for a longer period in life. There are some caveats in the Dunedin study. The gap between ADHD assessments was wide, making it hard to ascertain when ADHD symptoms first appeared between 15 and 38 years old. The source of information changed from parents in childhood to self-reports in adulthood. There were high levels comorbid disorders and substance abuse in adulthood, and the sample size was too small to adequately assess whether the endorsed ADHD symptoms should be attributed to these conditions. Likewise, the few cases with childhood-onset adult (i.e., persistent) ADHD was too small for adequate comparisons to the more numerous late-onset cases with adult ADHD. Despite the methodological soundness of the Dunedin study, the novelty of these findings raised questions about whether this would be a replicable finding in independent samples[85].

Following the New Zealand study, two other large population-based birth cohorts provided consistent evidence that many adults did not have childhood ADHD. One of these studies reported data from the 1993 Pelotas cohort in Brazil, and is part of this thesis (Article #1)[15]. The other was conducted by Agnew-Blais and colleagues in a British cohort of twins, the Environmental Risk (E-Risk) Longtudinal Twin Study[86].

The E-Risk cohort followed 2232 twins born in the United Kingdom from birth to age 18 with 91.3% retention. DSM-IV ADHD was assessed at ages 5, 7, 10 and 12, and then again at age 18[86]. Most (67.5%0 of the young adults with ADHD had not met criteria in any of the childhood assessments. As in the Dunedin study, there was no difference between late-onset ADHD and childhood-onset ADHD in terms of impairment and rates of mental health disorders in young adulthood. The E-Risk study also has some caveats. The sample size was too small to control for comorbid mental disorders in adulthood. While the gap between ADHD assessments was much smaller, the last age at assessment was at age 18, limiting conclusions about the stability of the late onset ADHD or the possibility of onset in older adults.

The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort followed 14701 children born in the United Kingdom from birth to age 17 with multiple dimensional assessments of ADHD using the hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ-H)[87]. In a categorical analysis of two time points, 47% of the adult ADHD cases had childhood onset, but 53% did not (n=244, representing 2.5% of the cases with symptoms above the threshold for high ADHD symptoms at age 17 but were below the threshold for borderline symptoms at age 7). The late-onset ADHD group represented the majority of adults with ADHD, resembling the evidence from the three previous studies. The most important limitation of this study is the reliance on screening instruments at all ages without a cut-off point based on internal calibration with a semi-structured instrument in the last assessment. This assessment was in late adolescence, and there was no control for comorbidities at this point.

Concerned with the differences between her own clinical experience and the findings from clinical samples compared to the novel findings from epidemiological samples, Dr. Mary Solanto wrote a letter to the *JAMA Psychiatry* criticizing some of the methods of the cohorts[88]. In our reply (Appendix #1), we acknowledge the limitations and suggest further studies to understand the phenomenon in the clinical context[89]. We then joined the Multimodal Treatment Study for ADHD (MTA) team to investigate the issue in the largest clinical trial ever conducted for ADHD (Appendix #2)[90].

Using a prospective long-term follow-up design, the incidence of late-onset ADHD was estimated in the group of children in the Local Normative Comparison Group (LNCG) without ADHD (N=258 of n=289 recruited from classmates) of the MTA[90]. These individuals were followed from childhood (ages 9-12) to adulthood (ages 23-26), and over the course of 14 years, they underwent eight comprehensive assessments, which included psychiatric evaluations to measure ADHD symptoms and related impairments. Diagnostic procedures utilized parent-, teacher-, and self-reports of ADHD symptoms, as well as for impairment, substance use, and other mental disorders. The dense and comprehensive assessments of the MTA contrast with the infrequent and limited assessments in the population-based studies with much larger samples. Thus, in the LNCG cases with late onset, evaluation of

context and timing of late-onset of ADHD symptoms was possible. It is informative to note that 53% of adolescents and 79% of adults who had late-onset ADHD were excluded because symptoms or impairment was better explained by exclusion conditions. Heavy marijuana use was the most common reason for exclusion, and the presence of other psychiatry disorders was the next most common. Based on the MTA assessment, there was no evidence for significant adult-onset ADHD, but there was compelling evidence for adolescent-onset ADHD. The comprehensive assessments of the MTA suggested that most adolescent-onset cases were adolescent-limited in which there was desistence of symptoms before adulthood.

Two other recent epidemiological investigations also raised doubts about the existence and validity of the late onset ADHD trajectory. The first reanalyzed data from the ALSPAC cohort: after defining late onset ADHD as those with high SDQ-H scores at age 17 and low SDQ-H scores at age 12, authors had looked at previous ADHD assessments[91]. Most of those with apparent late onset ADHD had high scores at least in one moment before age 12. Participants with genuine late onset ADHD, however, had a similar profile of neurodevelopmental impairments than children without ADHD. A second study was based on the High-Risk Cohort in Brazil[92]. Authors concluded that, while adolescent-onset ADHD was as frequent as reported in previous studies, the group had more cognitive impairments and a higher load of psychopathology in childhood than controls – late onset ADHD could, therefore, be a heterotypic continuity.

Clearly, the late onset ADHD trajectory remains a contradictory and debatable issue. This is first gap in the literature for which this thesis is dedicated to. Our aim was to provide new data, discuss and integrate the findings on late onset ADHD.

ii. Predicting the course of ADHD

While the novel hypothesis that the ADHD syndrome might emerge during adolescence or adulthood remains to be verified, the traditional neurodevelopmental perspective of childhood-onset ADHD has yet an unpredictable course. Even though it is well established that childhood ADHD may unfold into a lifelong persistent and impairing disorder or into complete recovery[5], little is known on what individuals have a high likelihood of

persistence[30]. The ability to identify such individuals in advance could implicate, for clinical practice, the need for intense surveillance and a long-term planning, resulting in better care. For research, it could provide the opportunity to search for biological underpinnings of a persistent disorder and perhaps tailoring interventions targeted at this high-risk group of patients.

The first step towards identifying who is at risk for any given outcome is to identify what individual factors are associated with this outcome in a longitudinal fashion. ADHD already leverages from a series of studies focused on the evaluation of potential risk factors for disorder's persistence[79,93-96]. Candidates include characteristics of the ADHD syndrome itself (severity, pervasiveness, subtypes), other co-occurring psychiatric disorders, gender, and intelligence, among others. However, the literature was not yet summarized into a comprehensive systematic review, neither had the effect sizes of candidate factors been aggregated into a meta-analysis.

Sophisticated approaches have used neuropsychological measures to predict the onset or persistence of ADHD during adolescence with inconsistent findings[97]. Longitudinal studies, measuring neuropsychological functioning and ADHD symptoms across development, have found associations between baseline and/or trajectories of neuropsychological measures and the remission or persistence of ADHD symptoms[98-100]. Other similar studies found no association[101-103]. Overall, current available evidence seems to be insufficient to support routinely clinical use of neuropsychology to inform on the course of ADHD symptoms.

A more advance step towards the identification of high-risk groups and a personalized medicine approach relies on the development of risk models that consider all risk factors at once to provide one single individualized estimation of risk for each person[104]. This has been already a standard procedure in other areas of medicine, such as Cardiology[105]. For instance, the well-known Framingham risk score for cardiovascular disease calculates, based on easily measured clinical characteristics, the individual risk of any given patient of a major cardiovascular event in the following 10 years[106]. This risk model, as many others, has drastically changed the medical practice and research in their fields, tailoring specific preventive and therapeutic interventions according to risk ranges.

In the field mental health, the adoption of this risk model approach is gradually increasing: on a systematic review that searched the literature up to 2014, 43 reports of prediction models in Psychiatry were identified – none of those predicting the course of ADHD[107]. At that time, authors called the attention to the lack of large-scale longitudinal studies, and the reliance on internal validation, rather than on external validation, of most published studies. Internal validation, despite leveraging on statistical techniques to reduce bias, might overestimate the measures of performance of the model due to overfitting – the process by which the model learns characteristics of that specific sample, which not entirely can be translated to other samples. With external validation, the model is tested only on unseen data, overcoming the issue of overfitting.

Posterior to the time span of this systematic review, large-scale, well-designed and externally validated attempts to predict mental health outcomes were conducted in the field. In the North American Prodrome Longitudinal Study, 596 clinical high-risk for psychosis participants were followed up for 2 years or up to conversion to a psychotic state[108]. Clinical predictors, such as younger age, lower memory performance, higher levels of suspiciousness and unusual though content were combined into a multivariable model with time-to-event regression, internally validated with bootstrap resamples. At external validation with independent sampling, performance was good with an Area Under the Receiver Operating Curve (AUC) of .79[109]. A much larger study using medical registers in Great Britain also tried to predict nonorganic psychotic disorders among 91199 high-risk individuals[110]. The derived model was also quite simple, using only data available from the registers: age, sex, ethnicity, and index diagnosis before transitioning to psychosis. However, performance measures were good at external validation, with an AUC of .79. A risk calculator for the prediction of Bipolar Disorder among 412 offspring of bipolar patients was developed in the Pittsburgh Bipolar Offspring Study[111]. They were followed from a mean age of 12 years old, during a 5-year follow-up. A time-to-event regression was modeled using measures of mood and anxiety, general psychosocial functioning, age at mood disorder onset in the bipolar parent, and age at each visit. This calculator was not externally validated, but internal validation with bootstrapping techniques yielded good discrimination, with an AUC of .76 and good calibration.

Overall, few large-scale longitudinal studies with proper external validation and sophisticated statistical techniques were conducted to predict the course of mental disorders through multivariable prediction models. Particularly, no study was ever conducted to predict the course of ADHD: either its remission or persistence for childhood ADHD, or the emergence of symptoms during adolescence for late onset ADHD. These are gaps in the literature that this doctorate thesis also aims to help fulfilling: to synthesize the evidence on predictors of ADHD persistence/remission/emergence; and to propose a prediction model with state-to-art methodology in the field to predict the course of ADHD throughout development.

Notably, the idea of advanced risk models might be associated to sophisticated and complex data, such as those obtained through neuroimaging, genetics, and neuropsychological measures. However, most of the main risk calculators available in other areas of medicine such as Cardiology [105] rely on relatively simple phenotypic information to generate accurate predictions. One of the reasons for the simplicity of the array of predictors of these tools is the focus on applicability in clinical settings through a wide range of available resources. The other might be because phenotypic data are still much more informative to these models, to a point where inclusion of other more complex kinds of data is superfluous. For instance, in 2011, the ADHD-200 Consortium announced a competition where they provided a public dataset of functional and structural neuroimaging of 973 ADHD cases and controls. The winner would be the research group that could develop the most accurate and discriminative model to parse out cases and controls based on the information provided. Surprisingly, the most accurate predictive model was the one that completely ignored the neuroimaging data, and relied only on simple phenotypic data[112].

iii. Relative immaturity and ADHD

A plausible rationale for the existence of so many developmental trajectories of ADHD, including remission, persistence, emergence and re-emergence of symptoms, is that dynamic environmental demands have a role in the expression of the phenotype[113]. It is reasonable to assume that two children with identical biological vulnerabilities for symptoms

might report very different levels of ADHD symptoms if they are exposed to different levels of academic and environmental demands. Likewise, if equal demands are imposed to children with equal biological vulnerabilities but different levels of developmental maturation (i.e., because of different chronological age), there is also a chance of different levels of phenotypic expression of ADHD symptoms. In fact, this effect of relative immaturity might be operating in modern societies and their school system. Children and adolescents who are born at the end of the school year calendar are up to a year younger than their classmates who are born at the beginning of the school year calendar. Their attentional demands are, however, mostly equal.

A number of studies show that children who are relatively immature compared to their classmates are most often diagnosed with ADHD[60-67]. For instance, studies leveraging cohorts of national medical registers from Sweden, Norway, Finland and Iceland all found greater incidences of ADHD diagnosis or medication use among children who were born in the last months of the calendar year[60-62,64]. Case-control studies investigated whether month of birth was unbalanced across diagnosed children and their peers[66,67]. In sum, three types of design verified the issue: epidemiological samples gathering registers of ADHD diagnosis; epidemiological samples using registers of ADHD medication; and clinical samples assessing relative immaturity within diagnosed children and adolescents. With few exceptions, independently of the methodological differences, all these studies confirm the association between relative immaturity and ADHD. However, this is an overlooked issue in clinical guidelines and manuals[114,115]. On the contrary, there is evidence reporting that this effect has increased in recent years, instead of disappearing due to increased awareness[60].

One explanation for the lack of awareness is the important gaps in the literature. First, representative studies that had actively collected the diagnosis of ADHD in children and adolescents in the community are missing, and only these could exclude the effect of referral bias. Second, there is not a pooled effect estimate for determining the size of this effect in the prevalence rates of ADHD clinical diagnosis. Third, even if month of birth is consistently associated with ADHD, other factors could be explaining the association – for instance, seasonality and weather issues at birth. Therefore, a more accurate design is needed to measure the extent of this association and to verify causality.

Objectives

General objective

To contribute for the understanding of possible developmental trajectories of ADHD throughout the life cycle and their associated factors.

Specific objectives

a. Verify the existence and the validity of a late-onset trajectory of ADHD in an independent population-based representative sample in Brazil – Article #1.
b. Systematically review the literature on risk factors for the persistence of ADHD, and summarize their effects with meta-analytic techniques – Article #2.
c. Develop and validate a risk model to predict the persistence, remission and emergence of ADHD during adolescence - Article #3.
d. Systematically review the literature on relative immaturity and ADHD, and summarize its effect with meta-analytic techniques – Article #4.
e. Investigate the issue of the relative immaturity effect and ADHD on three independent population-based samples in Brazil – Article #4.
f. Review the literature on methodological challenges of long-term longitudinal studies on ADHD – Article #5.
g. Review the literature on the debate around the validity of the late-onset trajectory of ADHD – Article #6.

Hypotheses

Regarding each of the abovementioned specific objectives, we had the following *a priori* hypotheses:

a. We will verify the existence of a substantial number of late-onset ADHD cases in our independent population-based sample, replicating the findings of previous epidemiological samples from New Zealand and the United Kingdom. These late-onset cases will have similar rates of impairment and functional outcomes as childhood-onset adults with ADHD.
b. We will identify clinical and demographic predictors of ADHD persistence, each of these associated with a small independent effect in summarized estimates of meta-analyses.
c. A multivariable prediction model of the course of ADHD throughout development with good prediction performance will prove to be a feasible attempt. Yet, external validation might be a challenging process in diverse designs and settings.
d. We will be able to summarize the effect of relative immaturity in a consistent and precise estimate of relative risk.
e. In the three independent samples, we will identify a dimensional effect of relative immaturity on ADHD symptoms, and changing the school calendar year will also change the month of risk for ADHD symptoms.
f. We will identify heterogeneity and methodological differences among longitudinal studies with ADHD children with important impact in the evaluation of their outcomes.
g. Detailed evaluation of methodological differences and theoretical backgrounds among studies evaluating late onset ADHD will provide insights into the reasons for discrepancies on findings of the existence and validity of the late onset disorder.

Ethical Considerations

All the studies included in this thesis have been approved by their respective Institutional Review Boards before data collection and analysis. Original studies included samples of several cohorts: the 1993 and the 2004 Pelotas Birth Cohorts; the E-Risk cohort; the ALSPAC cohort; the National Institute of Developmental Psychiatry High-Risk Cohort; and the MTA clinical study. All participants across all these samples provided written informed consent before inclusion in the study. Data were de-identified, and only raw data essential for analyses were shared with co-authors – therefore, attempts of identification of participants was not possible.

Article #1

With respect to specific objective a. Verify the existence and the validity of a late-onset trajectory of ADHD in an independent population-based representative sample in Brazil.

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ADHD does not always begin in childhood: Evidence from a large birth cohort

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Abstract

IMPORTANCE: The requirement of an age-of-onset in childhood has always been a key criterion for the diagnosis of Attention-deficit/hyperactivity disorder (ADHD) in adults, but recently it has become surrounded by controversy.

OBJECTIVE: To investigate whether impaired young adults with ADHD symptoms always have a childhood-onset disorder in a population-based longitudinal study.

DESIGN, SETTING AND PARTICIPANTS: Participants belonged to the 1993 Pelotas Birth Cohort Study, including 5,249 individuals born in Pelotas, Brazil, in 1993. They were followed up to age 18/19 years, with 81.3% retention.

MAIN OUTCOMES AND MEASURES: ADHD status was first ascertained at age 11 years using a screening instrument (Hyperactivity subscale of the Strength and Difficulties Questionnaire – SDQ) calibrated for DSM-IV ADHD diagnosis based on clinical interviews with parents using the Development and Well-Being Assessment (DAWBA). At age 18-19 years, ADHD diagnosis was derived using DSM-5 criteria, except age-of-onset. We estimated the overlap between these groups assessed at ages 11 and 18-19 years, respectively, and the rates of markers of impairment in these two groups compared to subjects without ADHD.

RESULTS: We found ADHD prevalence rates of 8.9% in childhood and 12.2% in young adulthood (without using the age-of-onset criterion). Both groups had increased levels of impairment in adulthood, as measured by traffic accidents, criminal behavior, incarceration, suicide attempts, and comorbidities. However, only 17.2% of children with ADHD continued to have ADHD as young adults, and only 12.6% of young adults with ADHD had the disorder in childhood.

CONCLUSIONS AND RELEVANCE: Our findings do not support the assumption that adult ADHD is necessarily a continuation of childhood ADHD. Rather, they suggest the existence of two syndromes that have distinct developmental trajectories.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) has been traditionally conceptualized as a neurodevelopmental disorder. Most recently, DSM-5 included ADHD in a specific section under

this umbrella.[1] 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.[2,3] A number of studies challenged the utility and validity of this criterion B.[4] The DSM-5 scientific committee decided to change the criterion to require symptoms before age 12, based on evidence that this threshold would capture almost every case presented in childhood, without raising the prevalence rate.[1,5] Furthermore, DSM-5 introduced the concept of adult ADHD as a disorder that begins in childhood and requires symptoms to be present before age 12.

A recent report by Moffitt and colleagues presented data that diverge from this traditional perspective.[6] In a representative birth cohort followed up to age 38, prevalence rates of childhood and adulthood disorder were in accordance with estimates from the literature (6% and 3.1%, respectively). However, the two groups showed only minimal overlap: 87% of those with adult ADHD did not have prior childhood ADHD, and 85% of those with childhood ADHD did not continue to have adult ADHD. Castellanos, in an editorial about this paper, emphasized the urgent need for replications to confirm or challenge these data.[7]

In the present study, we report findings from a prospective longitudinal study of a representative birth cohort in Brazil. We hypothesize that 1) prevalence rates of ADHD in childhood and young adulthood will be similar to that reported in the literature; 2) individuals with both childhood and adulthood ADHD will have higher levels of impairment markers than subjects without ADHD, and 3) groups will have little overlap. We extended the prior study by examining the effects of comorbid disorders on ADHD continuity.

Methods

Design and sample

Subjects enrolled in this study were participants in the 1993 Pelotas Birth Cohort. All children born in the year of 1993 in the city of Pelotas (5,249 individuals) were assessed at multiple time points and followed until age 18/19 years, with a retention rate of 81.3%. Further information on the cohort design can be found elsewhere.[8,9] The Institution Review Board of the Federal University of Pelotas approved the study. Written informed consent was obtained from all subjects.

The assessment at age 11 included data on child mental health using the Brazilian Portuguese Version of the Strengths and Difficulties Questionnaire (SDQ), parent report and self-report. A sub-sample of 280 subjects was interviewed with Development and Well-Being Assessment (DAWBA), and the optimal cut-off for ADHD disorder was estimated to be eight or more points on the SDQ hyperactivity scale as rated by parents.[10] The SDQ instrument accurately predicted ADHD diagnosis with an Area Under the Curve of 0.81 (95% CI 0.74 – 0.88) and the cut-off of at least 8 points had 85.7% sensitivity and 67.4% specificity for the diagnosis.

In the last assessment, subjects at age 18/19 years were interviewed by trained psychologists using specific modules for Major Depressive Disorder (MDD), Bipolar Disorder (BD), Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) modified from the Mini-International Neuropsychiatric Interview.[11] ADHD assessment was performed with a structured interview according to DSM-5 criteria (see eTable 1 and Matte et al., 2014).[12] For the present study, we did not require DSM-5 criterion B (age at onset) for diagnosis of young adult ADHD. We defined childhood ADHD as present when scores on the SDQ hyperactivity scale – parent version – were equal or higher to eight points and associated with impairment, defined by at least one point in the impact supplement.

We also created a secondary category defined as Young Adult ADHD without Comorbidity (YA-ADHD-WC) excluding from the young adult ADHD group those subjects with comorbidities, including MDD, BD, GAD, SAD, and regular use of illicit drugs. This procedure was done for secondary analyses to reduce confounding by these comorbidities that is likely to occur later in life, and might contribute to inattentive and/or hyperactive-impulsive symptoms. We also excluded these comorbidities from comparison groups without ADHD. The comparison groups were defined as those without Childhood ADHD (C-ADHD) for childhood comparisons (C-ADHD vs. subjects without C-ADHD), and those without YA-ADHD for adulthood comparisons (YA-ADHD vs. subjects without YA-ADHD and YA-ADHD-WC vs. subjects without YA-ADHD and comorbidities).

Correlates

Trained interviewers assessed correlates of tobacco use, illicit drug use, pregnancy, sexually transmitted diseases and criminal behavior using confidential questionnaires. Suicide attempts were evaluated as part of the assessment of MDD. We estimated IQ with an abbreviated

version of the Weschler Adult Intelligence Scale-third edition (WAIS-III).[13] Further details of assessments of correlates can be found in eTable 2.

Data analyses

We estimated differences between groups using chi-square tests for the following variables: percentage male, ADHD subtype, traffic accidents, illicit drug use, smoking, criminal behavior, correctional institution, comorbidities and teenage pregnancy. We used one-way analysis of variance for continuous variables: personal income, years of schooling, IQ. Effect sizes for continuous variables were estimated with Cohen's d. All analyses were performed using SPSS v20.0.

Results

Prevalence and sex distribution

Childhood ADHD (C-ADHD) was present in 8.9% (393) of the subjects evaluated at age 11. At age 18/19, 12.2% (492) of the subjects fulfilled all DSM-5 criteria for YA-ADHD, except age-of-onset. After excluding comorbidities, the prevalence of YA-ADHD-WC dropped to 6.3% (256 subjects). Subjects with C-ADHD had a male preponderance not observed among children without ADHD (63.9% vs. 47.9% males, $\chi2 = 36.679$, $p < 0.001$), while YA-ADHD group had a female preponderance (39% vs. 50.4% males, $\chi2 = 22.187$, $p < 0.001$), and this difference persisted after excluding comorbidities (YA-ADHD-WC = 44.9% vs. individuals without YA-ADHD and without comorbidities = 51.5 % males, $\chi2 = 4.022$, $p = 0.045$) (Table).

Persistence and overlap

Among the 393 subjects in the C-ADHD group, 15.3% (60) continued to have YA-ADHD (7.9% with at least one comorbidity, and 7.4% with no comorbidity), 73.3% (288) had no YA-ADHD in the 18/19 years assessment, and 11.5% (45) were lost to follow up (see Figure 1), resulting in a persistence rate of 17.2%. Furthermore, most C-ADHD cases presented very few symptoms in young adulthood (Figure 2), making it unlikely that a lower symptom cut-off would substantially change this result.

Among the 492 subjects in the YA-ADHD group, 12.2% (60) had C-ADHD, 84.6% (416) did not have C-ADHD, and 3.3% (16) of the subjects were not assessed with the SDQ at age 11, resulting in a prevalence of 12.6% of C-ADHD among the YA-ADHD group. Considering the 256 subjects in the YA-ADHD-WC group without comorbidities, 11.3% (29) had C-ADHD, and 85.9%

(220) did not have C-ADHD, and 2.7% (7) had not been assessed with the SDQ at age 11 (Figure 1), resulting in a prevalence of 11.6% of C-ADHD among the YA-ADHD-WC group. See also secondary analyses in eTables 3-5, checking the robustness of our findings.

ADHD Presentation in Young Adulthood

Inattentive presentation prevailed in all groups in young adulthood: those with C-ADHD who continued to have YA-ADHD (51.7%), YA-ADHD (53.3%) and YA-ADHD-WC (59%). (See Table for other ADHD presentations.)

Comorbidities and suicide attempts

Subjects with childhood ADHD had significantly higher rates of comorbidities in young adulthood compared to subjects without C-ADHD. At age 18/19, rates of MDD (7.2% vs. 3.8%, $\chi2 = 9.087$, $p = 0.003$), BD (4.2% vs. 1.5%, $\chi2 = 13.369$, $p < 0.001$), GAD (10.8% vs. 7.2%, $\chi2 = 5.489$, $p = 0.019$), SAD (10.2% vs. 6.5%, $\chi2 = 6.6$, $p = 0.01$), illicit drug use (10.8% vs. 6.8%, $\chi2 = 7.479$, $p = 0.006$) and tobacco smoking (25.9% vs. 13.3%, $\chi2 = 37.92$, $p < 0.001$) were all higher in the C-ADHD group. The YA-ADHD group had even higher levels of comorbidities, which were also significantly different to subjects without YA-ADHD for MDD (13.6% vs. 2.7%, $\chi2 = 132.066$, $p < 0.001$), BD (7.4% vs. 0.9%, $\chi2 = 106.634$, $p < 0.001$), GAD (24.9% vs. 5.1% $\chi2 = 238.475$, $p < 0.001$) and SAD (20.2% vs. 5%, $\chi2 = 153.086$, $p < 0.001$), and tobacco smoking (19% vs. 13.7%, $\chi2 = 9.032$, $p = 0.003$). However, we did not find significant differences for illicit drug use (9% vs. 7%, $\chi2 = 2.592$, $p = 0.107$). A self-reported suicide attempt in young adulthood was more likely among children with ADHD than in children without ADHD (10% vs. 6%, $\chi2 = 8.889$, $p = 0.003$), and among the YA-ADHD group than young adults without ADHD (15.2% vs. 5.1%, $\chi2 = 75.541$, $p < 0.001$). The difference remained significant even after excluding comorbidities (YA-ADHD-WC: 6.6% vs. 3.5% young adults without ADHD and without comorbidities; $\chi2 = 6.333$, $p = 0.012$). (See Table.)

Criminal behavior and incarceration

All three ADHD groups had higher levels of violent crimes compared to subjects without ADHD (C-ADHD: 28.7% vs. 14.5%, $\chi2 = 42$, $p < 0.001$; YA-ADHD: 24.4% vs. 14.4%, $\chi2 = 28.$, $p < 0.001$; YA-ADHD-WC: 18.5% vs. 11.8%, $\chi2 = 8.72$ $p = 0.003$). Accordingly, the three groups had significantly higher levels of incarceration compared to individuals without ADHD (C-ADHD:

4% vs. 0.9%, $\chi2 = 25.582$, $p < 0.001$; YA-ADHD: 2.8% vs. 1%, $\chi2 = 12.449$, $p < 0.001$; YA-ADHD-WC: 1.6% vs. 0.5%, $\chi2 = 4.216$ $p = 0.04$). (See Table.)

Teenage pregnancy and sexually transmitted diseases.

More females with C-ADHD had teenage pregnancies compared to girls without ADHD (21.9% vs. 13.2%, $\chi2 = 7.65$, $p = 0.006$). Differences in teenage pregnancy rates were not observed comparing YA-ADHD and YA-ADHD-WC groups to subjects without A-ADHD. A history of sexually transmitted diseases was more common in the YA-ADHD group than among young adults without ADHD (5.3% vs. 2.2, $\chi2 = 15.756$, $p < 0.001$), even controlling for comorbidities (YA-ADHD-WC vs. young adults without ADHD and comorbidities: 4.7% vs. 1.9%, $\chi2 = 8.297$, $p = 0.004$). The C-ADHD group did not have a statistically significant different rate of sexually transmitted diseases compared to children without ADHD (2.9% vs. 2.6%, respectively; $\chi2 = 0.133$, $p = 0.715$). (Table)

Traffic accidents

Suffering a traffic accident was significantly more likely among the ADHD groups than among subjects without ADHD (C-ADHD: 21.9% vs. 17.2%, $\chi2 = 4.874.$, $p = 0.027$; YA-ADHD: 23.2% vs. 16.7%, $\chi2 = 12.457$, $p < 0.001$; YA-ADHD-WC: 21.5% vs 16.2 %, $\chi2 = 4.636$, $p = 0.031$). (Table)

Personal income and years of schooling

C-ADHD, YA-ADHD and YA-ADHD-WC groups did not differ from subjects without ADHD in terms of personal income and completed years of regular schooling.

Intelligent Quotient

The C-ADHD and YA-ADHD groups had lower intelligent quotient (IQ) levels than subjects without ADHD, and this difference was larger for C-ADHD (97.17 vs. 89.74, ES = 0.61, $p < 0.001$) than for YA-ADHD (96.7 vs. 95.28, ES=0.12, $p = 0.013$) and YA-ADHD-WC (97.68 vs. 95.59, ES = 0.17, $p = 0.008$).

Discussion

The notion that adult ADHD is necessarily a continuation of childhood ADHD is an established assumption in the field. Recently, a population-based birth cohort provided initial evidence suggesting the opposite (i.e., 87% of adult ADHD cases without childhood ADHD).[6] In the current study, we extended the findings of Moffitt and colleagues for young adults using a

similar methodology. We identified that, among young adults with ADHD, 87.4% did not have childhood ADHD.

In the current study, young adults with self-reported ADHD symptoms had a consistent pattern of higher impairment than subjects without young adult ADHD, as determined by rates of traffic accidents, self-reported violent crimes, incarceration in correctional institutions and comorbidities, which are analogous with previous findings in the literature.[14-17,] Children and young adults with ADHD had higher rates of suicide attempts than their counterparts without the condition, which is also in accordance with the literature.[18] Because comorbidities might be responsible for the aforementioned differences, we ran the same analyses excluding subjects with co-occurring disorders from the ADHD group, and very similar results emerged, suggesting that comorbid disorders do not explain the adult-ADHD impairments.

Although the expected prevalence rate of childhood ADHD is around 5.3%,[19] we observed a notably inflated rate, around 8.9%. However, our estimate is similar to that reported by a prevalence study that also used a screening instrument.[20] Likewise, our adult ADHD prevalence rate was 12.2%, against a 2.5%-5% prevalence rate suggested by meta-analyses.[21,22] It is likely that this difference occurred because of the lower symptom cut-off required by the DSM-5 and because we did not require a childhood age-of-onset to make the diagnosis. Indeed, a previous report in the same population found an ADHD prevalence rate of 3.5% using the age-of-onset criterion.[12] Our estimate is considerably higher than that observed in the Dunedin cohort,[6] where they reported a 3.1% prevalence of ADHD in adults, even not requiring childhood age-of-onset. Such a difference might be explained by the fact that their sample was composed of subjects 20 years older, and there is a tendency for prevalence to decline with increased age.[23] A lower male/female ratio is expected in adult samples compared to child ones, but we found a particularly low male-to-female ratio of 0.64 : 1, which may indicate that females are over-represented in subjects with late-onset ADHD.

Our observed persistence rate of ADHD was 17.2%. This finding match perfectly the persistence rate estimated by a previous meta-analysis.[24] Indeed, the Dunedin cohort was the first population-based longitudinal sample to report an extremely low persistence rate of ADHD into adulthood (5%). Again, the difference with our estimate was expected because the Dunedin cohort is composed of older adults. It is important to bear in mind that our C-ADHD group

continue to present significant impairments in adult life despite not continuing to qualify for an ADHD diagnosis in adulthood. Three alternative hypotheses have been proposed to explain this finding: a) impairments are a residual effect of the disorder; b) impairments are due to the effects of persistent comorbidities; c) there is an illusionary bias (e.g., adults with ADHD do not perceive their ADHD symptoms). Future studies should try to elucidate these issues.

The main strengths of our study include a large representative sample not biased by clinical referral. Trained interviewers assessed our subjects at ages 11 and 18 with substantial retention. Thus, we were able to report estimates of the overlap between ADHD in children and in adults, as well as their correlates, with reasonable accuracy. On the other hand, some methodological limitations should be taken into account in the interpretation of the results. First, diagnosis of ADHD in childhood was made using a screening instrument (SDQ hyperactivity scale). However, it is important to bear in mind that psychologists using the DAWBA in a subsample of 280 subjects validated the SDQ hyperactivity scale cutoff scores against ADHD diagnosis in clinical interviews.[10] In addition, we checked a lower cut-off score that continued yielding significant lack of C-ADHD in subjects with YA-ADHD. Second, we relied only on parent reports for C-ADHD and self-report for YA-ADHD. This might artificially increase diagnostic disagreement because of different information sources. However, when using self-reported SDQ hyperactivity scores in childhood, both young adult ADHD groups (YA-ADHD and YA-ADHD-WC) were far below the threshold for childhood ADHD diagnosis according to parent reports (score = 8), confirming that the young adult ADHD cases had few ADHD symptoms in childhood. In addition, these assessment procedures reflect more accurately what frequently occurs in clinical practice, where childhood ADHD diagnosis relies much more on parental reports and adult ADHD diagnosis on self-report.[25] One could also question whether, if we had used parental reports of adult ADHD, a different group of ADHD cases in adulthood would have been identified. However, several previous investigations have found high agreement between self- and parent- reports for ADHD diagnosis in adults.[26] Moreover, our ADHD cases defined by self-report have a clinical, comorbidity and impairment profile similar to the one previously described for the disorder in adulthood. Finally, a recent report from our group suggests that even adult patients fulfilling DSM-5 ADHD diagnosis by self-report, for whom other informants did not report ADHD symptoms in childhood, have the same clinical profile and response to

treatment as those whose co-informants described ADHD childhood symptoms.[27] Third, we did not have a formal diagnosis of some psychiatric disorders that could be the primary source of inattention and/or hyperactivity-impulsivity in adults, like substance use disorders and personality disorders. Along the same line, diagnoses were ascertained with a structured interview rather than clinical judgment. Hence, the alternative explanation that another disorder might explain symptoms and impairment better than ADHD itself cannot be completely ruled out. However, 6.3% of the adult sample had ADHD without four important and frequent comorbidities or illicit drug use, and those subjects remained impaired compared to subjects without ADHD and comorbidities. A fourth limitation is that our impairment measure was based only on the subject's perspective; a rater-derived score based on functional correlates was not used. However, clinicians tend to see young adult patients without parents and to rely on self-perception about impairment more than on scales. Fifth, our results in a community sample cannot be extrapolated to clinical samples where the majority of the cases tend to be ADHD combined type with at least moderate severity. A final potential bias in our study, that indeed is inherent to the majority of population-based studies in Psychiatry, is the so-called false positive paradox that occurs when the rate of false positives based on the instrument used to assess the disorder is higher than the incidence of cases in the population.

In light of these findings, along with the study's strengths and limitations, we can draw some meaningful implications for practice and research. Above all, our findings do not support the premise that adult ADHD is always a continuation of childhood ADHD. Rather, they suggest the existence of two syndromes that have distinct developmental trajectories, with a late onset far more prevalent among adults than a childhood onset. This would not mean that ADHD could not be conceptualized as a neurodevelopmental disorder. Neurodevelopmental disorders may have a later onset, as is the case for Schizophrenia.[28] In both clinical practice and research, it is important to differentiate early and late onset disorders, and future investigations should test if they have different pathophysiology, treatment response and prognosis. In addition, adult ADHD cases with late onset have clear impairments and their clinical profile cannot be accounted for only the effect of comorbidities.

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Conflicts of Interest: Hans-Cristoph Steinhausen has worked as speaker for Medice and Shire during the last three years and he receives book royalties from Cambridge University Press, Elsevier, Hogrefe, Huber, Klett, and Kohlhammer publishers. James M Swanson acknowledges research support, advisory board membership, speaker´s bureau membership, and/or consulting for Alza, Richwood, Shire, Celgene, Novartis, Celltech, Gliatech, Cephalon, Watson, CIBA, UCB, Jansen-Cilag, McNeil and Eli-Lilly. Christian Kieling receives authorship royalties from ArtMed and Manole. Luis A. Rohde has received Honoraria, has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Janssen-Cilag, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He also received travel awards for taking part of 2014 APA and 2015 WFADHD meetings from Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical

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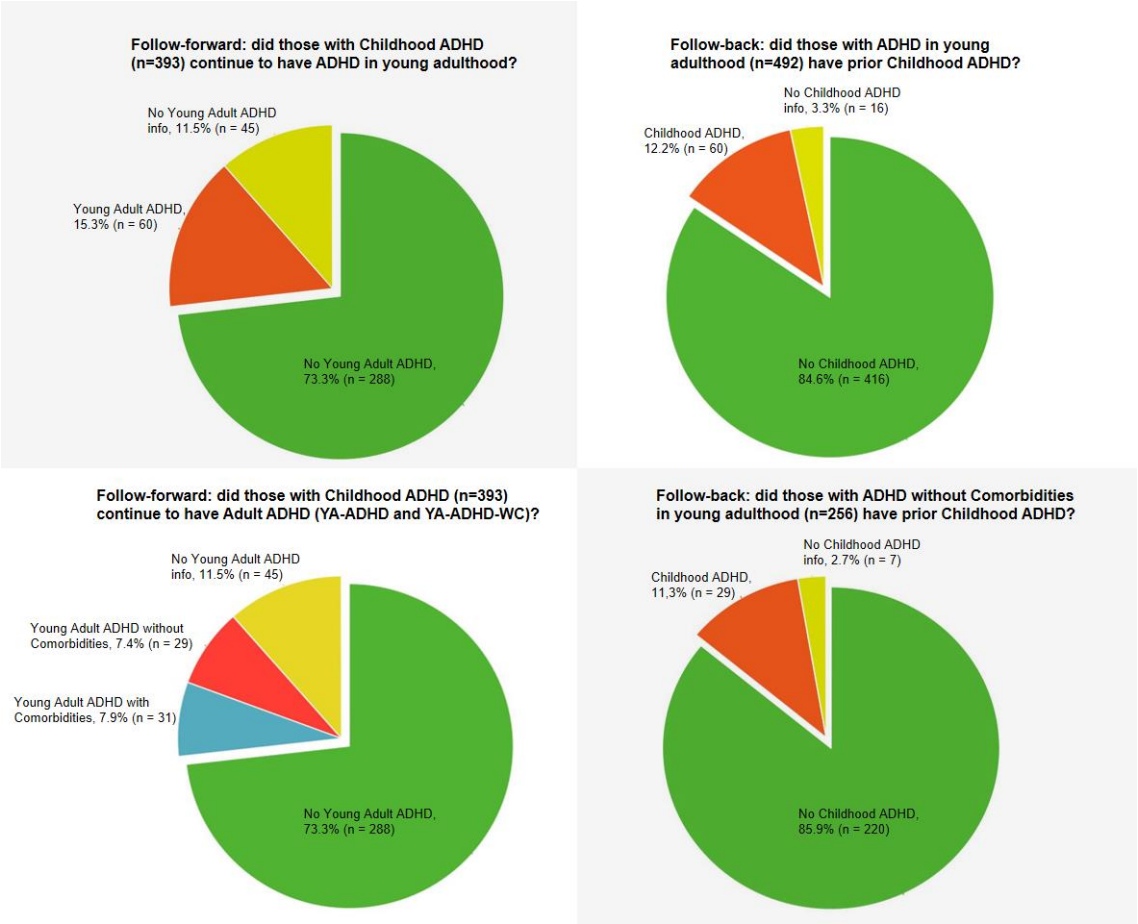
Figure 1. Follow-forward and follow-back analyses of C-ADHD, YA-ADHD and YA-ADHD-WC cases.



C-ADHD: Childhood ADHD group; *YA-ADHD:* Young Adult ADHD group; *YA-ADHD-WC:* Young Adult ADHD without Comorbidities group.

Figure 2. Number of young adult ADHD symptoms in C-ADHD, YA-ADHD and YA-ADHD-WC groups.

Y-axis represents number of subjects that reported the number of symptoms showed in the X-axis.
C-ADHD: Childhood ADHD group; *YA-ADHD:* Young Adult ADHD group; *YA-ADHD-WC:* Young Adult ADHD without Comorbidities group.

Table. Characteristics and outcomes of childhood ADHD (C-ADHD), young adulthood ADHD (YA-ADHD and YA-ADHD-WC) and non-ADHD comparisons in the 1993 Pelotas Birth Cohort Study.

	Childhood Comparisons			Adulthood Comparisons					
	W/o ADHD (n = 4033)	**C-ADHD (n = 393)**		**W/o ADHD (n = 3547)**	**YA-ADHD (n = 492)**		**W/o YA-ADHD w/o Comorbidity (n = 2874)**	**YA-ADHD-WC [b] (n = 256)**	
	%	**%**	**p-value**	**%**	**%**	**p-value**	**%**	**%**	**p-value**
Prevalence rate	91.1	8.9	--	87.8	12.2	--	91.8	8.2	--
Gender (Male)	47.9	63.9	< 0.001	50.4	39.0	< 0.001	51.5	44.9	0.05
ADHD presentation in adulthood [a]			0.43						
Inattentive	54.1	51.7	--	--	53.3	--	--	59.0	--
Hyperactive-impulsive	9.1	5.0	--	--	8.9	--	--	12.1	--
Combined	36.8	43.3	--	--	37.8		--	28.9	--
OUTCOMES	**%**	**%**	**p-value**	**%**	**%**	**p-value**	**%**	**%**	**p-value**
Traffic accidents	17.2	21.9	0.03	16.7	23.2	< 0.001	16.2	21.5	0.03
Criminal behavior - violent	14.5	28.7	< 0.001	14.4	24.4	< 0.001	11.8	18.5	0.003
Criminal behavior — any	16.6	30.9	< 0.001	16.5	27.1	< 0.001	13.7	20.7	0.004
Incarceration	0.9	4.0	< 0.001	1.0	2.8	< 0.001	0.5	1.6	0.04
Tobacco smoking	13.3	25.9	< 0.001	13.7	19.0	0.003	10.0	11.8	0.39
Illicit drug use	6.8	10.8	0.006	7.0	9.0	0.11	--	--	--
Depression	3.8	7.2	0.003	2.7	13.6	< 0.001	--	--	--
Bipolar Disorder	1.5	4.2	< 0.001	0.9	7.4	< 0.001	--	--	--
Generalized Anxiety Disorder	7.2	10.8	0.02	5.1	24.9	< 0.001	--	--	--
Social Anxiety Disorder	6.5	10.2	0.01	5.0	20.2	< 0.001	--	--	--
Suicide attempt	6.0	10.0	0.003	5.1	15.2	< 0.001	3.5	6.6	0.01
Teenage pregnancy	13.2	21.9	0.006	13.8	12.8	0.64	13.3	9.9	0.26
Sexually transmitted diseases	2.6	2.9	0.72	2.2	5.3	< 0.001	1.9	4.7	0.004
	M (SD)	**M (SD)**	**p-value**	**M (SD)**	**M (SD)**	**p-value**	**M (SD)**	**M (SD)**	**p-value**
Personal income	510.5 (419)	543.5 (315.9)	0.20	516.43 (422.9)	478.86 (263.6)	0.11	517.5 (449.6)	489 (281.7)	0.40
Years of schooling	8.63 (2.29)	8.45 (2.35)	0.15	8.61 (2.29)	8.57 (2.26)	0.70	8.62 (2.29)	8.56 (2.15)	0.68
Intelligence Quotient	97.2 (12.4)	89.7 (11.7)	< 0.001	96.7 (12.7)	95.3 (11.8)	0.01	97.7 (12.2)	95.6 (11.9)	0.008

C-ADHD: Childhood ADHD; *YA-ADHD:* Young Adults with ADHD; *YA-ADHD-WC:* Young Adults with ADHD without Comorbidity; *IQ:* Intelligence Quotient; M: Mean; *SD:* Standard deviation; [a] Comparison with chi-square in a 2x3 table considering young adult ADHD presentation in children with ADHD that continued to have ADHD in young adulthood and those from the non-ADHD group in childhood that developed ADHD in young adulthood. [b] Please note that YA-ADHD-WC represents 6.3% of the entire adult population and 8.2% of adults without comorbidities.

Article #2

With respect to specific objective b. Systematically review the literature on risk factors for the persistence of ADHD, and summarize their effects with meta-analytic techniques.

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Predictors of persistence of ADHD into adulthood: a systematic review of the literature and meta-analysis

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Conflicts of interest: Dr. Grevet was on the spearkers' bureau of Shire and Novartis. He received travel awards for taking part of a meeting sponsored by Shire and the World Congress on ADHD in 2015. Dr. Rohde was on the speakers' bureau/advisory board and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He also received travel awards for taking part of 2014 APA meeting and 2015 WFADHD meeting from Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. Dr. Kieling receives authorship royalties from publishers Artmed and Manole.

Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is traditionally conceptualized as a neurodevelopmental disorder that continues into adulthood in up to half of diagnosed cases. In light of current evidence, factors associated with the course of the disorder remain unknown. We performed a systematic review of the literature searching for risk markers from childhood that predicted the persistence of ADHD into adulthood. We reviewed 26,168 abstracts, and selected 72 for full-text review. We identified data from 16 studies, comprising six population-based retrospective samples and ten clinical follow-ups. We performed meta-analyses of factors evaluated by at least three studies. Severity of ADHD (OR 2.33, 95% CI = 1.6-3.39, $p < 0.001$), treatment for ADHD (OR 2.09, 95% CI = 1.04 -4.18, $p = 0.037$), comorbid Conduct Disorder (OR 1.85, 95% CI = 1.06-3.24, $p = 0.030$), and comorbid Major Depressive Disorder (OR 1.8, 95% CI = 1.1-2.95, $p = 0.019$) emerged as predictors already presented in childhood for ADHD persistence into adulthood. Further, we suggest that cohort studies be designed in order to clarify such an important question for research and clinical practice.

Key-words: ADHD; Adolescence; Risk factors; Persistence; Course; Prognosis.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common disorder,[1] traditionally conceptualized as resulting from abnormalities in neurodevelopment. Its course embodies one challenging scenario, since as many as half of affected children present a chronic disorder that persists beyond adolescence and throughout adulthood,[2] a trajectory that is associated with burden in many aspects of life.[3-5] Thus, from the clinical point of view, the identification of individuals with increased risk of persistence that may benefit from more intensive strategies aiming at long-term adherence is without any doubt of great value.

The impact imposed by ADHD in childhood and adolescence is highly recognized and documented by several studies.[6,7] Nonetheless, its burden in adulthood is still not always recognized, despite investigations clearly documenting it.[3,5,8,9] For example, behavioral disorders (ADHD and conduct disorder, CD) were included for the first time in the 2010 Global Burden of Disease Study,[10] but the impact associated with them was mostly restricted to the two first decades of life. Whereas ADHD and CD were reported to account for almost two million disability-adjusted life years (DALYs) between ages 15 and 19 years, they were associated with only two hundred thousand DALYs between ages 20 and 24 years. However, the developmental trajectory of these disorders does not suggest that they disappear or decrease their impact as sharply as suggested.[4] One explanation for the reduced burden of ADHD in older ages is the scarcity of follow-up studies.

The first studies to follow hyperactive children beyond the school years reported a tendency towards syndrome remission during adolescence.[11-13]

However, this is certainly not the case for every child affected with ADHD. Faraone and colleagues[2] pooled ADHD persistence rates from 10 samples in a systematic review and meta-analysis, reporting an estimate of 15% when a full syndrome in adulthood according to the DSM-IV criteria was required (using a 6 symptom cut-off). Moreover, this review also indicated that a higher proportion of individuals (up to 65%) remain presenting some level of the original symptoms and associated impairment.[2] A recent report by Moffitt and colleagues confirmed to a large extent these figures of persistence and further extended the knowledge on distinct developmental presentations of ADHD.[14]

Even in light of the best available evidence, it is impossible for a clinician to determine whether a child presenting with ADHD will sustain the condition through adolescence and adulthood, therefore preventing carefully planned long-term follow-up and treatment. Once available, prevention strategies could also play an important role in this group of patients. On the other hand, those with a naturally remitting course might benefit from a less intensive approach and counseling.

Although clinical prospective and retrospective studies might be informative for clinicians dealing with patients with the same characteristics of those from clinical samples, markers of ADHD persistence or remission coming from population-based studies are essential to understand the natural history of the disorder. Our objective is to identify the current knowledge in terms of factors associated with ADHD persistence or remission from childhood until adulthood through a systematic review of the literature. We hypothesize that no isolated marker will be homogeneously presented in different studies and the

heterogeneity of the methods in studies will prevent a complete understanding of the predictors of different ADHD trajectories from childhood to adulthood.

Methods

The search intended to find prospective or retrospective studies that had an assessment of ADHD status in childhood (operationalized as before age 12) and adulthood (operationalized as after age 18), and information (clinical, demographic, genetic, neurobiological) from childhood. The assessment of ADHD status in childhood should be based on interviews in clinical studies and on interviews or retrospective self-report in population-based studies. In order to address the question of which variable is associated with persistence of ADHD, it was required that the study reported the information both for the subjects who persisted as well as for those who remitted. We also included review articles about the course of ADHD to perform handsearch of reference lists. Our only exclusion criterion was if data came from intervention (pharmacological or psychosocial) studies, but no study was excluded by this criterion.

We searched three major literature databases: Medline, Web of Science and PsycINFO. We designed the algorithm in a composed structure with three sets of terms: one to capture different writings for ADHD; a second to address the longitudinal design required by the inclusion criteria; and a third comprising the vocabulary of risk markers. The final search expression was as follows: ("ADHD" OR "ADD" OR "attention deficit" OR "attention-deficit/hyperactivity" OR hyperactiv* OR overactiv* OR inattent* OR "hyperkinetic disorder") AND ("adult" OR "adults" OR "adulthood" OR "course" OR "lifetime" OR persist* OR "remission" OR "remits" OR declin* OR "lifespan" OR "stable" OR "stability")

AND ("risk factor" OR "risk factors" OR predictive factor* OR "risk marker" OR "risk markers" OR "protective factors" OR "protective factor" OR prognos* OR "follow" OR "longitudinal" OR "long term" OR "prospective" OR "predictor" OR "predictors" OR outcome* OR "later"). Two authors (A.C. and A.V.S.) independently reviewed the abstracts, and discussed disagreements with a third author (C.K.) (Figure 1). We searched genetic studies with the search terms described above with an additional set of terms: AND ("gene" OR "genetics" OR "gene-gene interaction" OR "epistasis" OR "pathway analysis" OR "genome-wide association study" OR "GWAS" OR "candidate gene study" OR "cross-disorder"), and a different date range: from June 1st, 2011 until April 20, 2015. Franke and colleagues[15] had already reviewed the literature prior to that date. One author (D.L.R.) reviewed the reference list of this review and additional abstracts using the database search strategy, and discussed findings with C.H.D.B.

Studies that were in accordance with the inclusion criteria or that could not be included based only in the content of the abstract were selected for a full-text review, and the references of these studies were also reviewed. Finally, we contacted experts in the area with the final list attached to ask for important publications that could have been missed. Two authors (A.C. and A.V.S.) independently extracted the following data from selected studies: sample setting, number of subjects enrolled, study design, age of first and last assessment, diagnostic instruments and disorder definition. They assessed predictors on persistence, including factors from childhood that were compared between those who persisted and those who outgrew the disorder. They also collected data on the magnitude of association, such as odds ratio (OR), risk

ratio (RR), or hazard ratio (HR), as presented in the studies. When no OR/RR was reported, but the frequency of persistence in two risk groups was available, we calculated OR in retrospective studies and RR in prospective studies, and 95% confidence intervals (95% CI) with standard procedure of 2x2 table. For continuous variables, authors extracted means and standard deviations and calculated Standardized Mean Difference (SMD) between the groups. When factors were assessed by at least three studies that provided sufficient data, we used meta-analytic techniques with random-effects model to estimate overall effect size using computed OR and 95% CI for all the studies included, using Comprehensive Meta-Analysis Software.[16] This study was approved by the Ethics Committee of Hospital de Clinicas de Porto Alegre, under the number 140618.

Results

Of the initial 32,375 abstracts (26,168 after exclusion of duplicates), we selected 72 original studies for full-text review, of which 12 were included in the final list. The handsearch of reference lists did not include new references. The expert consult retrieved two other studies (one book and one doctoral thesis). The search for genetic studies retrieved 862 new abstracts on the topic, included 36 articles for full-text review and selected two studies. The final list consisted of 16 studies (Table 1). We did not perform publication bias analyses due to the small number of studies included for each risk factor.

Sociodemographic features

Ten studies evaluated gender as a predictor of the course of ADHD, eight of them finding no difference in persistence between males and females

[17-25]. Two prospective studies had different results: Breyer and colleagues [26] observed a lower persistence for males (RR 0.68, 95% CI=0.5-0.91, p < 0.001), similarly to Cheung [27] (RR 0.76, 95% CI=0.68-0.85, p < 0.001). Eight samples were included in the meta-analysis (Figure 2A), resulting in a pooled OR of 1.23 (95% CI = 0.84-1.81, p = 0.295). Regarding socioeconomic status (SES) at childhood, three [19,26,28] reported no difference between persisters and remitters. Cheung *et al*. [27], however, observed a lower SES at baseline in the group that persisted compared to those who remitted (3.38 ± 1.01 vs. 4.41 ± 0.88, p = 0.01). Three studies were included in the meta-analyses (Figure 2H), resulting in a pooled SDM of 0.18 (95% CI = -0.23-0.59, p = 0.39). Four studies that evaluated intelligent quotient (IQ) at baseline were unanimous not finding any influence of this factor in persistence of ADHD [21,22,26,28]. We meta-analyzed data from three studies (Figure 2I), resulting in a pooled SDM of 0.03 (95% CI = -0.18-0.23, p = 0.8). Only one study [22] evaluated gestational age and birth weight and it did not find difference between the groups.

ADHD characteristics

Six studies evaluated severity of ADHD as a predictor of the course of the disorder. Four of these [17,19,23,24] reported significantly higher levels of persistence for individuals with severe impairment, with OR and RRs ranging from 1.31 to 3.37. Biederman and colleagues [20] and Chang and colleagues [21] found no significant difference in persistence related to severity. We included four studies in the meta-analysis (Figure 2C), resulting in a pooled OR of 2.33 (95% CI = 1.6-3.39, p < 0.001). Individuals who were treated for ADHD were more likely to continue to have the disorder at follow up according to

Kessler *et al*. [23] (OR 4.5, 95% CI = 1.7-11.8, p = 0.002), in a study that defined positive treatment history if the individual had any professional treatment before age 15, as well as to Chang *et al*. [21] (OR 9.56, 95% CI = 2.09-43.67, p = 0.004), that defined positive treatment if the individual used standard medication (i.e., any form of methylphenidate to an optimum dosage) for at least six months. This effect remained significant even after controlling for ADHD severity. However, this was not observed in four other studies.[19,20,24,26] We included five studies in the meta-analysis (Figure 2B), resulting in a pooled OR of 2.09 (95% CI = 1.04 -4.18, p = 0.037). Three investigations assessed age at onset. None of them found significant differences between persisters and remitters [17,19,20]. We could not perform meta-analysis due to insufficient data (table 2). Four studies evaluated the effect of diagnostic subtypes in the course of ADHD. Kessler and colleagues [23] reported that individuals with combined type, compared to those with either predominantly inattentive or hyperactive types, were at a significant higher risk for the persistence of ADHD into adulthood (OR 2.4, 95% CI = 1.3-4.2, p = 0.003). Yang and colleagues [29] reported that adults with combined subtype of ADHD in childhood had the most severe adult ADHD (p < 0.001). Lara and colleagues [24] found a greater persistence in individuals who reported only inattentive problems (OR 2.7, 95% CI = 1.3-5.6, p = 0.008), inattentive and sub-threshold impulsive-hyperactive (OR 5.1, 95% CI = 1.8-14.5, p = 0.002), and combined subtype (OR 12.4, 95% CI = 4.5 - 34.5, p < 0.001) when compared to those who reported only impulsive-hyperactive symptoms at childhood. Further, Cheung *et al*. [27] observed that persisters had higher scores of inattention, but

not of hyperactivity, in childhood (as rated by parents). We could not perform meta-analysis due to insufficient and incompatible data (table 2).

Comorbidities

Chang and colleagues [21] observed a higher persistence in individuals with comorbid oppositional defiant disorder (ODD) (RR 1.42, 95% CI = 1.14 - 1.76, p = 0.002). Barkley and Fischer [30] had similar results (RR 2.2, 95% CI = 1.51 - 3.22, p < 0.001). Two other studies [20,28] found no association between ODD and persistence. We included these four studies in the meta-analysis (Figure 2D), resulting in a pooled OR of 1.65 (95% CI = 0.75-3.65, p = 0.213). Comorbid conduct disorder (CD) was evaluated as a predictor of persistence by five studies [17,19-21,28], but only Biederman *et al*. [20] found a significant association. We included four studies in the meta-analysis (Figure 2E), resulting in a pooled OR of 1.85 (95% CI = 1.06-3.24, p = 0.03). Major depressive disorder (MDD) was a risk marker for the persistence of ADHD in the sample studied by Lara *et al*. [24] (OR 2.2, 95% CI = 1.1-4.3, p = 0.023), but not in three other studies [19-21]. We included three studies in the meta-analysis (Figure 2F), resulting in a pooled OR of 1.8 (95% CI = 1.1-2.95, p = 0.019). Biederman and colleagues [19] reported a higher persistence of ADHD in boys with multiple (two or more) anxiety disorders (p < 0.05), but this finding was not consistent with two other studies [20,21]. We could not perform meta-analysis due to insufficient data (table 2). The presence of three or more comorbidities increased the odds of persistence by 1.7 (95% CI = 1.1-2.6, p = 0.016) in the study by Lara *et al*. [24], while Chang *et al*. [21] found no such an association (RR 1.18, 95% CI = 0.82-1.71, p = 0.377).

Exposure to adversities and trauma

Lara and colleagues [24] found no association between trauma exposure and persistence (OR 1.3, 95% CI = 0.8 -2.3, p = 0.33), a finding consistent with that reported by Kessler *et al*. [23] (p = 0.71). Parental psychopathology increased the odds of persistence in two contexts, according to Lara *et al*. [24]: paternal anxiety-mood disorder (OR 2.4, 95% CI = 1.1-5.5, p = 0.033) and parental (mother or father) antisocial personality disorder (OR 2.2, 95% CI = 1.2-4.2, p = 0.014). In regard to exposure to adversities, Biederman and colleagues [20] reported higher persistence in girls with a first-degree relative affected with multiple (two or more) anxiety disorders ($p < 0.05$). The same study also found that children that lived with only one parent were at higher risk for persistence (RR 1.29, 95% CI = 1.07-1.55, p = 0.007), but this finding was not replicated in two other samples [19,26]. We included three studies that evaluated single parent family as risk marker of persistence in the meta-analysis (Figure 2G), resulting in a pooled OR of 1.08 (95% CI =0.36-3.25, p = 0.892).

Neuropsychological measures

Roizen [28] studied the performance in neuropsychological tests, including working memory, visual motor integration, visual sequential memory, omission-commission performance test, among others, as a risk factor for persistence of ADHD. The author has also created a neuropsychological factor, developed with the average of the z-scores of all the tests. None of the variables were associated with persistence, including the neuropsychological factor (OR 0.70, 95% CI = 0.25-1.95, p = 0.496). Cheung *et al*. [27] also

evaluated neuropsychological measures, including reaction time variability, commission errors, omission errors, choice impulsivity, digit span forward, digit span backward, among others, finding no association with persistence of ADHD.

Electroencephalogram profile

Clarke and colleagues [31] investigated thirty-eight boys diagnosed with ADHD and 38 controls, performing EEG assessments at a mean age of 9.8. They found that the ADHD group had a higher theta activity and decreased beta and delta activity compared to controls, and a higher theta/beta ratio, which was consistent with previous reports in the literature. The authors followed the individuals for 11 years until adulthood and had their ADHD status reassessed. Interestingly, those who outgrew the disorder had a baseline EEG pattern that was the most divergent from that of the control group, being responsible for most of the difference between ADHD and control groups reported at baseline. This could possibly mean that those whose symptoms are due to brain abnormalities that result in an altered electrical activity detected by the EEG have a tendency to remission as a result of brain maturation through development.

Genetics

Li and colleagues [32] evaluated the effect of two single nucleotide polymorphisms (SNPs) in the dopamine receptor D4 (*DRD4*) gene (rs1800955, rs916455) on ADHD persistence in a small Chinese sample of adults (n = 193). Although there was no evidence of association with the rs1800955

polymorphism, they found a significant effect of the rs916455 on ADHD persistence. After 11 years of follow-up, 56% of individuals carrying the T allele were considered remitters, compared to only 26.6 % of individuals not carrying this allele (HR = 1.03, 95% CI = 1.00-1.05, p = 0.018). Biederman and colleagues [33] examined the role of three candidates genes (*DRD4*, dopamine transporter - *DAT1*, and serotonin transporter - *5HTT*), which had been previously associated with ADHD, on the course of this disorder. Authors aggregated data from three samples, encompassing 563 individuals. Survival analyses revealed no significant effects of polymorphisms in *DAT1* (HR = 1.02, 95 % CI = 0.68 -1.52, p = 0.923) and *5HTT* (HR = 1.13, 95 % CI= 0.67-1.89, p = 0.644) genes. However, a variable number of tandem repeats (VNTR) polymorphism in exon 3 of the *DRD4* gene (*DRD4* 48bp-VNTR) was significantly associated with the course of ADHD (HR = 1.66, 95 % CI = 1.02-2.69, p = 0.040). At the age of 25 years, 76% of the individuals carrying the *DRD4* 7-repeat allele still had the diagnosis of ADHD, while this same estimate was 66% in individuals not carrying this allele.

Discussion

In many areas of medicine, the advance in the establishment of accurate prognosis for chronic disorders has led to meaningful improvements in the development of target intervention and personalized care.[34] ADHD, despite being one of the most studied health conditions[35], lacks such relevant clinical data. This is, to our knowledge, the first systematic review assessing risk markers for the persistence of ADHD from childhood into adulthood. We searched the literature in three databases reviewing more than 26,000

abstracts, searched the references of pre-selected studies, and contacted experts in the area of ADHD and follow-up studies to evaluate our final list and suggest missing references. Nonetheless, the literature proved to be scarce and asymmetric in the field: out of more than 20,000 articles published on ADHD only in Medline until April 20, 2015, we found only 16 studies that looked into the course of ADHD from childhood into adulthood focusing on risk factors – what represents 0.08% of the literature on the disorder.

Furthermore, the studies evaluated assorted factors that, in many cases, do not enable enough comparisons or meaningful conclusions. The role of comorbid ODD, for example, was investigated by four studies with divergent results. Other important issues, such as exposure to trauma, lifetime adversities, genetic factors, and perinatal factors, were evaluated by even fewer studies. However, meta-analytic techniques enabled some more solid and interesting conclusions. A severe presentation of ADHD, treatment for ADHD, and comorbid conduct disorder and major depressive disorder in childhood were significantly associated with persistence of symptoms into adulthood (Figure 2). These findings have important implications for clinical practice and research. Children with this profile could receive specialized care as they have a known tendency to persist with an impairing disorder throughout development. Meanwhile, researchers willing to develop preventive interventions could benefit from the present review to select children at risk for persistence.

The fact that ADHD treatment emerged as a risk marker of persistence was a surprising result. However, there are important issues involving this particular finding. For example, it is self-evident that a child is more likely to receive treatment if presenting with a severe disorder, which was the most

consistent marker of persistence in our meta-analysis. On the other hand, two of the five studies included have found a significant association with treatment, which led them to run the analysis controlling for severity, and the effect did not disappear.[21,23] In this case, an alternative explanation for the observed phenomenon is that the instruments used to measure severity in those studies may not be so sensitive, neglecting some of the manifestations that makes a clinician inclined to start treatment. In addition, the overall effect has a high inconsistency index, which reflects the heterogeneity of the studies, especially in terms of design and factor definition.

According to our and meta-analysis, female gender was not associated with ADHD persistence into adulthood. Based on theoretical models of ADHD, we expected that female gender would emerge as a significant risk factor, since the male-to-female ratio in clinical samples goes from 3:1 in childhood to around 1:1 in adulthood[36,37], suggesting that males had a tendency to outgrow the disorder, while females had a tendency to persist. Our results do not support this hypothesis. However, gender differences in externalizing disorders are influenced by treatment referral bias and are a good example of an analysis that would benefit from prospective, population-based designs.

Our findings should be interpreted under the light of limitations. The results of any systematic review and meta-analyses hinge on the methodological quality of included studies. Six of the studies included were retrospective and vulnerable to an increased recall bias. The other ten derived from clinical samples, making them subject to a higher selection bias. We have not found any prospective, population-based study that addresses the topic. Long-term follow-up studies are faced with issues of diagnosis definition:

children and adult evaluation made use of different criteria, challenging the interpretation of persistence. Furthermore, reports were limited by the set of factors available for assessment, as most studies were clearly not designed with the primary purpose of evaluating risk markers for the persistence of ADHD. Finally, we assessed risk marker for one possible trajectory of ADHD (i.e., from childhood to adulthood). Clinical cohorts of individuals with ADHD firstly diagnosed in adulthood and followed for several years also suggest that different risk factors might operate in determining persistence during this age range or that these patients represent a different subset in ADHD clinical samples [38].

The present review identified an overlooked question of research in the ADHD literature. The current knowledge about risk markers of the course of ADHD is still unsatisfactory to guide clinical practice. We recommend that prospective, population-based cohort studies should address this issue. Such studies will provide valuable insights on ADHD across the lifespan.

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Figure 1. Search strategy

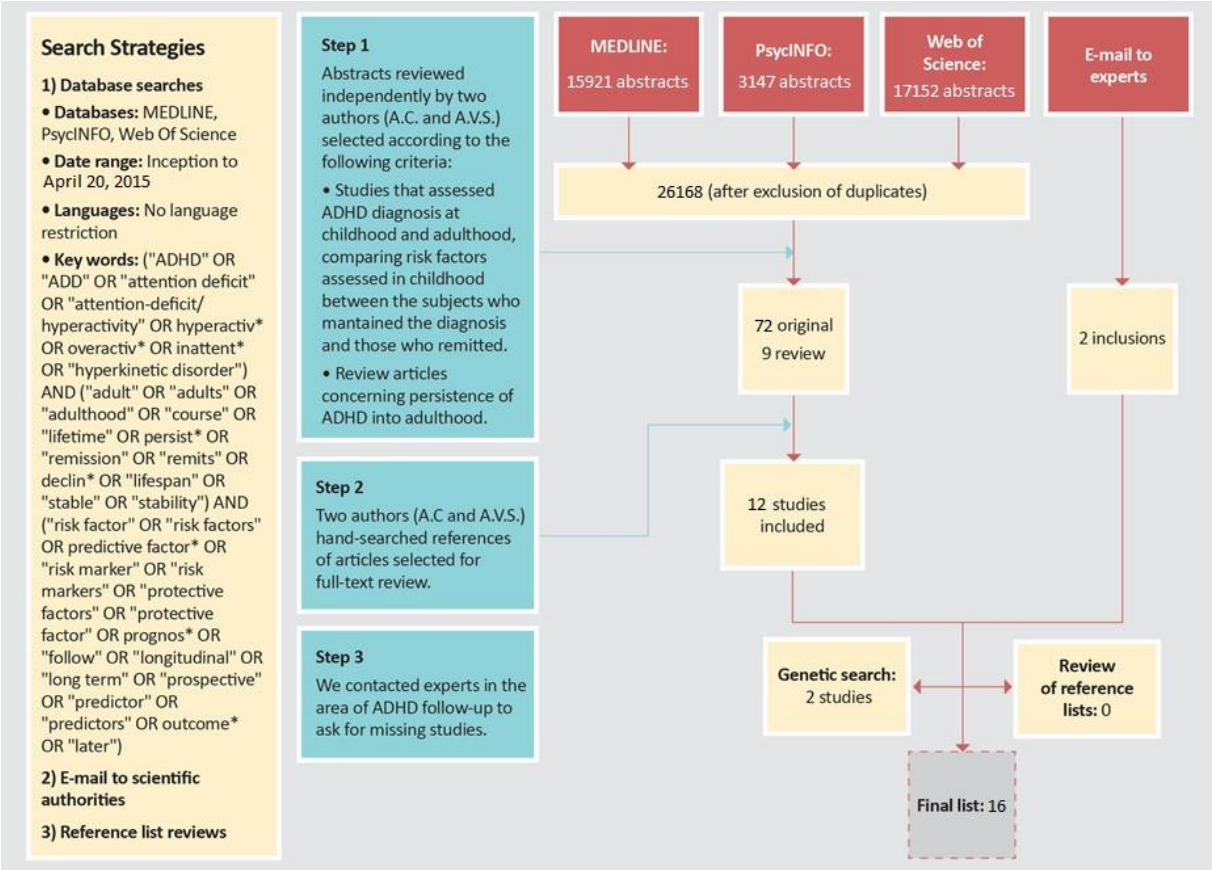
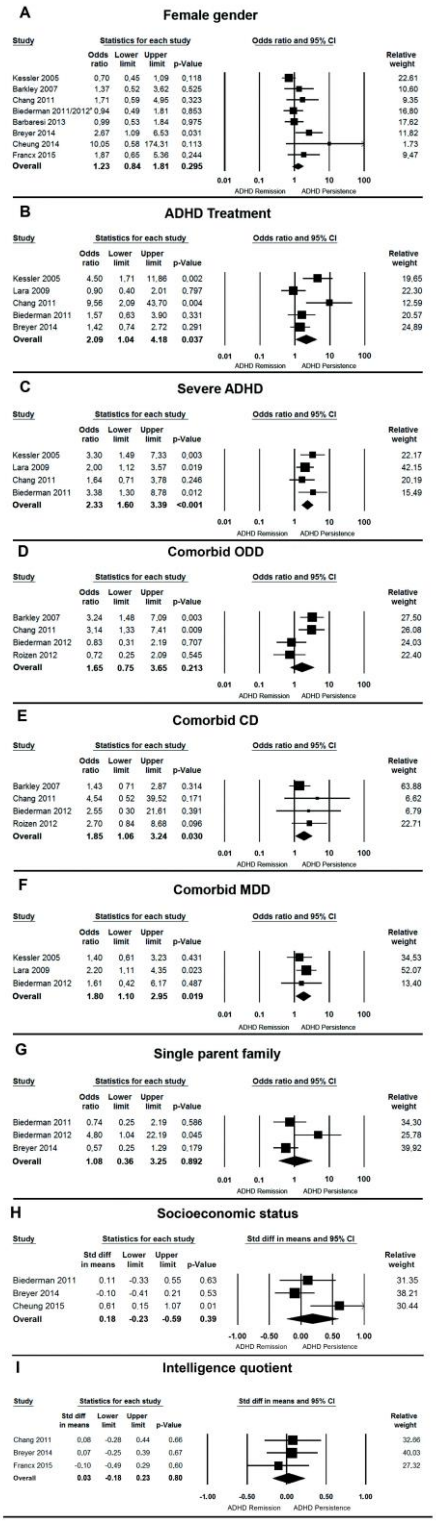


Figure 2. Meta-analyses of selected* risk markers of ADHD persistence.



ADHD Attention-deficit/hyperactivity disorder *ODD* Oppositional defiant disorder *CD* Conduct Disorder *MDD* Major depressive disorder.

Note: All analysis used random-effects model to estimate weights of individual studies. Values of association of each study may differ of those reported in the text because of transformation to odds ratio even in prospective studies.

* We selected markers when data from at least three studies were available to include in the meta-analysis.

For this analysis, we estimated odds ratios including two parallel samples by Biederman [19,20] that had similar design but included boys and girls only.

Article #3

With respect to specific objective c. Develop and validate a risk model to predict the persistence, remission and emergence of ADHD during adolescence.

In press in the Epidemiology and Psychiatric Sciences

Abstract word count: 241; **Text** word count: 3317; **Figures:** 2; **Tables:** 3.

A risk calculator to predict adult Attention-deficit/Hyperactivity disorder: generation and external validation in three birth cohorts and one clinical sample.

Short title: A risk calculator to predict adult ADHD.

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ABSTRACT

AIM: Few personalized medicine investigations have been conducted for mental health. We aimed to generate and validate a risk tool that predicts adult Attention-Deficit/Hyperactivity Disorder (ADHD).

METHODS: Using logistic regression models, we generated a risk tool in a representative population cohort (ALSPAC – UK, 5113 participants, followed from birth to age 17) using childhood clinical and sociodemographic data with internal validation. Predictors included sex, socioeconomic status, single-parent family, ADHD symptoms, comorbid disruptive disorders, childhood maltreatment, ADHD symptoms, depressive symptoms, mother's Depression, and intelligence quotient. The outcome was defined as a categorical diagnosis of ADHD in young adulthood without requiring age at onset criteria. We also tested Machine Learning approaches for developing the risk models: Random Forest, Stochastic Gradient Boosting, and Artificial Neural Network. The risk tool was externally validated in the E-Risk cohort (UK, 2040 participants, birth to age 18), the 1993 Pelotas Birth Cohort (Brazil, 3911 participants, birth to age 18), and the MTA clinical sample (US, 476 children with ADHD and 241 controls followed for 16 years from a minimum of 8 and a maximum of 26 years old).

RESULTS: The overall prevalence of adult ADHD ranged from 8.1% to 12% in the population-based samples, and was 28.6% in the clinical sample. The internal performance of the model in the generating sample was good, with an Area Under the Curve (AUC) for predicting adult ADHD of .82 (95% confidence interval [CI], .79 to .83). Calibration plots showed good agreement between predicted and observed event frequencies from 0 to 60% probability. In the UK birth cohort test sample, the AUC was .75 (95% CI, .71 to .78). In the Brazilian birth cohort test sample, the AUC was significantly lower – 57 (95% CI, .54 to .60). In the clinical trial test sample, the AUC was .76 (95% CI, .73 to .80). The risk model did not predict adult Anxiety or Major Depressive Disorder. Machine learning approaches did not outperform logistic regression models. An open-source and free risk calculator was generated for clinical use and is available on-line at https://ufrgs.br/prodah/adhd-calculator/.

CONCLUSIONS: The risk tool based on childhood characteristics specifically predicts adult ADHD in European and North-American population-based and clinical samples with comparable discrimination to commonly used clinical tools in internal medicine and higher than most previous attempts for mental and neurological disorders. However, its use in middle-income settings requires caution.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is consistently associated with an increased risk of several adverse health and social outcomes, including poor education achievement, risky sexual behaviors and premature mortality (Cortese *et al.*, 2013, Chang *et al.*, 2014, Dalsgaard *et al.*, 2015, Faraone *et al.*, 2015). ADHD might begin in childhood and persist throughout adulthood, or it may remit spontaneously in around half of the cases (Caye *et al.*, 2016b). Recent evidence suggested that subthreshold symptoms can get worse over time, causing the emergence of a full-blown syndrome only in adulthood (Caye *et al.*, 2017), although the topic is still under debate in the literature (Cooper *et al.*, 2018, Manfro *et al.*, 2018). Although some risk factors for the persistence or emergence of adult ADHD are known (Caye *et al.*, 2016b, Caye *et al.*, 2016c), the attending psychiatrist is currently unable to correctly predict the course of the disorder based on clinical assessments of children or to propose a preventive intervention for those at risk.

One issue might be the inability to combine what is already known about risk factors. Although mental disorders arise from multiple risk factors, previous studies frequently define risk for targeted preventive interventions on the basis of a single risk factor, for instance, an affected first-degree relative or presence of subthreshold symptoms (Brent *et al.*, 2015, Taylor *et al.*, 2015, Buntrock *et al.*, 2016). Meanwhile, multivariable risk scores such as the Framingham risk score for cardiovascular disease have been one of the main frameworks for the study of preventive strategies in other areas of medicine.

Our aim was to develop and validate a multivariable risk calculator that estimates the individual risk of ADHD in late adolescence/young adulthood based on childhood characteristics. ADHD lends itself easily to the development of a risk calculator for the following reasons: First, its adverse health and social consequences are well established (Asherson *et al.*, 2016). Second, it is widely accepted that its roots are in early childhood, although some argue the full syndrome might develop later in some individuals (Moffitt *et al.*, 2015, Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016a). Third, being a neurodevelopmental disorder, early intervention has the potential to change brain development and improve later clinical outcomes (Shaw *et al.*, 2006). Fourth, there is substantive evidence to support *a priori* hypotheses about specific childhood risk factors (Caye *et al.*, 2016b).

Method

Our methods follow well-established probability models in medicine and recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (Collins *et al.*, 2015). We developed the predictive model in one *a priori* selected sample and validated it independently in three external samples (TRIPOD analysis type 3). We selected the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort as the generating sample based on the following *a priori* defined criteria: population-based sample, largest sample.

Samples and participants

ALSPAC

The (ALSPAC) is a prospective birth cohort study in the UK. Pregnant women with expected delivery dates between April 1st, 1991 and December 31st, 1992, were invited to participate. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Further details on assessments can be found elsewhere (Boyd *et al.*, 2013). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). For the current study, we included 5113 subjects that were assessed for ADHD in childhood (age 7 or 10) and in the last available assessment (age 17).

E-Risk

The Environmental Risk (E-Risk) Longitudinal Twin Study is a prospective birth cohort study designed to represent the UK population. In 1999-2000, investigators enrolled 1116 families with same-sex 5-year-old twins (N=2232) born from January 1st, 1994 to December 4th,1995 (Moffitt and Team, 2002). The study was approved by the Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee, and parents gave informed written consent. Further details can be found elsewhere (Moffitt and Team, 2002). For the analyses, we included 2040 subjects with data on ADHD in childhood (ages 5, 7, 10 or 12) and in young adulthood (age 18).

Pelotas 1993

The 1993 Pelotas Birth Cohort is a prospective longitudinal birth cohort set in Brazil. In 1993, mothers of all children born in the city of Pelotas were contacted and 5249 children were enrolled. The study was approved by the institutional review board of the Federal University of Pelotas, and participants provided written informed consent.

Further information on the cohort design can be found elsewhere (Goncalves *et al.*, 2014). For the current study, we included 4039 participants that had complete ADHD assessment at age 18 to 19 years old.

MTA

The Multimodal Treatment Study of Children with ADHD (MTA) is the largest clinical trial and observational follow up conducted with children with ADHD. In the first phase of the study, investigators enrolled 579 children aged 7 to 10 years old with ADHD and assigned them to 14 months of one of four groups of management. Two years after baseline, 515 consented to enter an observational follow-up and a local normative comparison group of 289 classmates (258 without ADHD) was added. Assessments were conducted at 12, 14, and 16 years after baseline. Informed consent (parental permission and child assent) was obtained for all participating families, using forms approved by both local institutional review boards and the NIH. Detailed design and methods have been presented in previous publications (1999). We included 717 subjects with any complete ADHD assessment in young adulthood (mean age 24).

Assessment and definition of the outcome variable

In each sample, the outcome was a dichotomous ADHD definition in late adolescence or young adulthood. In ALSPAC, participants' parents completed the hyperactive subscale of the Strengths and Difficulties Questionnaire (SDQ-HS) at 17 years of age. The scale showed excellent discrimination against a DSM-IV diagnosis derived from the Development and Well-Being Assessment (DAWBA) conducted in a subsample of 1673 participants (AUC = ·89, 95% CI ·81 to ·96). The best cut-off score to define diagnosis was at least 6 points on the SDQ-HS (sensitivity = 83·3%, and specificity = 83·3%). In the E-Risk, ADHD was ascertained at age 18 years using structured interviews based on full DSM-5 criteria (Agnew-Blais *et al.*, 2016). In the MTA sample, ADHD symptoms were derived from the parents´ Conners Adult ADHD Rating Scale (CAARS). At least five DSM-5 symptoms of inattention and/or hyperactivity were required for the symptom criteria. Impairment was evaluated with the Impairment Rating Scale (IRS), which has strong psychometrics and accurately identifies impairment in adults with ADHD (Sibley *et al.*, 2012). This diagnostic approach was chosen because it has better diagnostic accuracy than a semi-structured interview in this sample (Sibley *et al.*, 2017b). In the Pelotas cohort, trained psychologists interviewed the participants at 18 to 19 years old with a structured interview for ADHD based on DSM-5 criteria (Caye *et al.*, 2016a). A strict age-at-onset criterion was not required to define ADHD in young adulthood to take into account recent evidence suggesting a significant prevalence of late onset ADHD presentation (Moffitt *et al.*, 2015, Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016a).

Assessment and definition of predictor variables

We selected the following predictor variables assessed in childhood: female sex, socioeconomic status (SES), mother's depression, intelligence quotient, maltreatment, ADHD symptoms, depressive symptoms, oppositional defiant behavior and conduct disorders, and single parent family. All predictors were collected before age 12, with the exception of intelligence in Pelotas, which was measured at age 18. Their selection was based on extensive review of previous reports in the literature and a meta-analysis conducted by our group (Moffitt *et al.*, 2015, Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016a, Caye *et al.*, 2016b). We have included all variables that were available across the four samples with some level of comparability, without performing univariate analysis or stepwise techniques for variable selection. Definition of predictors was defined a priori according to relevant literature in the field. Further details are provided in on-line eTable 1.

Statistical analysis

When developing a predictive model in multiple samples, a recommended approach consists in selecting and tuning the best model in one *a priori* selected sample and assessing its performance fo in the remaining independent samples for external validity. Because the evaluation of internal performance within the same sample where the model was derived is affected by overfitting, internal validation optimism correction should be performed. Among the most accepted techniques for internal validation is bootstrap resampling.

We have developed the predictive model in the ALSPAC cohort. We ran a logistic regression including outcome (ADHD at last assessment) as the dependent variable and all eligible predictor variables as covariates. We inspected linearity assumptions of continuous variables by plotting the predictor and the logit of the outcome, and trough Box-Tidwell regressions. We derived the model using linear splines of equal sample sizes (with knots at 25^{th}, 50^{th}, and 75^{th} percentiles) in the ADHD symptoms variable, and this model had better fit indexes (AIC, BIC). Multiple imputation with chained equations (10 imputations) using the remaining predictors was used to deal with missing

values in the predictor variables. We used a fixed number of 10 iterations and assessed convergence with trace plots. In the ALSPAC cohort, for each of the 1000 bootstrap resamples, we have performed pooled regression coefficient estimates and variance across imputations with the command *mi estimate* in Stata (Rubin, 1987). We evaluated the predictive discrimination of the probability model calculating the area under the receiver operating characteristic curve (c statistic) of the estimated probability against the actual outcome as an index of model performance. We have assessed optimism of internal validation with bootstrap inference using 1000 replications with the R package *rms* (Harrell et al., 1996). We have assessed internal and external model calibration with calibration curves, plotting predicted probabilities against observed frequencies. Extreme predictions at the right end of the distribution (highest risk) including less than 1% of the sample at risk were excluded of the calibration analyses to avoid instability of the estimates, and these ranges are not shown in each graph. Multiple imputation and model generation were conducted in Stata MP 13.0. Finally, we tested the predictive discrimination of the same predictors using Machine Learning approaches with the R package *caret* (see eMethods).

We performed several sensitivity analyses to assess the robustness of our findings. We analyzed the performance (measured by the c-statistic) of the model among individuals who endorsed a very low number of ADHD symptoms at baseline (operationalized as equal or below the median of each population) in ALSPAC, E-Risk and Pelotas samples. We had also analyzed the performance (measured by the c-statistic) of the model excluding one variable at each time. Finally, we present the variation of the predicted probability within fixed levels of ADHD symptoms to assess the contribution of the remaining variables to the model.

Results

The number of participants with a dichotomous definition of adult ADHD and the frequency of childhood predictors in each sample can be found in Table 1.

Performance of the predictive model in the generating sample

All variables entered in the probabilistic model were used for the calculation of the estimated risk of the individual (Table 2). Only ADHD symptoms were corrected with splines. The predictive model discriminated between adult ADHD vs. no adult ADHD with an AUC of ·82 (Bootstrap-corrected 95% CI, ·80 to ·83, $p < .001$), which indicates very good discrimination (Figure 1). Correction for optimism with bootstrapping yielded an AUC of ·81. The calibration plot showed that predicted probability and observed frequency of adult ADHD closely agreed throughout the entire range of risk (0 to around 50% - Figure 2). The bias-corrected calibration curve was nearly identical (eFigure 1). The AUC varied within a range of ·74 to ·82 in sensitivity analyses taking out one predictor at a time (eTable 2 in Supplemental material). Proposed probability cut-offs are presented with sensitivity, specificity, positive predictive value and negative predictive value in eTable 3 in Supplemental material.

Performance of the predictive model in a validating cohort sample in the same country

In the E-Risk study, the predictive model discriminated between adult ADHD vs. no adult ADHD with an AUC of ·75 (Bootstrap-corrected 95% CI, ·71 to ·78, $p < .001$), which indicates fair discrimination (Figure 1). The calibration plot showed reasonable agreement between predicted and observed event frequencies, especially in the lower range of risk (Figure 2). The discrimination was the same when restricting the sample to randomly selected non-siblings (eTable 4 in Supplemental material).

Performance of the predictive model in a validating sample in a middle-income country

In the Pelotas cohort, the predictive model discriminated between adult ADHD vs. no adult ADHD with an AUC of ·57 (Bootstrap-corrected 95% CI, ·55 to ·60, $p < .001$), which indicates poor discrimination (Figure 1). There was low agreement between estimated probability and observed frequency of the outcome (Figure 2).

Performance of the predictive model in a validating clinical sample in a country with similar income

In the MTA, the predictive model discriminated between adult ADHD vs. no adult ADHD with an AUC of ·76 (Bootstrap-corrected 95% CI, ·73 to ·80, $p < .001$) (Figure 1). The calibration plot showed that predicted probability and observed frequency of adult ADHD closely agreed throughout the entire range of risk (0 to around 70% - Figure 2), although the model had underestimated event frequency consistently.

Performance of the predictive model within participants with very low endorsement of ADHD symptoms in childhood

We tested the performance of the model for predicting late-onset ADHD in population samples, among only participants that endorsed few ADHD symptoms in childhood – the median or lower number of symptoms in their respective populations. The model had fair discrimination in these subgroups, except for the Pelotas sample in which the model already had poor discrimination (Table 3).

Performance of the predictive model removing one predictor at a time

We tested the model taking out one predictor at a time (eTable 2). The most relevant individual predictor was the level of ADHD symptoms in childhood. However, the model still had fair performance in the model without ADHD symptoms in childhood, with an AUC of ·74 (95% CI, ·72 to ·76, p < .001).

Variation of the predicted probability within fixed levels of ADHD symptoms

We assessed the predicted probabilities of an adult ADHD diagnosis at any fixed level of ADHD symptoms, considering maximum variation of the remaining factors (see eFigure 2). The observed variance indicates that ADHD symptoms are not the only relevant predictive factor in the model. These findings analyzed together clearly indicate that this is not a model based on just one variable.

Specificity of the predictive model in predicting ADHD

Considering that E-risk is the population cohort with the most comprehensive assessment of comorbid mental disorders, we tested model's discrimination predicting adult Anxiety and Major Depressive Disorder. The performance was significantly lower than for ADHD, showing specificity for ADHD compared to other forms of adult psychopathology (eTable 5 in Supplemental material).

Risk calculator and robustness of findings

Predictive discrimination estimates using three different machine-learning approaches were almost the same (see eTable 6 in Supplemental material). In a secondary analysis, we also have developed one comprehensive predictive model with all samples at once, using site as one more predictor variable (see eTable 7; eFigure 3). A risk calculator can be found at http://www.ufrgs.br/prodah/adhd-calculator/.

Discussion

The widespread use of tools that predict clinical outcomes in medical practice has promoted development and testing of preventive interventions, but this approach has been rarely attempted for mental health (Bitton and Gaziano, 2010). We generated a probability model to predict adult ADHD in a large birth cohort in the UK, with very good discrimination – AUC of ·81 after optimism correction – and calibration. This performance compares to the most used clinical tools in Medicine (Morrow *et al.*, 2000). Recent attempts for mental health reported risk scores with good calibration (Fusar-Poli *et al.*, 2017, Hafeman *et al.*, 2017). These studies lacked, however, a consistent external validation with completely independent samples.

Our next step was to validate the score in independent samples. First, we tested the score in another UK birth cohort, the E-Risk. Its performance for predicting adult ADHD was similar. This is an important finding because several risk models in mental health did not replicate well even in samples from similar settings (Kivipelto *et al.*, 2006, Anstey *et al.*, 2014). Since data generated in population samples frequently do not translate to clinical samples (Weissman *et al.*, 2011), we tested the performance of the score in the MTA study, the largest clinical trial ever conducted for ADHD. As for ALSPAC and E-risk, the score worked well with good discrimination and calibration. We then tested the score in a third birth cohort from Brazil. We observed that the score was much less accurate with an AUC of ·57. This finding is not surprising, since previous evidence suggests that the predictive discrimination of risk tools is lower in diverse sociocultural and ethnic populations (Chia *et al.*, 2015). However, since predictor factors assessment in Pelotas was the most heterogeneous, observed low discrimination might have been an effect of measurement error.

Models that predict a diagnosis of chronic disorders often include premorbid signs and symptoms of the disease as predictive factors. For example, the factor that increased discrimination the most in the recently published calculator for psychosis was the index diagnosis when presenting to secondary care, where Psychotic disorders had the greatest weight compared to other disorders such as mood disorders (Fusar-Poli *et al.*, 2017). Although this is a valid approach, other variables must also add to prediction, otherwise models would be tautological. Therefore, we also validated the score in subjects with low endorsement of ADHD symptoms in childhood. The performance was good even in this sensitivity analysis. In addition, we assessed probabilities of an adult ADHD diagnosis at any fixed level of ADHD symptoms, allowing maximum variation of the remaining factors. Finally, we checked discrimination of the model removing each factor at once. Findings suggested that although ADHD symptoms are the most important overall predictor, the complete model works as a necessary refinement and a model without ADHD symptoms has good discrimination as well.

We also conducted other secondary analyses to assess robustness of our findings. We tested the impact of using other statistical methods on our results. We observed that the discrimination of the prediction models remained stable regardless of chosen statistical methods. Finally, we tested the hypothesis of whether the score was specific for the prediction of ADHD. This is an important proof-of-concept: personalized medicine has always been a challenge for the area of psychiatry, as it has been shown consistently that most identified biomarkers and risk factors associated with one mental disorder are also associated with several others (Cross-Disorder Group of the Psychiatric Genomics *et al.*, 2013). We observed that the score was specific for ADHD, not predicting Major Depressive Disorder or Anxiety Disorders.

Previous cohort investigations included in the present study did not find significant childhood DSM dichotomous ADHD diagnosis in the trajectory of late onset ADHD (Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016a). Thus, it might seem surprising that childhood ADHD symptoms predict adult ADHD. The MTA report also highlighted the importance of child ADHD subthreshold symptoms in adult ADHD in cases where formal DSM diagnosis were not found in childhood (Sibley *et al.*, 2017a). Since this approach was not the main focus of previous cohort studies (ADHD subthreshold symptoms), this might explain why childhood ADHD symptoms predict adult ADHD even in cohorts where childhood dichotomous diagnosis was not relevant for adult ADHD.

Our findings should be interpreted considering a set of limitations. First, the design and assessments of different samples were not uniform, limiting the discrimination of the score in the validating samples. Adult ADHD, for instance, was measured with a scale rather than with a structured interview in the generating sample, but not in the validating samples. It is possible, therefore, that the proposed estimated predictive discrimination in validating samples might actually be an underestimation. Further validating efforts with assessments that more closely resemble those of the generating sample might observe higher AUCs. However, this could also be seen as strength of the study, since observed discrimination indices are considered good, even with different methodologies implemented in individual studies. Second, there was attrition in the generating sample's assessments. Nevertheless, potential selection bias does not appear to affect the prediction of outcomes in this cohort, as shown in previous publications (Boyd *et al.*, 2013). Also, we have used multiple imputation techniques to deal with missing values. Third, the observed positive predictive value in selected cut-offs reaches a maximum of 61·8%, while the negative predictive value is much higher throughout prediction. Although this might be considered insufficient, we ought to remember that the positive predictive value depends much on the prevalence of the studied condition, and we are working with population-based samples where the base rate of the condition is low. As a comparison, the Framingham risk score, that is also a tool developed in the general population, yields a positive predictive value of up to 30-40%. The risk score for Bipolar Disorder reports a positive predictive value of up to 32%, even among offspring of Bipolar patients (a high-risk sample). Fifth, it is important to note that other variables that are related to ADHD could have been part of the risk score like prematurity and ADHD in first degree relatives. However, they were not available for testing in the 4 data sets and our guide for risk factors was evidence-based guided by a previous meta-analysis (Caye *et al.*, 2016b). Accordingly, the predicted probability provided by the model should be considered an estimate probability obtained with a pre-specified set of variables.

What is the clinical utility of this score, provided that previous literature already has shown that most variables included in our model that are non-specific risk factors for mental disorders and ADHD symptoms in childhood, as expected, are key predicted risk factor for adult ADHD? No previous effort combined all these variables in a single risk calculator. Therefore, the only information that clinicians could offer was that some variables, like comorbidity with CD/ODD in childhood, increase the risk of persistence of ADHD. By using this calculator, attending clinicians can identify high-risk individuals to inform parents and guide decisions.

Thus, we propose a multivariable risk model to predict ADHD in young adulthood based on childhood factors that has good discrimination in both population and clinical settings. Clinicians can use the model to guide long-term decisions based on identification of children at high risk for future adult ADHD diagnosis. Also, it provides a framework for testing the effectiveness of preventive interventions focused on high-risk individuals. Furthermore, the score might be used to identify at-risk individuals for investigating neurobiological features including brain development. The lower discrimination observed in a middle-income country urges the discussion of how globally generalizable are the risk models that are currently being widely used in clinical practice. Indeed, even the well-established Framingham cardiovascular risk model is being subjected to criticism for its wide variation in performance across different populations. Therefore, future attempts to improve the current model should include setting-specific recalibration analyses that should then be translated to specific risk calculators to be used across different settings. Also, we suggest that cohorts use more standardized methods of collection of predictors and outcomes in Psychiatry for the study of risk factors, so that we can disentangle whether failure to replicate is due to heterogeneity of methods or population. Hence, our work adds to the need for validation of risk models in low and middle-income countries.

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Availability of data and material: Due to constraints on the data sharing permissions of the samples included in this study, we are not allowed to share the data for public use.

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Table 1. Frequency of young adulthood ADHD and of childhood predictors across the four samples

	ALSPAC (n = 5113)	**E-Risk (n = 2040)**	**MTA (n = 717)**	**Pelotas (n = 4039)**
Adult ADHD	486 (9·5%)	166 (8·1%)	205 (28·6%)	492 (12·2%)
Female sex	2619 (51·2%)	1071 (52·5%)	153 (21·3%)	2061 (51·0%)
Socioeconomic status				
Upper	868 (18·6%)	401 (19·7%)	136 (18·9%)	763 (19·6%)
Middle	2172 (46·4%)	966 (47·5%)	356 (50·7%)	1775 (45·6%)
Lower	1637 (35·0%)	665 (32·7%)	210 (29·9%)	1358 (34·9%)
Single parent	519 (11·8%)	450 (22·6%)	190 (26·5%)	882 (22·7%)
ODD or CD	157 (3·4%)	602 (29·5%)	304 (43·6%)	275 (7·0%)
Maltreatment				
Not detected	2084 (41·0%)	1609 (78·9%)	384 (55·3%)	2475 (67·0%)
Probable	2568 (50·5%)	312 (15·3%)	279 (40·1%)	672 (18·3%)
Severe	430 (8·5%)	119 (5·8%)	32 (4·6%)	548 (14·8%)
Lifetime Depression of the mother[a]	1850 (36·3%)	990 (48·5%)	326 (48·2%)	1881 (48·4%)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
IQ	106·9 (16·3)	98·9 (15·6)	103·1 (19·5)	96·5 (12·5)
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Depressive Symptoms[b]	0 (1)	1 (2.5)	5·4 (6·7)	4 (4)
Number of ADHD symptoms[c]	2 (6)	1·5 (3·3)	8·3 (9·6)	4 (5)

ADHD *Attention-deficit hyperactivity disorder* ODD *Oppositional Defiant Disorder* CD *Conduct disorder* SD *Standard deviation* IQR *Interquartile range* IQ *Intelligence quotient*

a. Definition of lifetime depression of the mother was designed to be very sensitive, either by multiple assessments and/or by applying a very low threshold (further details on Table S1 of Supplementary material).

b. ALSPAC: Number of DSM-IV depressive items endorsed. E-Risk, MTA: Children's Depressive Inventory (CDI) score. Pelotas: Emotional subscale score of the SDQ.

c. ALSPAC, E-Risk, MTA: number of DSM-IV ADHD items endorsed. Pelotas: Hyperactivity subscale score of the SDQ.

Note: reported values before multiple imputation. Because each factor may have missing values, we report total number of participants and a proportion where the denominator is the total number of valid subjects.

Table 2. The probability model in the generating sample (n = 5113)

Predictors	**OR (BC 95% CI)**	**BC p-value**
Female sex	·72 (·58 - ·89)	·003
Socioeconomic status	-	-
Upper social class	*reference*	-
Middle social class	1·58 (1·15 – 2·16)	·004
Lower social class	1·55 (1·11 – 2·15)	·010
Single parent family	1·19 (·90 – 1·58)	·215
ADHD symptoms – 0-25th	3·77 (2·09 – 6·79)	< ·001
ADHD symptoms – 25-50th	1·19 (1·02 – 1·40)	·031
ADHD symptoms – 50-75th	1·13 (1·05 – 1·22)	·001
ADHD symptoms – 75-100th	1·18 (1·12 – 1·25)	< ·001
ODD or CD	1·81 (1·21 – 2·71)	·004
Childhood maltreatment	-	-
No detected maltreatment	*reference*	-
Probable maltreatment	1·28 (1·01 – 1·64)	·045
Severe maltreatment	1·35 (·93 – 1·95)	·115
Depression of the mother	1·41 (1·13 – 1·75)	·002
Intelligence quotient[a]	·89 (·85 - ·95)	< ·001
Depressive symptoms (z-score)[b]	1·00 (·92 – 1·10)	·940

OR *Odds Ratio;* ODD *Oppositional Defiant Disorder;* CD *Conduct Disorder;* ADHD *Attention-deficit hyperactivity disorder*

BC *Bootstrap-corrected*

a. We report the OR for a 10-point change in the intelligence quotient scale.

b. Due to the OR of 1·00 for depressive symptoms, we have omitted this variable from the on-line calculator.

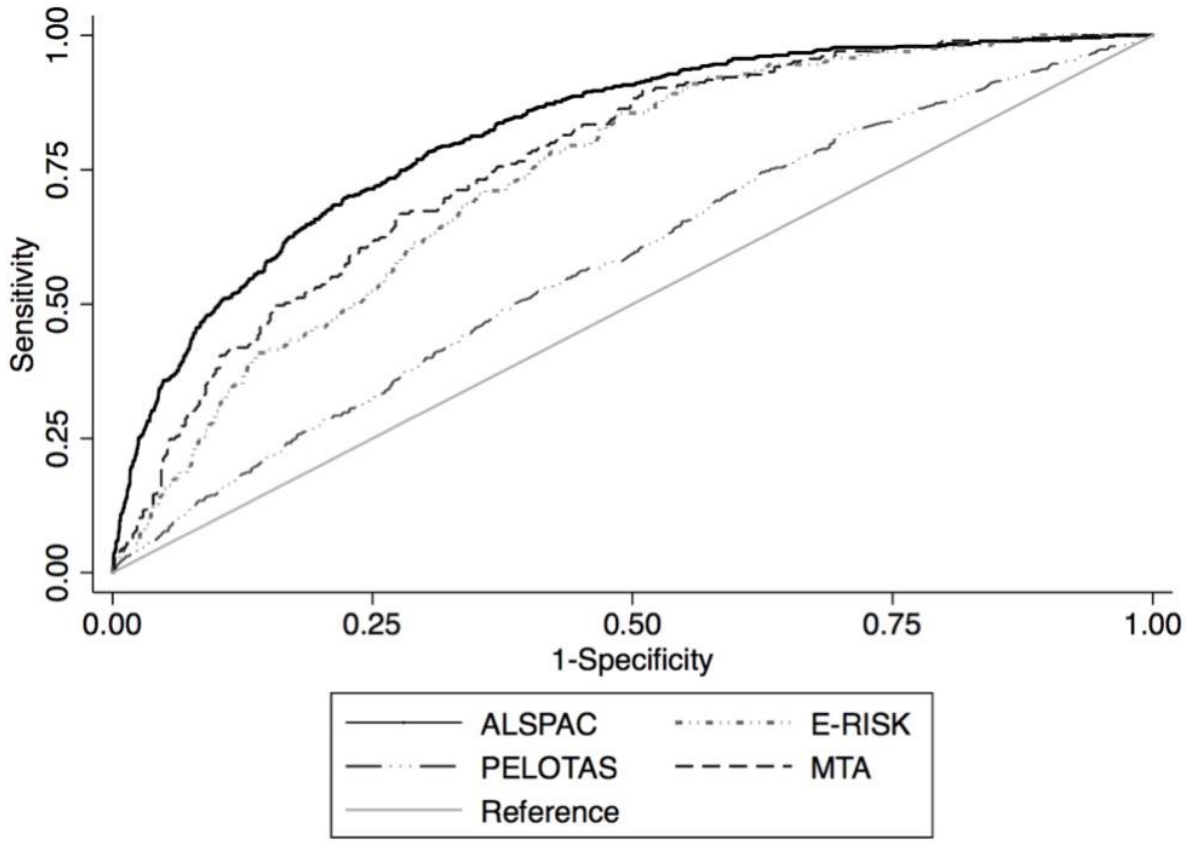
Table 3. Performance of the score for individuals with very low ADHD childhood symptoms.

	AUC	**BC 95% CI**	**BC p-value**
ALSPAC (n = 2688)	·77	·72 – ·82	< ·001
E-Risk (n = 1099)	·78	·71 - ·86	< ·001
Pelotas (n = 2135)	·56	·52 - ·60	< ·001

BC Bootstrap-corrected

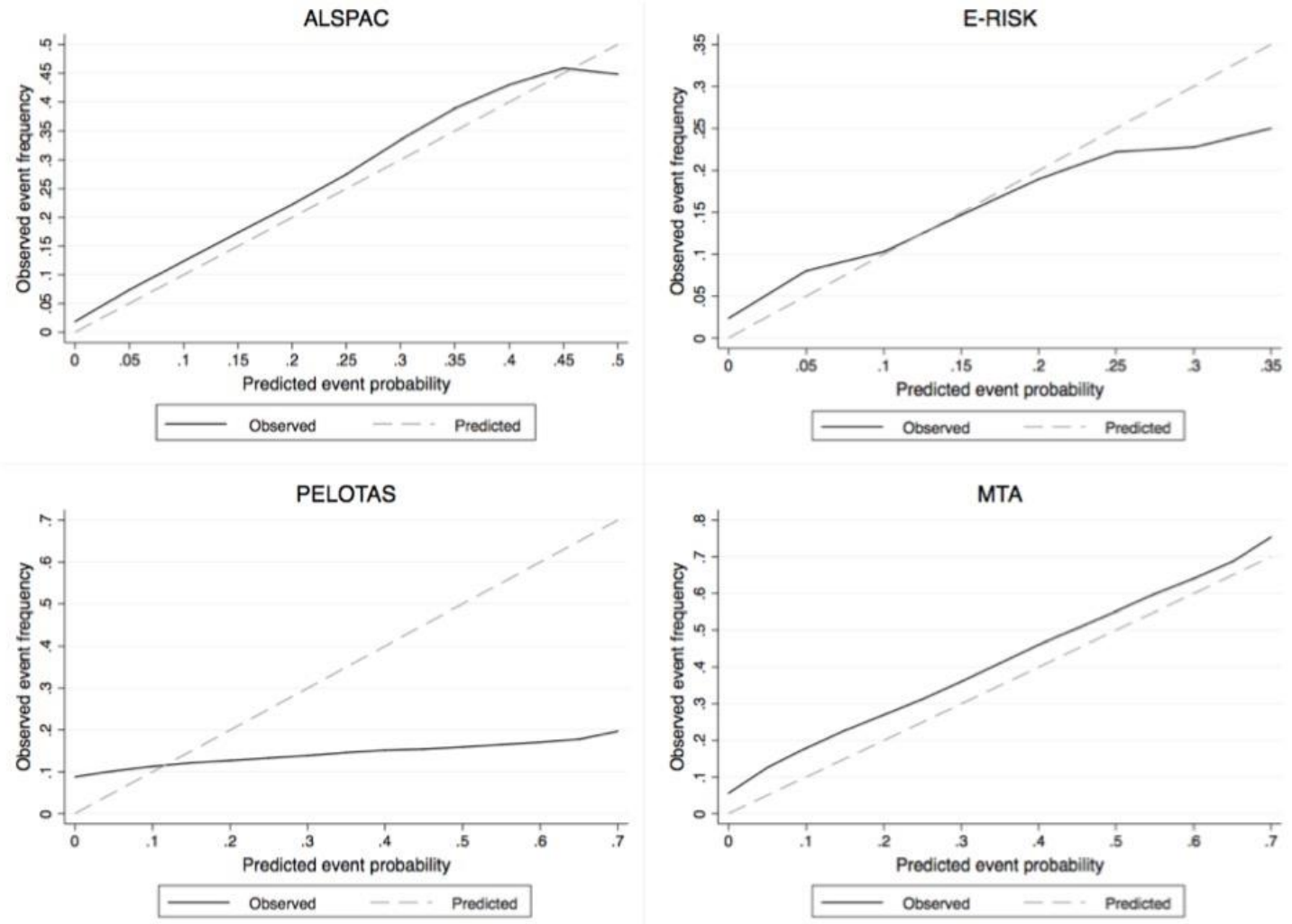
ROC analyses were done only in participants with low endorsement of ADHD symptoms in childhood. Low endorsement was defined as median number of symptoms or below the median of their respective population (ALSPAC: 2 or less ADHD symptoms; E-Risk: 1 or 0 ADHD symptoms; Pelotas: the median or less than median (4) in the hyperactivity subscale of the SDQ).

Figure 1. Receiver operating curves in the four samples.



Receiver operating characteristic curves in each each cohort plotting Sensitivity and 1-Specificity for the predicted probabilities generated by the risk calculator against adult ADHD as the classificatory variable.

Figure 2. Calibration curves in the four samples.



Calibration curves in each cohort plotting the predicted probabilities generated by the risk calculator (x-axis) against observed adult ADHD frequency (y-axis). Dashed diagonal line represents perfect calibration.

Article #4

a. *With respect to specific objectives d. Systematically review the literature on relative immaturity and ADHD, and summarize its effect with meta-analytic techniques and e. Investigate the issue of the relative immaturity effect and ADHD on three independent population-based samples in Brazil.*

Under review in the Journal of the American Academy of Child and Adolescent Psychiatry

Running title: Relative age and ADHD.

Relative younger and attention-deficit hyperactivity disorder: data from three epidemiological cohorts and a meta-analysis.

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Conflicts of interest: Arthur Caye, Giovanni Abrahão Salum, Ary Gadelha, Helen Gonçalves, Sandra Petresco, Tiago Neuenfeld Munhoz, Ana Maria Baptista Menezes, Arthur Gus Manfro, Pedro Mario Pan and Christian Kieling report no conflicts of interest. Luis Augusto Rohde has received grant or research support from, served as a consultant to, and served on the speakers' bureau of Eli Lilly and Co., Janssen, Medice, Novartis and Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by Dr Rohde have received unrestricted educational and research support from the following pharmaceutical companies: Eli Lilly and Co., Janssen, Shire and Novartis. Dr Rohde has received authorship royalties from Oxford Press and ArtMed and travel grants from Shire to take part in the 2018 APA annual meeting and from Novartis to take part of the 2016 AACAP annual meeting. Rodrigo A. Bressan has received research grants from Janssen Cilag, Novartis, Roche and the governmental funding research agencies: CAPES, CNPq and FAPESP (2016/022465 and 2011/50740-5); has been a forum consultant for Janssen, Novartis and Roche; and has participated in speaker bureaus for Ache, Janssen, Lundbeck and Novartis. Alicia Matijasevich, Iná S. Santos and Aluísio JD Barros are supported by the Brazilian National Research Council (CNPq).

Key-words: ADHD; Development; Immaturity; Relative age.

ABSTRACT

OBJECTIVE: To investigate the effect of relative younger age on Attention-deficit hyperactivity disorder (ADHD) symptoms and diagnosis through three population-based cohorts and a meta-analysis of the literature.

METHOD: Individuals included in this study were participants of three community-based cohorts in Brazil: the 1993 Pelotas Cohort (n=5,249), the 2004 Pelotas Cohort (n=4,231), and the Brazilian High Risk Study for Psychiatric disorders (HRC study, n=2,511). We analyzed the effect of relative younger age on ADHD symptoms and diagnosis in actively collected data. For the meta-analysis, we searched MEDLINE, PsycINFO and Web of Science databases from inception through December 25th, 2018. We selected studies that reported measures of association between relative immaturity and an ADHD diagnosis. We followed the Meta-analysis of Observational Studies in Epidemiology guidelines. The protocol for meta-analysis is available on PROSPERO (CRD42018099966).

RESULTS: In the meta-analysis, we identified 1,799 potentially eligible records, from which 25 studies including 8,076,570 individuals (164,049 ADHD cases) were analyzed with their effect estimates. The summarized relative risk of an ADHD diagnosis was 1.34 (95% Confidence Interval, 1.26 to 1.43, $p < .001$) for children born in the first four months of the school year (relatively younger). Heterogeneity was high ($I^2 = 96.7\%$). Relative younger age was associated with higher levels of ADHD symptoms in the 1993 Pelotas cohort (p=.003), in the 2004 Pelotas cohort (p=.046) and in the HRC study (p=.010).

CONCLUSION: Children and adolescents who are relatively younger compared to their classmates have a higher risk of receiving an ADHD diagnosis. We recommend caution in the interpretation of the relative risk of the meta-analysis due to high heterogeneity. Clinicians should consider the developmental level of young children when evaluating ADHD symptoms.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood and adolescence, affecting around 3.4 to 5.3% of school-aged children worldwide[1]. It is characterized by persistent patterns of inattention, hyperactivity, and impulsivity that are inappropriate for the developmental stage of the child or adolescent[2]. Parents and teachers frequently compare their offspring and students to their classmates, who are usually grouped within a one-year range at school. Clinicians will, most of the times, rely on their report to set the threshold between clinically relevant ADHD symptoms and typical development[3]. However, there is relative immaturity within the same classroom: children and adolescents who are born at the end of the school year calendar are up to a year younger than their classmates who are born at the beginning of the school year calendar. This represents an even larger difference among the youngsters. When children enter the first grade, 12 months of difference between those born in the beginning of January and end of December accounts for around 15% of their age.

Several studies show that children who are relatively younger compared to their classmates have a higher likelihood of receiving a diagnosis of ADHD[4-11]. These reports essentially reflect three types of data: epidemiological samples gathering registers of ADHD diagnosis[4-6]; epidemiological samples using registers of ADHD medication[8,9]; and clinical samples assessing relative immaturity within diagnosed children and adolescents[10,11]. With few exceptions, regardless of methodological differences, all those studies agree that being relatively younger within the school year is a risk factor for an ADHD diagnosis, but the estimates are variable, with risk ratios ranging from 1·12 to 2·43 considering only positive and significant associations. Recent systematic reviews have confirmed that the effect of

relative younger age is consistently observed across different settings and methodologies[12,13]. A meta-analysis yielded a risk ratio of 1.27[14], however some limitations might limit its interpretation: the electronic search was relatively narrow; it was not registered in a protocol database, such as PROSPERO; and there was high heterogeneity that remained unexplored by meta-regression.

Despite the apparent wealth of data, clinical guidelines and textbooks in the field do not mention the issue of relative younger age[15,16]. In fact, Sayal and colleagues, using the Finnish medical registers, observed that this effect has increased in recent years, instead of disappearing due to increased awareness[4]. Three possible limitations in the literature might be responsible for the lack of relevance given to the topic. First, we are not aware of any epidemiological representative studies that had actively collected the diagnosis of ADHD in children and adolescents in the community. Medical registers, for instance, rely on diagnosis made in referred youth. Therefore, the findings could reflect an effect of referral bias. Second, albeit the effect of month of birth is consistent across countries regardless of seasonality, no longitudinal study tested the causality assumption of relative immaturity by observing whether a change in the school calendar year would produce a symmetrical change in the period of risk for ADHD. Third, although most studies agree in that there is a positive and significant association, the lack of a summarized effect estimate might limit the understanding of the extent and relevance of relative younger age for the assessment and diagnosis of ADHD.

We aimed to investigate the issue of relative younger age and ADHD with a two-fold approach. In the original data phase, we analyzed the association of month of birth with actively collected ADHD symptoms and diagnosis in three independent community cohorts

in Brazil. Two of these cohorts comprise individuals born in the same city 11 years apart. During this period, a change in the educational legislation has changed the calendar cutoff date for school entry. On a cohort born during the 1990s, the oldest children were born in January 1st, while the youngest children were born in the December 31st. In a cohort born during the 2000s, the oldest children were born in April 1st, and the youngest were born in March 31st. We could then analyze whether the effect of month of birth on ADHD symptoms and diagnosis would change in accordance with the school cut-offs (supporting the relative age hypothesis) or if it would remain fixed in the original position (supporting alternative mechanisms). After, we performed a systematic review and meta-analysis to estimate a pooled relative risk of ADHD among children and adolescents who are younger than their classmates. We made three hypotheses: a) the effect will be in the same direction in the three original samples, b) the period of risk will have shifted due a modification in the calendar date cutoff for school entry in one sample, c) the meta-analysis will provide a consistent, significantly positive risk estimate.

Methods

ORIGINAL SAMPLES WITH ACTIVELY COLLECTED SYMPTOMS

Samples

Individuals included in this study were participants of three epidemiological cohorts in Brazil: the 1993 Pelotas Birth Cohort, the 2004 Pelotas Birth Cohort, and the Brazilian High Risk Study for Psychiatric disorders (HRC study). In 1993 and 2004, all children born in the city of Pelotas were enrolled in these cohorts and followed at multiple time points up to age

22 (for those born in 1993, n = 5,249) and 11 (for those born in 2004, n = 4,231) with retention rates of around 80%. The school entrance legislation was modified in Brazil in 2010, so that the school entrance cutoff birthdate, traditionally December 31st (reference for the 1993 Cohort), was changed to March 31st (reference for the 2004 Cohort). The institutional review board of the Federal University of Pelotas approved the studies. The HRC study enrolled 2,511 children and adolescents aged 6 to 14 years old in schools from Porto Alegre and São Paulo in Brazil, after a screening phase with an enriched risk design (for all participants, the cutoff reference date was December 31st). The Ethics Committee of the University of São Paulo approved the study. Written informed consent was obtained from all participants of the cohorts. Further information on the overall design of these cohorts can be found elsewhere[17-19].

Assessment of categorical ADHD diagnosis

In the 2004 Pelotas cohort, children were evaluated with the Development and Well-Being Assessment (DAWBA) to evaluate ADHD as per DSM-IV at 6 and 7 years of age, when participants were in the first and second grades. In the HRC study, we used the DAWBA to evaluate ADHD as per DSM-IV when participants were 6 to 14 years old and in the first to eighth grade. In the 1993 Pelotas cohort, we used the hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ-H)[20] parent report at 11 years of age, when participants were in the fifth grade. We used a cutoff of 8 points in the SDQ-H plus one impact point to define ADHD, according to previous studies[21]. The SDQ-H was tested against the DAWBA interview in a subsample of 280 participants[22]. The SDQ-H discriminated an ADHD diagnosis with an Area Under the Curve of 0.81 (95% CI 0.74 – 0.88) and the cutoff of at least 8 points had 85.7% sensitivity and 67.4% specificity (Table S1).

Assessment of dimensional ADHD symptoms

In the 2004 Pelotas cohort, we used the SDQ-H parent report at 6 and 7 years of age. In the HRC study, we used the SDQ-H parent report when participants were 6 to 14 years old. In the 1993 Pelotas cohort, participants were assessed with the SDQ-H parent report at age 11 years old.

Statistical analyses

We classified participants as relatively younger (born in September to December in the 1993 Cohort and HRC study, and in December to March in the 2004 Cohort) and relatively older (born in January to April in the 1993 Cohort and HRC study, and in April to June in the 2004 Cohort). We compared rates of ADHD among those categories calculating relative risks. For the dimensional analyses, we analyzed the linear effect of younger age on ADHD symptoms by performing a set of linear regressions with the SDQ-H scores as the dependent variable and day of birth as the independent variable. The offset for birthday (day 0) was defined as January 1st for the 1993 Cohort and HRC study, and as April 1st for the 2004 Cohort. To assess the specificity of the findings, we also performed the same set of regressions with the other subscores of the SDQ as dependent variables. For visualization, we plotted the relationship between birthday and ADHD scores with *lowess* smoothed means. All the analyses were conducted in R v. 3.4.4 with, packages *glm* and *ggplot2*.

SYSTEMATIC REVIEW AND META-ANALYSIS

Data sources and search strategy

This systematic review follows recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[23]. We conducted a systematic literature search in MEDLINE, Web of Science and PsycINFO electronic databases from inception through December 25th, 2018. We combined search terms using Boolean operators to derive the following search strategy: *ADHD[mesh] AND ("relative age" OR "relative immaturity" OR "birth" OR younge*).* We selected studies that investigated the effect of relative younger age in children and adolescents (age range up to 18). No restrictions were placed on the language of publication, publication date, or location of the study. Electronic searches were supplemented by hand searching the reference lists of studies selected for full-text review, and searching studies that cited the selected studies. The protocol for this systematic review and meta-analysis is available on PROSPERO (CRD42018099966).

Study selection

Two authors (A.C. and S.P.) independently reviewed the abstracts and selected articles for full-text review, and discrepancies were discussed with a third author (L.A.R.). Eligibility criteria for inclusion in the systematic review were: cohort, case-control or cross-sectional studies comparing the prevalence or incidence of ADHD among children and adolescents born in specific months of the year; data had to be original and published in peer-reviewed literature (except for the search of studies citing selected investigations); ADHD could be determined by semi-structured interviews, specific scales, clinical diagnosis, or by a proxy definition of receiving specific medication for ADHD. For inclusion in the meta-analysis, there had to be either raw data allowing calculation of relative risk, or a reported measure of

effect that could be included in the meta-analysis. Further, we included in our meta-analysis the data from the three original samples reported in this study.

Data extraction

Two authors (A.C. and S.P.) independently extracted data from eligible studies using a standardized form. We extracted author, year of publication, year of data collection, study design, definition of outcome, instrument of assessment, mean age, age range, raw data for exposure and outcome, effect estimates and their confidence intervals. Discrepancies were discussed with a third author (L.A.R.).

Bias and quality assessment

We evaluated publication bias visually with a funnel plot and statistically with the Egger's test. We evaluated the quality of the studies with the Newcastle-Ottawa Scale[24]. Two authors (A.C. and S.P.) independently rated the items of the quality scale for the included studies, and discrepancies were discussed with a third author (L.A.R.).

Statistical analysis

We performed random-effects meta-analyses to calculate overall pooled estimates of the relative risk of an ADHD diagnosis between children and adolescents who are relatively younger compared to relatively older.

We selected a four-month period (for instance, September to December compared to January to April) to set as our standard comparator because this was the most available period across included studies. When the study did not provide data for the four-month period, we used the closest time frame available. When the study did not provide raw data or relative risk, we included in our meta-analyses other estimates of effect that have similar calculation procedures, such as odds ratio (converted to relative risk), incidence ratio, or prevalence ratio. We conducted sensitivity analyses to evaluate results including only more homogeneous studies concerning design and effects. These analyses were conducted with the R statistical package version 3.4.4[25], package *metafor*[26].

Results

Relative immaturity and categorical ADHD diagnosis

We observed a nonsignificant effect of being born in the last four months of the year and receiving an ADHD diagnosis in the 1993 Cohort (RR=1.11, 95% CI .88 to 1.41, p=.410) and in the HRC study (RR=1.36, 95% CI .89 to 2.08, p=.195), and a significant effect in the same direction in the 2004 Cohort (RR=2.02, 95% CI 1.11 to 3.70, p=.028).

Relative immaturity and ADHD symptoms

We observed a linear relationship between birthday and ADHD symptoms in the 1993 Cohort (beta=.03, p=.003), in the 2004 Cohort (beta=.03, p=.045), and in the HRC study (beta=.06, p=.010), and this effect was specific for ADHD symptoms (Table 1). The linear relationship

shifted from January to December (in the 1993 Cohort and HRC) towards April to March (in the 2004 cohort) (Figure 1).

Search results

The electronic search produced 1799 records after exclusion of duplicated and reference list review. Of these, 39 full-text articles were reviewed after the screening of abstracts. Seventeen articles were excluded based on eligibility criteria. The three original studies described here were included in the quantitative synthesis. Overall, 25 studies with 30 samples were included in the meta-analysis (Figure S1, Table S2)[4-6,8-11,27-40]. The main characteristics of the included studies are outlined in Table S3.

Results of the meta-analysis

The 25 studies included a total of 8,076,570 individuals, of whom 164,049 were ADHD cases. The relative risk ranged from 0.96 to 2.39 among the 25 studies (30 samples) included. Most samples were epidemiological (24/30), considered diagnosis as an outcome (19/30), and drawn information from registers (17/30). The quality of the studies ranged from 3/9 to 9/9 in the Newcastle-Ottawa Scale, and 12 studies had maximum quality (Table S2). The pooled risk ratio was 1.34 (95% CI 1.26 to 1.43, $p < .001$) (Figure 2). Heterogeneity was high (I^2=96.7%, Tau^2=.0194, $p<.001$). There was asymmetry at funnel plot visualization (Figure S2), and the Egger's test was significant ($z = 2.239$, $p = .025$). A set of sensitivity analyses showed that results were consistent even changing several methodological choices (Table 2). Separate meta-analyses of only boys or girls showed no difference by sex (RR 1.32 vs. 1.32, Table 2). Meta-regression analyses identified that epidemiological samples (compared to

clinical samples) yielded larger estimates of relative age effects, while ascertainment of the outcome (ADHD) by report (as compared to clinical interviews) yielded smaller estimates of relative immaturity effects (Table 3). Quality of the study was inversely associated with the magnitude of the effect. The full model of the meta-regression accounted for 33.6% of heterogeneity, but there was still high residual heterogeneity. Leave-one-out analyses indicated that no individual study was responsible for substantially affecting the summary estimates or the heterogeneity (Table S4).

Differential effect by age

Six studies reported different effects according to the age of participants, all indicating higher effects of relative age in younger samples (Table S5).

Discussion

Our findings suggest that the effect of relative age is still observable when symptoms are actively collected in community samples. In the 2004 Cohort, the relative risk was higher than the estimated in the meta-analysis and in the other two samples. This was expected, however, due to the younger age of the children (6 to 7 years old), which causes the difference in their relative age to be more relevant compared to their absolute age. In the 1993 Cohort and in the HRC study, the effect was in the expected direction, albeit non-significant, probably due to a relatively small sample size and the older age of the children. For instance, in the 1993 Cohort, individuals were 11 years old, close to the age when the relative immaturity effect is expected to become non-significant (see Table S5).

Second, we observed a linear relationship between days of relative younger age and actively collected parent-reported ADHD symptoms in our three samples. This finding provides evidence that there is no clear-cut definition for defining relative younger age, but that the effect lies in a continuum. In these analyses, we could also observe that the effect was specific for ADHD, not affecting other areas of mental health measured by the SDQ.

This effect is not likely to be a result of seasonal factors, as it has been observed in both northern and southern hemispheres, where school calendars follow distinct patterns. Furthermore, by analyzing data from two longitudinal birth cohorts assessed in the same city 11 years apart, we had the unique opportunity to evaluate whether the association with between month of birth and ADHD diagnosis was due to the relative age of the child in relation to their classmates. After new educational law in Brazil changed the cutoff for school entrance from December 31st to March 31st, the direction of risk for ADHD also shifted, matching the school calendar year (Figure 1).

Finally, we summarized the evidence provided by 30 samples with a systematic review and meta-analysis. We found a relative risk of 1.34 for a child or adolescent who is relatively younger (born in the last 4 months of the school calendar year) to receive a diagnosis of ADHD when compared to a classmate who is relatively older (born in the first 4 months of the school calendar year). However, we identified a high heterogeneity among studies, and as we could not find methodological factors that sufficiently accounted for this heterogeneity, we recommend caution in using this aggregated estimate. Interestingly, we did not find any effect of sex on the relative age effect. In our meta-analysis, the relative risk was virtually the same in samples that only included boys or girls. This suggests that, although ADHD is more

common among boys, developmental differences are equally important for both sexes during the evaluation of inattention, hyperactivity and impulsivity in school aged children.

A previous quantitative review including seven studies from higher prescribing countries has found a relative risk of 1.27 of receiving ADHD medication among those who are relatively young[14]. The confidence intervals of the current study and of the previous meta-analysis overlap, indicating coherency of the findings. However, there were some methodological differences between the reviews. For instance, we decided to include a larger number of studies in the same main analyses and to explore the effect of qualitative restrictions through sensitivity analyses (see Table 2) and meta-regression (see Table 3). Therefore, we could clarify that changing major methodological decisions (for instance, type of sample, sex, quality of studies) would not yield significant changes in the estimate of the relative age effect, which ranged from a relative risk of 1.26 to 1.37.

Our findings should be read in the context of some other limitations. First, in the 1993 Cohort, we assessed categorical ADHD with a screening instrument, albeit validated against the gold-standard in a subsample. The SDQ-H does not evaluate all ADHD symptoms, neither the presence of symptoms in more than one setting. Therefore, relying in this instrument for the evaluation of a DSM-IV diagnosis is an extrapolation that might have led to non-significant effects of relative age on ADHD. Similarly, for the linear analyses, the SDQ-H has weaker psychometric properties than a broad ADHD scale including all the symptoms. Second, we relied only in parent rated symptoms in our samples and in the studies included in our meta-analysis. It could be the case that teacher rated symptoms were even more affected by relative age differences, since they are directly comparing children within the classroom. Third, due to limitations of the data available in the cohorts, we had to include

participants with different ages in each of the samples. This could have affected the comparison of effects between the samples, since the effect of relative age has a tendency to decrease towards development. Fourth, the quality of many studies was low, and our meta-analytic summary ultimately depends on the quality of the studies included in the review. Furthermore, we identified publication bias in the funnel plot and Egger's test, which can only be partially adjusted with the trim-and-fill technique. According to our analyses, the bias occurred as a tendency to suppress negative findings, and therefore overestimating the effect size. At last, we recommend caution in generalizing the results of the three Brazilian epidemiological samples to other contexts.

We conclude that the effect of relative age on ADHD diagnosis seems to be consistent and not negligible. Therefore, organization of education in modern society might impact in ADHD prevalence rates worldwide especially in younger ages. Inappropriate demands among very young children might make clinicians perceive developmental immaturity as ADHD-like symptoms. This confusion might not come without harm, with undue labelling and treatment. Society should discuss if the current educational model is the best option available, especially when establishing similar goals for children at the same grade but with up to 15% age difference. However, it is important to realize the complexity of the issue. Some studies refraining younger children to enter elementary first grade have not promoted expected positive outcomes[41]. In this context, more studies should investigate the issue of relative age and ADHD with actively collected symptoms in representative, epidemiological samples.

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Tables and figures

Table 1. Linear effects of birthday on SDQ subscores.

	Sample					
	Pelotas 1993		Pelotas 2004		HRC study	
SDQ subscore	*Effect*	*p-value*	*Effect*	*p-value*	*Effect*	*p-value*
Hyperactivity	**·03**	**·026**	**·03**	**·045**	**·06**	**·010**
Emotional	·00	·133	·01	·318	·02	·366
Peers	·02	·083	·00	·804	·02	·249
Conduct	·01	·180	·01	·298	·03	·101
Prosocial	·00	·996	·00	·907	-·01	·632

Note: the effects represent the change in the SDQ subscores for every 30 days of relative immaturity.

Table 2. Results of the meta-analysis changing methodological decisions and selecting only boys or girls

	Parameters of the meta-analysis				
Restriction or change	*Estimate [RR] (95% CI)*	*p-value*	*Heterogeneity [I^2]*	*Publication bias (Egger's test)*	*No· of samples*
Original	1·34 (1·26 – 1·43)	< ·001	96·7%	z = 2·239, p = ·025	30
Trim and fill	1·30 (1·22 – 1·38)	< ·001	97·2%	z = ·229, p = ·819	35
Only with reported/calculated RR	1·37 (1·28 – 1·46)	< ·001	89·5%	z = 1·463, p = ·144	23
Only epidemiological samples	1·35 (1·26 – 1·44)	< ·001	97·2%	z = 2·569, p = ·010	26
Only epidemiological samples (trim and fill)	1·29 (1·20 – 1·38)	< ·001	97·7%	z = ·424, p = ·671	32
Only 4-month period	1·28 (1·21 – 1·34)	< ·001	83·2%	z = 2·133, p = ·033	17
Only 4-month period (trim and fill)	1·26 (1·19 – 1·32)	< ·001	82·2%	z = ·149, p = ·881	21
Only diagnosis as an outcome	1·37 (1·29 – 1·46)	< ·001	85·1%	z = ·160, p = ·873	19
Four restrictions at once	1·31 (1·24 – 1·39)	< ·001	69·1%	z = ·100, p = ·920	7
Only boys	1·32 (1·20 – 1·41)	< ·001	87·6%	z = 1·585, p = ·113	12
Only girls	1·32 (1·18 – 1·49)	< ·001	89·5%	z = ·003, p = ·973	12
Only high quality studies (Newcastle >= 7)	1·36 (1·27 – 1·47)	< ·001	97·7%	z = 2·637, p = ·008	19
Only high quality studies (trim and fill)	1·30 (1·21 – 1·39)	< ·001	97·7%	z = ·547, p = ·585	25
Excluding the original Brazilian studies	1.35 (1.26 – 1.43)	< .001	97.1%	z =2.229, p = .026	27
Excluding the original Brazilian studies (trim and fill)	1.30 (1.22 – 1.39)	< .001	97.5%	z = .321, p = .748	31

Table 3. Meta-regression including sampling, period of risk, outcome type, outcome ascertainment, and quality of the study

	Estimate [RR]	**95% CI [RR]**	**p-value**
Intercept	1.64	1.24 to 2.18	< ·001
Sampling			
Clinical	*Reference*	-	-
Epidemiological	1.79	1.20 to 2.67	·005
Outcome			
Diagnosis	*Reference*	-	-
Medication	.92	.82 to 1.03	·162
Ascertainment			
Interview	*Reference*	-	-
Register	1.13	.94 to 1.37	·204
Report	.72	.54 to .96	·024
Newcastle castle	.90	.84 to .97	·003
Months	1.01	.96 to 1.07	·601
Test of moderators: QM (df = 6) = 12·287, p = ·060			
Amount of heterogeneity accounted for (R^2) = 33·6%			
Residual heterogeneity (I^2) = 88·5%, p < ·001			

RR Relative Risk / CI Confidence Interval

The meta-regression table provides the estimates in relative risks considering each methodological factor as a predictor. The intercept is the relative risk provided all studies in reference values (Sampling=Clinical, Outcome=Diagnosis, Ascertainment=Interview, Newcastle=3, and Months=1). To find the relative risk for a different combination of methodological factors, one can multiply the Intercept by the estimates provided.

Figure 1. Dimensional effect of days of relatively younger age on ADHD scores in the three samples.

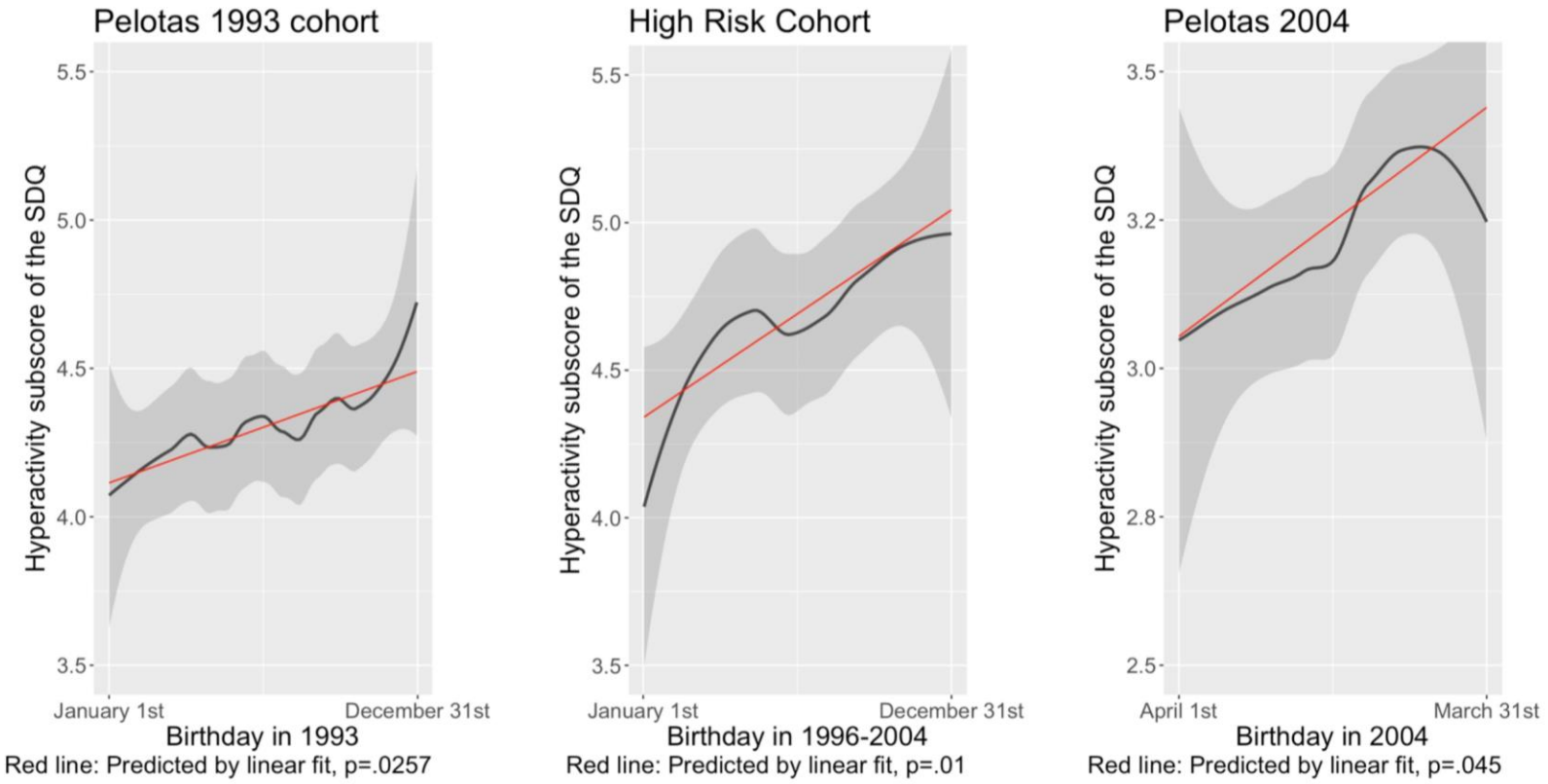
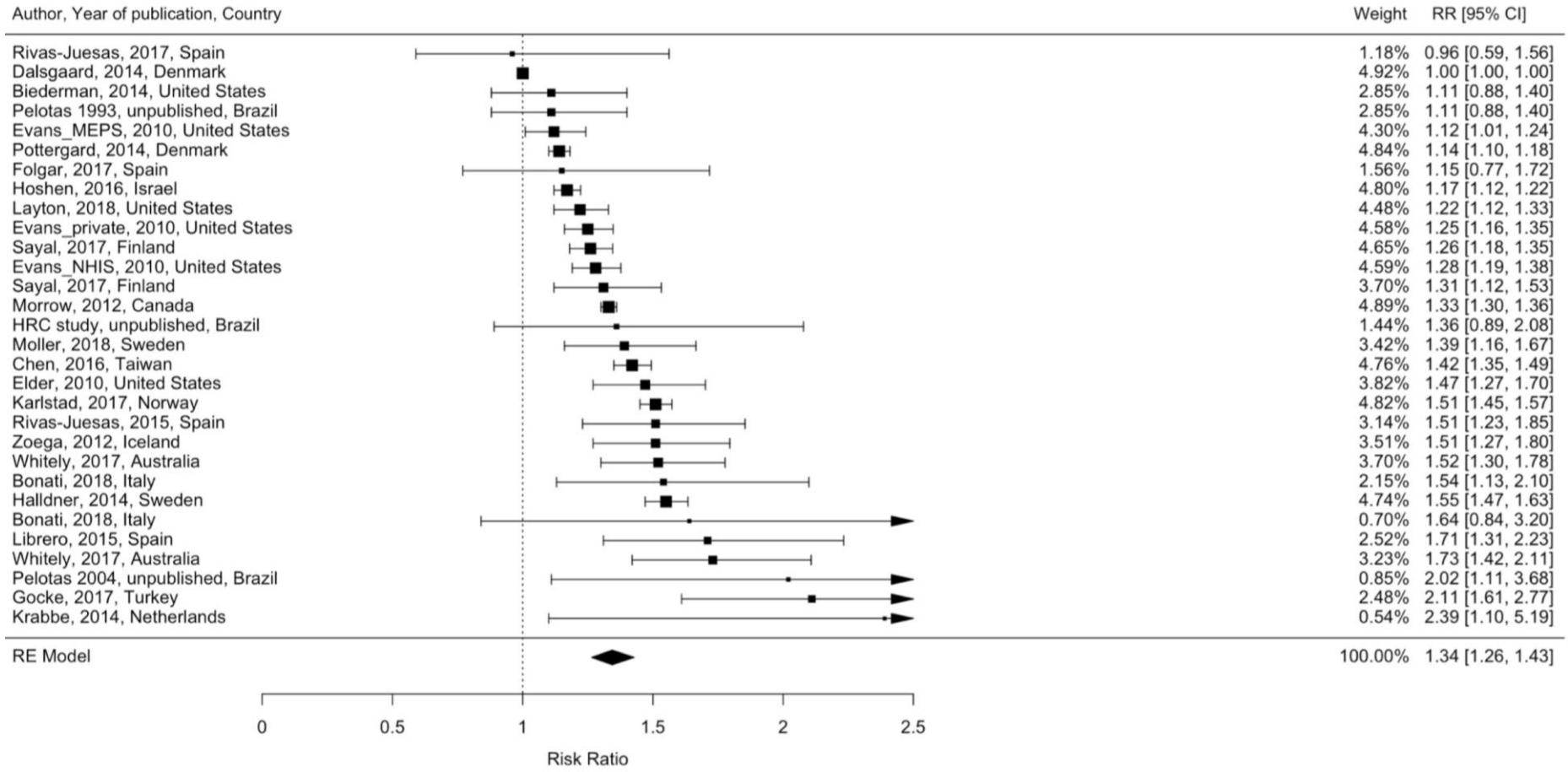


Figure 2. Forest plot – relative risk of an ADHD diagnosis among the youngest in class.



Article #5

h. *With respect to specific objective* f. *Review the literature on methodological challenges of long-term longitudinal studies on ADHD.*

Published in the Current Psychiatric Reports

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

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membership, and/or consulting for Alza, Richwood, Shire, Celgene, Novartis, Celltech, Gliatech, Cephalon, Watson, CIBA, UCB, Janssen-Cilag, McNeil, and Eli-Lilly. Other authors have no conflicts of interest to declare.

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).

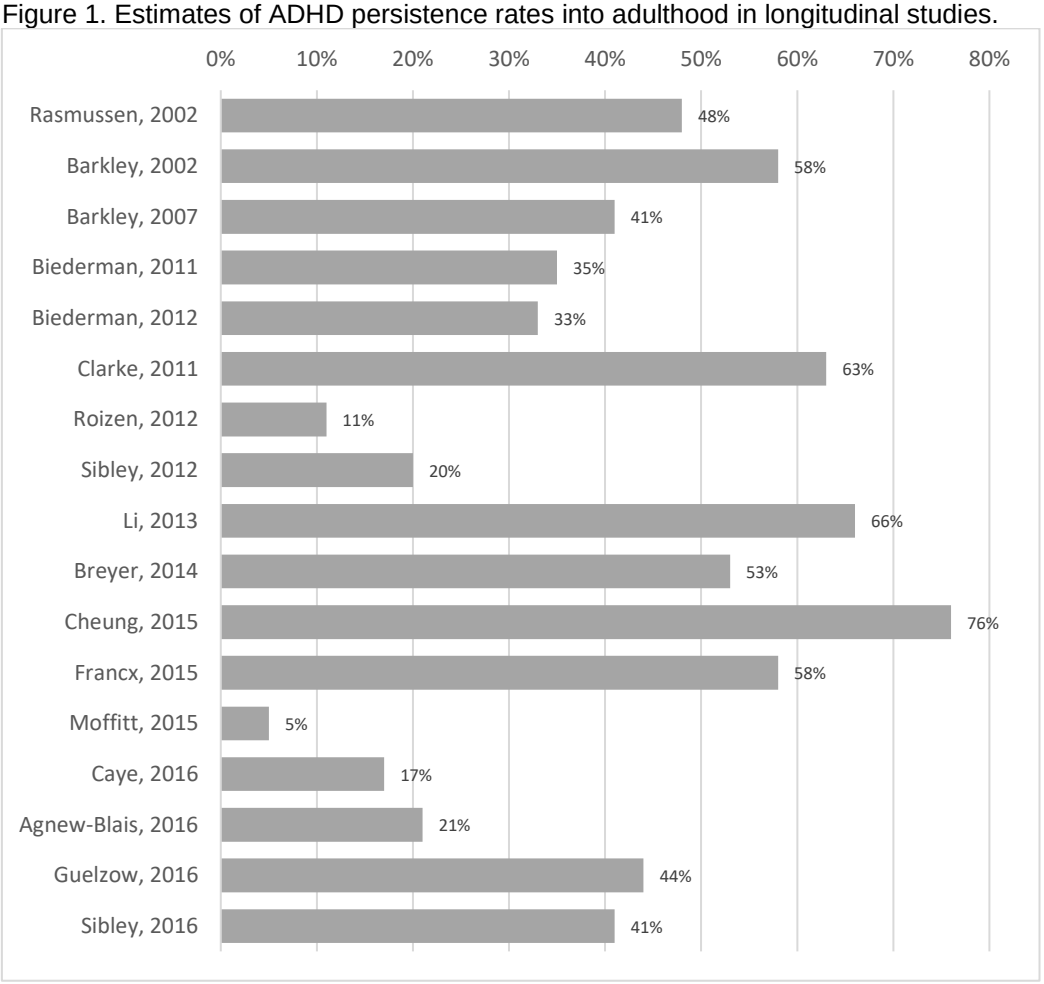
In an analysis of predictors in childhood for the adult-onset ADHD cases, the British study [11] found that higher IQ, and lower externalizing and internalizing scores differentiated the adult-onset individuals from the ADHD persistent group. One possible explanation for this would be that high intelligence 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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Article #6

With respect to the specific objective g. Review the literature on the debate around the validity of the late-onset trajectory of ADHD.

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Late-onset ADHD: understanding the evidence and building theoretical frameworks

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Conflicts of interest: Dr. Luis Augusto Rohde has been a member of the speakers' bureau/advisory board and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Medice, Novartis, and Shire in the last 3 years. He receives authorship royalties from Oxford Press and ArtMed. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. He also received travel awards from Novartis and Shire to attend the 2015 WFADHD and the 2016 AACAP meetings. Other authors have no conflict of interest to declare.

ABSTRACT

Purpose of review: The traditional definition of Attention-Deficit/Hyperactivity Disorder (ADHD), assuming onset in childhood, has been challenged by evidence from four recent birth-cohort studies that reported most adults with ADHD lacked a childhood categorical ADHD diagnosis.

Recent findings: Late-onset of symptoms was evaluated in the long-term follow-up of the Multimodal Treatment study of ADHD (MTA). In most cases, other factors were present that discounted the late onset of ADHD symptoms and excluded the diagnosis of ADHD.

Summary: We offer two theoretical frameworks for understanding the ADHD trajectory throughout the life cycle: 1) the complex phenotype model; and 2) the restricted phenotype model. We conclude that (a) late-onset (after age 12) is a valid trajectory for ADHD symptoms, (b) the percentage of these cases with onset after adolescence is yet uncertain, and (c) the percentage meeting exclusion criteria for diagnosis of ADHD is influenced by the rigor of the methodology used to obtain evidence and whether or not DSM exclusionary criteria are applied.

KEYWORDS: ADHD; Persistence; Late-onset; Course; Development;

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by an impairing and chronic pattern of symptoms with onset in childhood [1, 2]. By the traditional definition, adults with ADHD are individuals with child-onset who did not experience desistence of symptoms. In accordance with this assumption, the DSM-5 ADHD committee placed ADHD in the Neurodevelopmental disorders section, along with Autism Spectrum Disorders and Intellectual Disability. The criterion of onset of symptoms in childhood was modified from 7 to 12 years of age, but this definition of ADHD still excludes the diagnosis for patients who report late onset of symptoms in adolescence and adulthood [1].

Despite consistent evidence from clinical follow up studies that childhood ADHD persists into adulthood in approximately half of cases [3-5], epidemiological studies indicate a far smaller proportion of adult cases with this developmental pathway (i.e., childhood onset and persistent ADHD) [6, 7].

In the last two years, four reports on population-based studies suggested symptoms of ADHD emerging during or after adolescence in most cases of adult ADHD [8-11]. The literature is currently referring to this condition as *late-onset or adolescent/adult-onset ADHD*. Previously, investigators have challenged categorical thresholds for the age of onset criteria for ADHD [12-14], and others have described adult ADHD and its treatment [15, 16]. The novelty introduced by the recent studies is the possibility that the late-onset trajectory might be the rule rather than the exception. Here, we review and discuss the available evidence, and propose theoretical models to explain the phenotype of late-onset ADHD and discrepancies between epidemiological, community, and clinical samples.

FINDINGS FROM FOUR BIRTH COHORTS SUPPORTING LATE-ONSET ADHD

The Dunedin Study

This study followed a representative cohort of 1037 individuals from birth to age 38 with 95% retention [8]. DSM-III ADHD (requiring age of onset before age 7) was assessed at ages 11, 13 and 15. When participants were 38, DSM-5 ADHD was assessed without applying the age of onset criterion. Reasonable estimates of prevalence were obtained at each age, but the ADHD cases at age 11 (6% of the cohort in childhood) and age 38 (3% of the cohort in adulthood) consisted of essentially non-overlapping sets: 90% of adult cases (28 of 31) lacked a childhood history of ADHD, and only 5% of the childhood cases (3 of 61) showed persistence of ADHD.

There are some relevant criticisms of this study. The follow-up covered a very long time span, and the gap between ADHD assessments was wide (especially since adult ADHD was not anticipated and thus was not assessed at follow-up at age 20), making it hard to ascertain when ADHD symptoms first appeared. Furthermore, the source of information was from informants (parents) in childhood and from self-reports in adulthood (although informant reports were obtained and showed persistence of symptoms in childhood ADHD cases that self-report did not). Although high levels of comorbid disorders and substance abuse in adulthood were reported, it was not possible to adequately assess whether the endorsed ADHD symptoms should be attributed to these conditions.

Given the unexpected findings from the Dunedin cohort, the field was initially skeptical and recognized the need of replication [17]. Two independent birth cohorts, the E-Risk study and the 1993 Pelotas Birth-cohort study, were used to investigate whether the late-onset ADHD hypothesis would be confirmed or rejected in other samples [9, 10, 18].

The E-Risk Study

The E-Risk cohort followed 2232 twins born in the United Kingdom from birth to age 18 with 91.3% retention. DSM-IV ADHD (without the criterion of onset before age 7) was assessed at ages 5, 7, 10 and

12, and then again at age 18. Among the young adults diagnosed with ADHD, 67.5% failed to meet criteria in any of the childhood assessments. But, as in the Moffitt et al (2015) study, there was no difference between late-onset ADHD and childhood-onset ADHD in terms of impairment and rates of mental health disorders in young adulthood [9].

Similar to the Dunedin study, there were some weakness of this study. The study design and protocol did not allow for adequate control for comorbid mental disorders in adulthood. While the gap between ADHD assessments was much smaller, the last age at assessment was at age 18, limiting conclusions about the stability of the late onset ADHD or the possibility of onset in older adults.

The 1993 Pelotas Study

The 1993 Pelotas cohort followed 5249 individuals born in Brazil from birth to age 18 and 19, with 81% retention. The cohort was evaluated for ADHD with the hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ-H) calibrated for DSM-IV ADHD diagnosis using the Development and Well-Being Assessment (DAWBA) at age 11. At age 18 and 19, ADHD was assessed with a structured diagnostic instrument according to the DSM-5 criteria in clinical interviews with psychologists (without the age of onset criterion). In this sample, most (87.4%) of the adult ADHD cases lacked history of childhood ADHD. This rate was not changed when considering only individuals without current psychiatric comorbidities that could mimic ADHD symptoms, like Major Depression, Bipolar Disorder, Anxiety Disorder and Substance Abuse Disorders [10].

The major criticism to the Pelotas study is that the childhood assessment of ADHD was with a screening questionnaire. Another limitation is that the last age of assessment was in young adulthood. Furthermore, there was a change in source of information from childhood (parent-report) to young adulthood (self-report).

The ALSPAC study

The ALSPAC cohort followed 14701 children born in the United Kingdom from birth to age 17 with multiple dimensional assessments of ADHD using the SDQ-H. Data from 9757 individuals (those with at least two assessments) were evaluated with latent class analysis. The best-fit model did not include a trajectory of rising ADHD symptoms. However, in secondary analysis of two-time points, of the 460 cases with symptoms above the cutoff suggesting ADHD at age 17, 47% (n=261) had childhood onset, and 53% did not (n=244), defined by being above the symptom threshold at age 17 but below it at age 7 [11].

The most important limitation of this study is the reliance on screening instruments at all ages without a cut-off point based on internal calibration with a semi-structured instrument in the last assessment. This assessment was in late adolescence, and there was no consideration of comorbidities or substance use when making diagnoses.

Critical appraisal of the strengths and limitations of the population-based samples

These four studies taken together present a strong empirical case for the presence of ADHD-like symptoms that first emerge in adolescence or young adulthood, and that most of the adults with ADHD symptoms do not report onset in childhood. What are some strengths of the 4 studies? The samples ascertained were representative of their populations. The longitudinal design put aside the question of recall bias that hampers conclusions of retrospective case-control studies [19]. In general, assessment methods were those used in the majority of population studies in the mental health arena. In doubtful cases, like in the childhood assessment of the Brazilian study, sensitivity analyses were conducted systematically.

What are some conclusions from the 4 studies? It is clear that some individuals report late-onset, impairing ADHD symptoms. However, the interpretation of these symptoms remains unclear without comprehensive longitudinal assessments across development. It is possible that endorsed symptoms represent neurocognitive effects of many other conditions that were not considered when making adult

diagnoses, including heavy substance use, medication side effects, overlapping symptoms with disorders such as depression or anxiety, or the results of a physical illness, and head trauma among others. In addition to the age of onset criterion, the DSM-5 criteria state that the diagnosis of ADHD should not be made if the symptoms can be attributed to or better explained by these factors. Also, the impact of differences in the source of information used for diagnosis (i.e., informant-report in child-onset cases and self-report in adult-onset cases) cannot be discounted. Reliance on self-report may result in opposite biases for cases referred for treatment at different ages -- under-reporting in cases referred by others in childhood (more false negatives) and over-reporting in cases self-referred in adulthood (and more false positives) [20].

FINDINGS FROM THE MTA STUDY

An alternative design was used for the Multimodal Treatment of ADHD Study (MTA), and it provided data to address some of the limitations of the population-based cohort studies. Using a prospective long-term follow-up design, the incidence of late-onset ADHD was estimated in the group of children in the Local Normative Comparison Group (LNCG) without ADHD (N=239 of 289 recruited from classmates) followed from childhood (ages 9-12) to adulthood (ages 23-26). They underwent eight comprehensive assessments, which included psychiatric evaluations to measure ADHD symptoms and related impairments. Diagnostic procedures utilized parent-, teacher-, and self-reports of ADHD symptoms, as well as assessment for impairment, substance use, and other mental disorders [21].

The dense and comprehensive assessments of the MTA allow evaluation of context and timing of late-onset of ADHD symptoms in the potential cases of late onset ADHD. Starting with lenient criteria using symptom ratings only (to guard against false negatives), almost half of the LNCG cases were considered as potential cases. After applying the DSM-5 exclusion criteria, only 8 cases remained with late-onset ADHD (see Table 1), suggesting that 3.3% of the LNCG subjects had a late onset trajectory. But it is informative to note that 73% of the adolescents and 92% of the adults who were classified as late-onset based on symptom cutoff, impairment and pervasiveness criteria in the MTA protocol (table 1, line 3) were eventually excluded from an ADHD diagnosis because symptoms or impairment were better explained by other conditions -- or were considered late-identified rather than late-onset (i.e., the case met childhood ADHD criteria after baseline but before age 12 or the case had full threshold ADHD symptoms reported by teachers but not parents at baseline). Regarding comorbid conditions, heavy marijuana use was the most common reason for exclusion, and the presence of other psychiatry disorders was the next most common. Based on the MTA assessments, the majority of late-onset cases were adolescent-onset cases time-limited presentation indicated by desistence of symptoms prior to adulthood. In addition, the majority of adult-onset cases occurred only in conjunction with a complex psychiatric history of other disorders.

The MTA also has limitations. For example, it did not obtain comprehensive data on many other factors (e.g., physical illnesses, personality disorders, injuries, and medical treatments) that also may have contributed to the emergence of late-onset symptoms, and despite the 16-year follow-up, the final assessment of the participants was in early adulthood (i.e., ages 23-26).

UNDERSTANDING THE EVIDENCE

Four population-based cohorts comprising more than ten thousand individuals estimated that most cases with adult ADHD (53% to 90% across the studies) had an age-of-onset after childhood. Those adult-onset cases had similar patterns of impairment and negative outcomes as the childhood-onset cases. In contrast, the MTA follow-up of the LNCG group (with ADHD excluded in childhood) evaluated how methodological differences in assessment of symptoms affected estimates of persistence [22]. In the childhood-onset ADHD cases, the persistence rate in adulthood varied from 1.9% to 61.4% (depending on the source, method, and criteria used to define persistence), and because of this, the rate of adult-onset ADHD varied from 0% to 17% (depending on the diagnostic methodology applied).

An additional evaluation [21] noted the proportion of late-onset cases was concentrated in adolescence rather than in adulthood, and the manifestation of symptoms later desisted, suggesting an episodic rather than consistent profile during adolescence. Major questions exist about how to understand and integrate the findings from population-based and samples.

Estimating rates with comparable definitions

In the comprehensive assessment of the LNCG of the MTA, Sibley et al [21] used a sequential evaluation. The starting point was a broad definition of symptom presence (i.e., the "or-rule" for high symptom ratings by either parent or self-report), chosen intentionally to avoid false negatives. This resulted in a high rate of cases with *de novo* symptom presence with late- onset (n=112, 46.9%), which was expected to be implausibly high. Based on sequential application of additional criteria to exclude cases based on lack of impairment, lack of cross-situational manifestation, late onset, substance abuse, and other mental disorder, almost all late-onset cases (n=104, or 92.9%) met some exclusion criteria that overruled the symptom-based diagnosis (see Table 1).

Three population-based studies also considered the two criteria responsible for most (67.9%) of the exclusions in the MTA study (impairment and pervasiveness of symptoms – see Table 1). If the MTA method stopped at this point, the estimated prevalence of late-onset ADHD among the LNCG would be 15.1%, exceeding the rate reported based on the methods used for the population-based studies, probably because of the inclusion of both self and parent report. This comparison of the clinical MTA study and population-based studies focuses our discussion on the way and purpose of applying further criteria responsible for the remaining exclusions in the MTA: definition of late onset and symptoms due to substance abuse or other mental disorders.

Definition of late onset

The population-based samples had different approaches to consider the definition of childhood ADHD: positive DSM-III criteria at ages 9, 13 or 15 [8]; positive DSM-IV criteria at ages 5, 7, 10, or 12 [9]; above threshold score in the SDQ-H (calibrated by DSM-IV criteria) at age 7 [11] and at age 11 [10]. Any individual was deemed late-onset ADHD if full categorical criteria was met in adulthood but not in childhood. The methods for the population-based studies assumed that full threshold ADHD in childhood should be required to define ADHD as childhood-onset.

In the MTA, individuals in the LNCG with ADHD at baseline were excluded. However, in a further step, individuals that had fulfilled DSM-IV criterion A (ADHD symptoms) by at least one source using ratings on the SNAP-IV scale from any assessment before age 12 were also excluded. Thus, the MTA methods were more rigorous in including subjects as potential late-onset cases with ADHD than the population-based studies, since individuals only above the symptomatic threshold without any other ADHD criteria (pervasiveness and impairment) in childhood were excluded.

If subthreshold or situationally dependent cases in childhood are not excluded, this may add noise to the conceptual question: can ADHD really emerge in adulthood in individuals with very few or no symptoms in childhood? It is important to note that scores just above a normative cut-off in the SDQ-H was also required to define childhood-onset ADHD in secondary analyses in two of the population-based samples, reducing the numbers of late onset ADHD cases. However, these analyses retained a substantial group of individuals in the late-onset group and they continue to have marked impairment in adulthood.

Symptoms due to substance abuse and other mental health disorders

The comprehensive evaluation in the MTA allowed for assessment of timing of symptom manifestation on a case-by-case basis to determine whether late-onset ADHD preceded or was secondary to substance use and other mental health disorders. Two of the population-based samples also tried to account for comorbid conditions that commonly arise during adolescence and can mimic ADHD symptoms. Removing individuals with comorbid mental health conditions excluded many late onset cases (from one half to two

thirds in the population-based samples), which is similar to the observations in the clinical MTA sample. However, it is important to note that in the MTA, cases of late-onset ADHD were permitted to display comorbidities as long as those comorbidities were not considered the cause of the reported ADHD symptoms.

The similarities in comorbid rates suggest that the important issue is not the differences in the samples or their assessments of comorbidities, but rather it is about how to use this information -- whether to consider concurrent or previous psychiatric disorders as exclusions when determining the nature of late-onset ADHD symptoms. In a disorder like ADHD where, independently of the trajectory, the pattern of comorbidities is high [23-25], this is a difficult clinical question.

Additional Relevant Issues: Sample differences between epidemiological and clinical studies and change in information source

A recent investigation in a clinical sample from an adult clinic for ADHD showed a very low rate of adult-onset subjects (6.9%). Even though this single site study might suffer from referral bias, the pattern seems to resemble those from other ADHD clinics. Classical studies document that epidemiological and clinical investigations select different samples in Medicine in general and particularly in Psychiatry [26, 27]. For example, clinical samples of ADHD tend to present a higher proportion of ADHD with a combined presentation while epidemiological samples tend to have higher prevalence rates of a predominantly inattentive type. In addition, the profile of comorbidities might be different between these two types of studies [26]. Lopez et al found that adult-onset-cases had a higher educational level, a more frequent inattentive ADHD presentation, a less severe ADHD, but similar rates of comorbid psychiatric disorders than persistent ADHD cases from childhood to adulthood [28]. It is reasonable to speculate that in ADHD epidemiological samples, there might be an overrepresentation, compared to adult clinical samples, of ADHD cases with a predominantly inattentive presentation, less severity, lower rates of comorbidities, higher cognitive resources, and more family supportive environments in childhood. These protective factors may increase rates of late-onset cases in epidemiological samples compared to clinical samples, as demonstrated in Figure 1.

On the other hand, epidemiological samples might be more prone to a phenomenon called “the false positive paradox.” As extensively documented, the reliability of the ADHD diagnosis based on subjective information acquired by interviews or rating scales for documenting symptoms is far from perfect. If the false positive rates were very low, the differential impact of reliability would not be great when comparing findings from population-based and clinic-based studies. But if these rates are high, the impact on the population-based samples may be exaggerated, due to the large number of non-ADHD cases that would be multiplied by the false positive rate. When the false positive rate for adult assessments is higher than the prevalence, the number of false positive cases may be higher than the number of true positive cases. This issue assumes more relevance in epidemiological studies using screening instrument to assess adult ADHD, like the ALSPAC study, but tend to produce less impact in studies (like the Dunedin cohort) that used the same gold-standard diagnostic procedures as the clinical studies.

Finally, one of the most important differences in the studies’ designs concerns change of information source. Three population-based samples relied on parental report in childhood and on self-report in adulthood. Relying on different informants for ascertaining psychiatric diagnosis may generate non-overlapping groups, since agreement between informants is known to be low [29]. There are two main arguments that mitigate the effect of the change of information source in those studies.

The first argument is conceptual. The external validity of the choice of methods in the population-based studies is clear, since in the real-world scenario, clinicians will ascertain psychiatric diagnosis in adulthood in most cases with self-report only. According to this view, changing the source of information is the lesser of two evils, because relying on parent report to make the diagnosis in adulthood will impede translation to clinical practice.

The second argument is data-driven. The Dunedin and the E-Risk studies had more than just self-report of symptoms: these population-based studies showed that late-onset ADHD individuals had higher ADHD

symptoms in adulthood than control individuals according to co-informant reports (but the informant-report was also high in childhood onset cases with low self-report of symptoms in adulthood). The ALSPAC study relied on parent reports in all time points. What these analyses suggest is that the self-reported symptoms in adulthood are confirmed by other sources of information, and that there seems to be an undeniable trajectory of late-onset ADHD in some cases even when the source of information is not changed.

The MTA study dealt with the change of information source quite differently [see Sibley et al [21]]. Self and parent reports were aggregated with specific rules for each DSM criterion during adolescent and adulthood. For symptom criterion, the “or rule” was used for item level (each symptom). For impairment criterion, only parent report was used in adolescence and the “or rule”/item level (each impairment) was used in adulthood. For pervasiveness criterion, the “and rule” was used. Ratings of adult ADHD symptoms by the two sources did show large differences by source (see Swanson et al [30]) suggesting lower self- ratings than parent-ratings.

In conclusion, the data from the MTA study do not necessarily conflict with the data from the four population-based samples, but the interpretation differs. To facilitate a consensus on the interpretation of the data from these studies, we present below two theoretical models offering accounts of the data on late-onset ADHD.

THE COMPLEX PHENOTYPE OF CHRONIC DISEASES HYPOTHESIS

The current understanding of most chronic conditions in medicine is that a clinical phenotype arises out of intricate and complex interactions between biological and environmental factors [31]. For example, type 2 diabetes syndrome is clearly affected by environmental pressure, especially obesogenic factors. However, we know that obesity is not necessary nor sufficient to cause type 2 diabetes, because biological pressures, like genetic predisposition, are essential in the equation [32].

The complex phenotype model can be easily applied to ADHD (Figure 1). There is substantial evidence that inattention and hyperactivity-impulsivity symptoms behave as traits to which an arbitrary cut-off applies [33-35]. Neurobiological pressures - for example, the level of brain cortical maturation and integrity of the white matter tracts - might affect these traits [36, 37]. But environmental pressures also affect traits, for instance, the level of demand and supportiveness of the family or peers. Importantly, *none of those pressures are expected to be stable over lifetime*. How does this explain the traditional course of childhood-onset ADHD? In Figure 1, 8 examples are presented. Some individuals who are at the extreme of the trait in childhood may experience a maturation of neurodevelopment during adolescence [2] - if everything else remains stable, this could result in remission or desistence of symptoms (1A). Others could experience some level of initial normalization of the symptomatic profile due to neurobiological maturation, but later an age-related increase in environmental demands (e.g., when entering university) occur and the symptoms reemerge (1B). In a different group, behavior may not normalize at all, and this would be manifested as persistence of symptoms (1C). Individuals with moderate neurobiological pressure but environmental conditions that allow for early compensation (e.g., very supportive families) that is not present later (e.g., after moving out and accepting a demanding job), may manifest late onset of symptoms (1D). Another group may encounter environmental pressure in late adolescence that dissipates later, resulting in transient symptoms (1E). Brain injuries [38] and substance abuse [39, 40] can increase neurobiological pressure in the long-term, resulting in late onset and persistent symptoms (1F). And these factors can operate concurrently, bringing individuals from one extreme to the other, with late onset and persistent symptoms (1G) or early onset and desistent symptoms (1H).

In this application of the complex phenotype model, the evaluation is empirical and focused on manifestation of symptoms and trajectories over time. The causes (that usually are unobserved) are not assumed or used to distinguish the trajectories over time.

The model of unstable complex biological and environmental pressures not only explains the finding of late-onset ADHD, it *predicts* it, as well as every other possible ADHD trajectory. To deny the late onset of ADHD would ignore half of the possible trajectories of ADHD symptoms (see panels 1D, 1E, 1F, and 1G).

As an analogy, we could imagine how physicians in the second half of the nineteenth century, already aware of the typical type 1 diabetes syndrome, came to learn of the existence of a similar syndrome of polyuria and polydipsia that arises later in life and is preceded by other clinical conditions. Considering the complex phenotype model, type 1 diabetes would arise from a very high biological pressure, depending very little of the environmental pressure to reach a diagnostic threshold on blood glucose levels. Type 2 diabetes, on the other hand, arises much later in life due to the fact that it depends moderately of biological and environmental pressures. Likewise, diabetes is usually preceded or occurs concurrently with many comorbidities [41]. This comorbid profile does not mean that type 2 diabetes does not exist!

THE RESTRICTED PHENOTYPE HYPOTHESIS

As in the complex phenotype model, behaviors that underlie ADHD symptoms are assumed to be influenced by multiple biological and environmental factors in the restricted phenotype model. However, the restricted phenotype model places limits on these factors, accepting that some but not all are associated with ADHD (e.g., as specified by the DSM criteria). The diagnosis of ADHD is excluded when symptom manifestation is preceded by (or is concurrent with) the appearance of environmental factors (i.e., trauma, deprivation), physical disorders (i.e., hypothyroidism, dementia), injury (i.e., concussion), or side effects of medication or illicit substances (i.e., chemotherapy, marijuana, pharmacological side effects), which may plausibly elicit symptoms of inattention, impulsivity, or hyperactivity. The restricted phenotype model does not question whether the multiple trajectories of ADHD symptoms occur, but instead asks whether likely underlying causes (even though typically unobserved) of these trajectories should be invoked to exclude the diagnosis of ADHD in some individuals.

The restricted phenotype model was applied to the late onset ADHD cases in the MTA by comparing diagnosis at multiple assessments points over time when the participants are in different stages of development (childhood, adolescence, and adulthood). Figure 2 shows an initial assessment (in childhood) and a later assessment (e.g., in adolescence or adulthood). Only 4 alternative are presented: (2A) high levels in childhood and later in development (childhood-onset and persistent ADHD symptoms), (2B) low levels in childhood and high levels later (bona fide adult onset ADHD that is due to multiple biological and environmental factors and their interaction), (2C) low levels in childhood and high levels later due to other factors (adult-onset ADHD excluded due to other disorders or conditions), and (2D) high levels in childhood but not later in development (childhood-onset but desistent ADHD symptoms).

Figure 2 emphasizes that a critical clinical focus of assessment of late onset ADHD is to assign cases with the same trajectories to different groups (i.e., to 2B or 2C). This requires attributing possible reasons for increasing symptoms over time (i.e., from childhood to adolescence or adulthood) to classify late onset ADHD as a bona fide diagnosis (2B) or to exclude the diagnosis (2C).

The restricted phenotype model suggests late onset ADHD may be a separate disorder in some cases, but it does not necessarily exclude all cases with late onset of ADHD symptoms. For example, bona fide late-onset ADHD is shown in Figure 1D for cases in which the manifestation of ADHD symptoms in childhood is overcome by compensation that reduces the severity of ADHD symptoms (and thus childhood-onset is not recognized), but the symptoms emerge later in adolescence or in adulthood, when environmental demands are greater and compensation is no longer sufficient.

CONCLUSIONS

The clinical message suggested by these two alternative models of late-onset ADHD is that it may be important to compare symptoms at multiple points over time instead of just evaluating symptoms at just one point in time, and concurrently to evaluate other factors that may be the underlying cause of symptoms. The difference between the models may be merely a difference in emphasis on how to use unobservable factors (i.e., possible causes rather than just manifestation of symptoms). Thus, a major

question for the field is “Which of these factors are permissible as legitimate causes of late onset ADHD symptoms and which should be considered exclusionary”? A critical theoretical issue is the degree to which ADHD symptoms are associated with a limited number of specific possible causes (the narrow-restricted phenotype model), or whether ADHD symptoms are considered to be non-specific manifestations of an unlimited number of causes (the broad complex phenotype model).

It is important to recognize that in the literature reviewed here, late-onset of ADHD symptoms occurred in all assessed samples (2.7% in the Dunedin sample, 5.4% in the E-risk study, 6.3% in the Pelotas sample after excluding assessed comorbidities, 2.5% in the ALSPAC investigation and 3.3% in the MTA). Also, it is important to recognize that the prevalence of adult DSM ADHD (i.e., including several symptoms in childhood) ranges between 2.5 to 4.4% [42, 43]. In the studies reviewed here, the lowest estimate for late-onset ADHD (2.1% for the most restrictive definition in the MTA – see table 1, last line) represents 48% of the highest prevalence rate estimated for adult ADHD (4.4%). So, late onset ADHD does not seem to be a negligible condition.

Many questions remain about late-onset ADHD, and we end this review with a list of some of these that we believe should direct research on this important topic: (a) what defines a bona fide late-onset ADHD? (b) what is its prevalence? (c) Is there a developmental limit to onset of the symptoms (only in adolescence or also in adulthood)? (d) Are there more neurobiological and genetic similarities or differences between late onset and child-onset cases? With respect to clinical practice, the findings discussed above suggest that clinicians should not discard the possibility of an ADHD diagnosis in adults just because they were not able to track ADHD symptoms in their childhood. However, a careful assessment of pervasiveness and impairment and of any other potential causes explaining/mimicking the ADHD symptoms in adulthood is strongly recommended. In sum, a careful assessment using all DSM-5 ADHD criteria except age-of-onset is fundamental when evaluating adults. In cases where comorbidities such as general anxiety disorder, depression or cannabis use might better explain adult-onset symptoms, these conditions should be treated prior to extending a diagnosis of ADHD.

REFERENCES OF IMPORTANCE

Reference	How it adds to the literature
REFERENCES OF MAJOR IMPORTANCE	
● ● Moffitt et al (2015)	The first time that the late-onset ADHD was reported in an analysis of long-term outcome in a longitudinal (four-decade) birth cohort in New Zealand.
● ● Sibley et al (in press)	This analysis of the LNCG group of the MTA suggested that diagnosis of most cases with late-onset ADHD symptoms observed in their sample were excluded due to alternative probable causes of the symptoms.
REFERENCES OF IMPORTANCE	
● Sibley et al (2016)	This systematic review has documented that methods of adult diagnosis is a major factor in the variation of ADHD persistence estimates.
● Agnew-Blais et al (2016)	An UK longitudinal cohort study 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 study found similar results in regard to the late-onset ADHD and tested for multiple confounding factors in secondary analyses.
● Riglin et al (2016)	Another UK longitudinal population-based cohort study reporting the existence of late-onset ADHD.

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Tables and figures

Table 1: Cumulative exclusion of late-onset cases in the LNCG of the MTA

	Adolescent-Onset		Adult-Onset		Total late-onset[a]		Cumulative exclusion	Present in the cohorts?
	%	n	%	n	%	n	%	
Meets DSM-5 ADHD symptom criterion	40.2%	96	19.7%	47	46.9%	112	-	Yes
+ clinically significant impairment	13.4%	32	16.7%	40	23.8%	57	49%	Yes
+ cross-situational symptoms	9.2%	22	10.0%	24	15.1%	36	67.9%	Yes
+ late-onset[b]	5.4%	13	5.9%	14	9.6%	23	79.5%	No
+ not due to substance abuse	4.6%	11	2.9%	7	6.7%	16	85.7%	No[d]
+ not due to other mental disorder	2.5%	6	0.8%	2	3.3%	8	92.9%	No[d]
Absence of subthreshold childhood symptoms (less than 3 childhood symptoms of IN and H/I)[c]	1.3%	3	0.8%	2	2.1%	5	95.5%	No

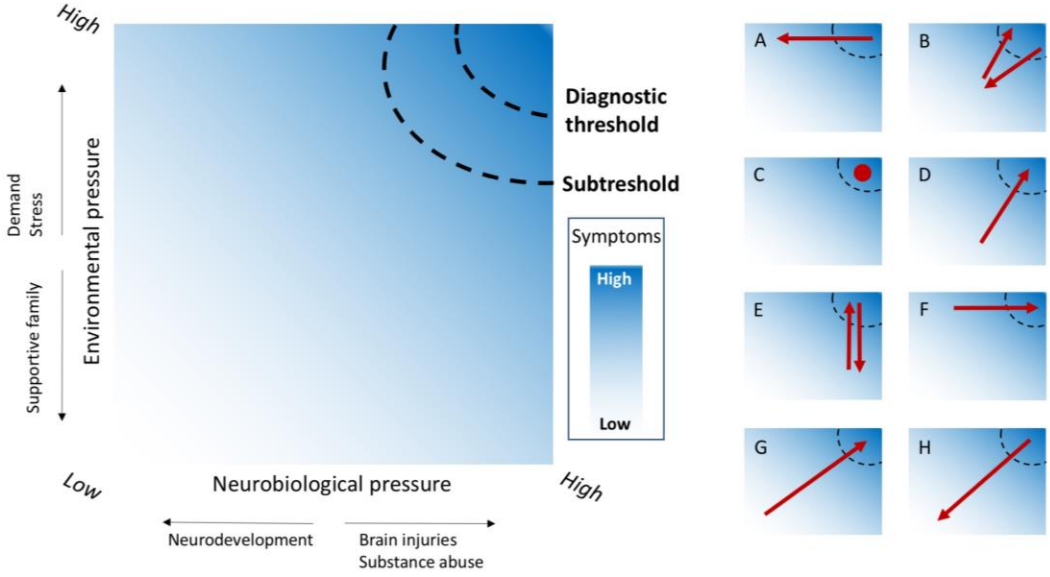
a. The total number of subjects (adolescent- and adult-onset cases) initially screened symptom-positive that are excluded by each criterion. Note that adolescent and adult-onset groups overlap because case who were excluded in adolescence were given a second chance to be evaluated for adult-onset ADHD. There were 31 cases that were evaluated as potential late-onset cases in both age periods.

b. As discussed below, the MTA applied a second criterion to define ADHD as late-onset besides lack of categorical diagnosis of DSM ADHD, which was absence of symptom criterion in SNAP rating scales before age 12 according to both parents and teachers. The cohorts did not apply this additional criterion.

c. A final methodological refinement proposed in the MTA to exclude any clinically relevant ADHD phenotypic trace in childhood for adult-onset cases.

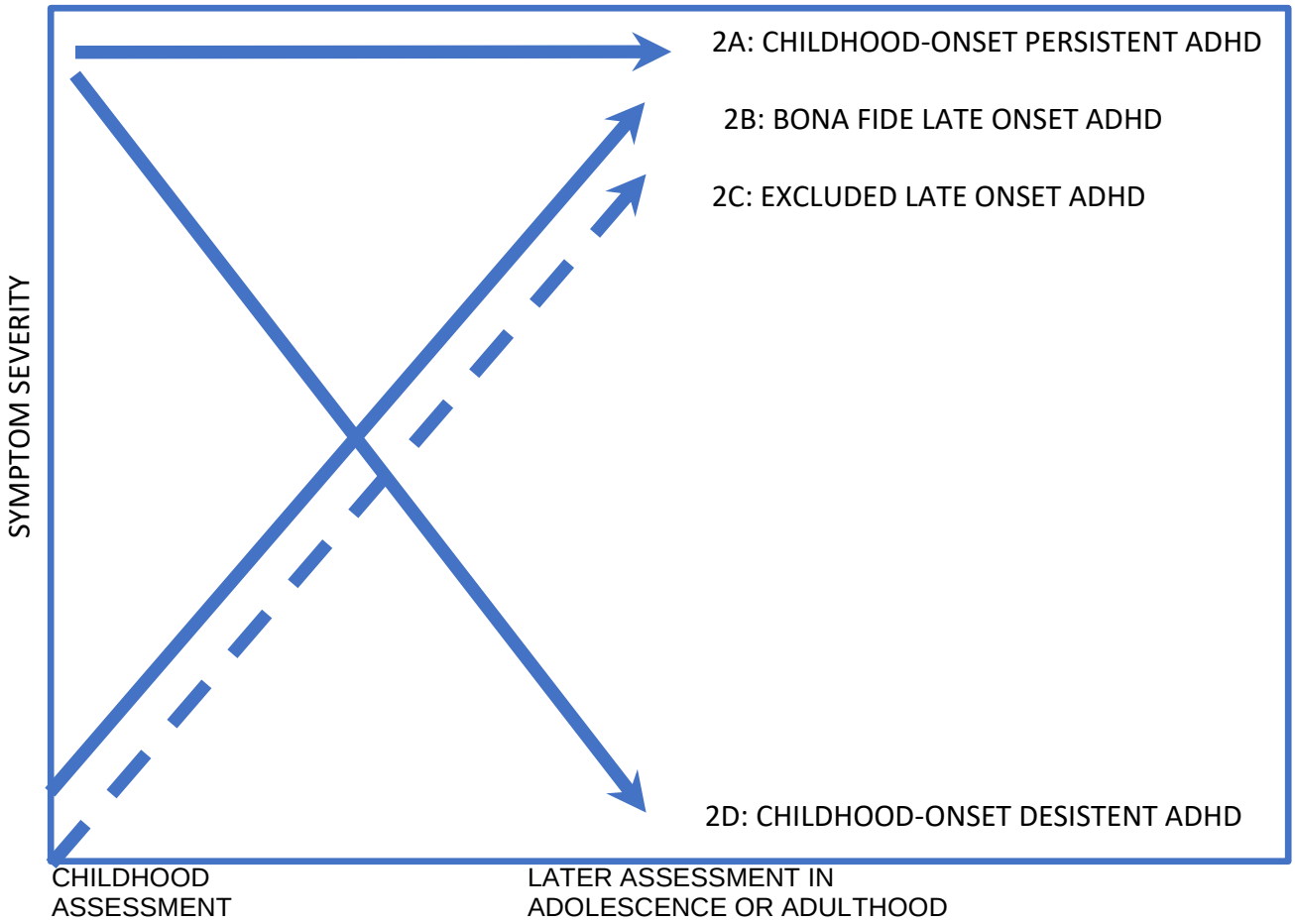
d. Although performed in some epidemiological samples, we are assuming that assessment was not as comprehensive as in the MTA study.

Figure 1. The complex phenotype of chronic diseases model applied to ADHD trajectories



A) remission or desistence of symptoms; B) initial normalization of the symptomatic profile, but later symptomatic reemergence; C) persistence of symptoms since childhood.; D) late onset of symptoms; E) transient symptoms; F) late onset and persistent symptoms; G) another late onset and persistent symptomatic trajectory; H) early onset and desistent symptoms.

Figure 2: The Restricted Phenotype Model of ADHD



Final considerations

The neurodevelopmental course of ADHD encloses challenging and complex unanswered questions. This is a field where several important paramount findings by previous investigations had slowly built a sound framework upon which new evidence can be appraised, debated, possibly improving or updating an already solid knowledge. Therefore, we both extensively reviewed the literature and produced new evidence in this thesis.

Our contributions can be summarized as follows: We provided one of the first longitudinal evidences of the existence and validity of late-onset ADHD (Article #1). We had also contributed to a clinical independent study that found results that were, to a certain extent, contradictory to ours (Appendix #1). We have then joined the principal investigators of this last study to review the entire literature so far available on late-onset ADHD and to provide possible rationales for the discrepant findings (Article #6).

In the quest for relevant predictors of ADHD persistence and an individualized perspective of risk determination, we had systematically reviewed the literature and meta-analyzed summarized effects of association between a series of predictors and the persistence of ADHD for the first time in the literature (Article #2). Furthermore, we had reviewed what are the challenges of conducting long-term longitudinal studies about ADHD, and how methodological decisions influence observed findings (Article #5). Leveraging from the knowledge of these two studies, we were able to develop a multivariable risk model to predict adult ADHD joining three large birth cohorts and one large clinical sample. This risk model was generated and independently validated within these samples, and an open-source free risk calculator for clinical use was made available on-line (Article #3).

Similarly, when we focused on clarifying the issue of relative immaturity and its effect on ADHD diagnosis, our approach was two-fold. We conducted a systematic review, meta-analysis and

meta-regression of the available literature on the effect estimates of relative immaturity on ADHD. Confirming the lack of a longitudinal population-based and actively assessed design, we analyzed data of three population-based cohorts in Brazil, providing new sound evidence on the matter. Both these studies, the original studies and the review, are included in Article #4.

How can we join the findings of this thesis into one developmental framework? First, by considering that the expression of ADHD symptoms is not a static dichotomy, but instead lies on a dynamic continuum that arises from the interplay of environmental and neurobiological pressures. These can change with time. When children enter school, their environmental demand suddenly increases, and ADHD will be expressed according to their underlying neurobiology. We demonstrated that children who are relatively immature because of their younger age in class will express more ADHD symptoms determined by their neurodevelopmental stage and their environmental demands. Moving forward in our framework, neurodevelopment occurs rapidly in adolescence and tends to complete by young adulthood. Accordingly, childhood-onset ADHD symptoms tend to reduce, but this is not true for all individuals. We investigated predictors of this failure to remit – as would be expected – and developed a tool that parses out these individuals in advance, for clinical and research purposes. Going even further, by young adulthood, again environmental pressures usually increase, and interact with otherwise hidden neurobiological factors. For instance, many young adults move away from their parents – sometimes losing positive environmental factors – and start college in high-demand, competitive academic environments. We, along with others, provided evidence that many young adults with a clinical presentation of ADHD had their age at onset after childhood, while their impairment and adverse outcomes associated with the disorder were the same as the childhood-onset cases.

We conclude this thesis by acknowledging both our small but significant contributions to the field of research of the neurodevelopmental course of ADHD, and the several open questions that are left to be answered. The validity and existence of the late-onset trajectory still needs to be further explored in independent samples with even more scrutiny than the studies had so

far provided. For instance, current studies mostly consider only two time-points in their definition of late-onset ADHD, leaving either adolescence or young adulthood uncovered by their designs[113]. An ideal approach is to use thorough repeated assessments with long-term follow-ups in large scale studies, estimating precise age-at-onset instead of categorical definitions such as “adolescent-onset” or “adult-onset”. Nevertheless, the combination of these features in one single study is yet unavailable. Another challenge is to disentangle the role of heterotypic continuity on the emergence of ADHD after childhood. Most reports identified higher rates of childhood psychopathology among individuals with late onset ADHD [15,86,91]. Sophisticated mediation and moderation analyses in samples with repeated dimensional measures could explore to what extent this psychopathology drives later onset of ADHD symptoms. The consideration of neurobiological features, for instance, with genetic and neuroimaging approaches, could further clarify the nature of this novel syndrome. Three investigations already reported lower genetic risk scores for ADHD in late onset ADHD individuals[84,87,92]. However, these polygenic risk scores were derived with traditional childhood-onset ADHD samples – therefore, these findings might mean that late onset ADHD is driven by other causal pathways, instead of a smaller biological load.

The development of more sophisticated risk models could aid research and care of ADHD, and other areas in mental health. The inclusion of other types of data could improve accuracy of the model proposed in this thesis – for instance, family history, polygenic risk scores, neuroimaging and complex neurocognitive measures. Prematurity, which is an established risk factor for ADHD[116], should also be considered in further studies. An ideal design would convey several kinds of data measured in baseline, with long-term follow-up assessments including repeated measures of thorough evaluations of the outcome – a categorical and dimensional diagnosis of ADHD. Independent replication in diverse settings remains a challenge, and should always be pursued in such efforts. A complex matrix of predictors would then require advanced methods of statistical prediction, such as deep learning methods with automated selection of prediction variables. However, the informative power of complex and sophisticated predictors, such as neuroimaging data, should be weighed against the loss of clinical usefulness in settings with

fewer resources. In previous predictive models, phenotypic data outperformed complex functional and structural neuroimaging data in predicting the diagnosis of ADHD[112].

Not only technical, but also ethical considerations should be considered when developing predictive models in Psychiatry. The first and foremost issue relates to the uncertainties that are inherent to this kind of approach. Even when our model is accurate, it often goes wrong for certain individuals. For those, there are undeniable consequences of predicting an outcome that will never occur – and all the clinical management that might come with this forecast. Likewise, underestimating someone's risk might have serious consequences, especially if any effective preventive intervention would have been available. A sensible way of reducing the harm is to provide information on risk on a continuum – for instance, an 80% risk - rather than binary, and with confidence intervals, instead of a clear-cut number. Either way, these uncertainties should be thoroughly discussed with the patient by the attending physician, who should be aware of the limitations of the method. Another issue relates to the utility of prognosis when no specific intervention is available. Taking the case of our own prognostic model for ADHD, no preventive intervention ever tested has been effective so far for reducing the risk of future ADHD. Therefore, taking into consideration the potential harms of informing the prognosis of any individual, will the actual benefits surpass these harms? These questions could be further clarified on randomized clinical trials where preventive interventions are tested on at-risk individuals.

The identification of a consistent effect of relative immaturity should be followed by evaluations of the functional outcomes of the younger children along development. Importantly, not only data, but also a deeper theoretical discussion, is lacking in the case of relative immaturity and ADHD. Conceptual questions remain open: Who are these children that present an ADHD phenotype when facing educational demands higher than they can handle, real ADHD or ADHD phenocopies? Are the ADHD symptoms causally related to their relative immaturity or associated to other causes associated to the immaturity and not yet identified? Should they be considered valid cases of ADHD, and therefore referred and treated? Or should

their difficulties be addressed on their own school environment? These questions actually cross the field of mental health care through the boundaries of the organization of the educational system. If it is the case that these children and their parents are actually reporting impairing symptoms due to the insensible way the educational demands are tailored in the first years of schooling, it might be the case that educational reforms are needed to properly address this issue. Nevertheless, just delaying school entry might not be sufficient or recommendable. An observational study found no academic benefits for children with ADHD whose entry was deliberately delayed when they were followed up years later[117]. This study was, however, biased by the higher likelihood of the severe cases to be red-shirted compared to more mild ADHD cases. The failure to neutralize the issue of relative immaturity with common sense interventions only reinforces the need for more research that is informed by the data from the mental health and educational fields. Furthermore, the issue of relative immaturity seems to transcend the academic environment. Researchers have found that birth month was unevenly distributed in high performance environments such as national sports competitions and among leading politicians: those relative older were found to be overrepresented in such selected populations[118-120]. In this sense, more research is needed to more comprehensively understand the scope of the phenomenon and how should society deal with it.

Appendix

In the following pages, we present the remaining publications that occurred during the doctorate of the Ph.D candidate, but that are either not directly related to the topic of the thesis, or that were not leaded by the Ph.D candidate.

Appendix #1

Published in the JAMA Psychiatry.

ADHD is not only a child-onset neurodevelopmental disorder

We thank Dr. Solanto for her interest in our paper and for providing some thoughtful ideas on how to understand these intriguing similar findings from three population samples based in different continents that challenge the notion of attention-deficit/hyperactivity disorder (ADHD) as only a child-onset neurodevelopmental disorder.[1,2,3] Dr. Solanto suggests that our study might have missed a substantial proportion of cases of ADHD predominantly inattentive type (ADHD-PI) in childhood, consequently decreasing the rate of adult ADHD with roots in childhood. She based this hypothesis on the idea that we had collected data on ADHD symptoms in childhood before DSM-IV criteria.

In fact, the 1993 Pelotas Birth Cohort collected data on childhood ADHD in 2004, a decade after DSM-IV was launched. However, as mentioned in the paper, we assessed childhood ADHD with a screening instrument that emphasizes hyperactive-impulsive symptoms. Considering the potential lower performance of the instrument for ADHD-PI subtype, Dr. Solanto`s hypothesis makes a lot of sense and warrants proper testing.

In 2004, a subsample of 288 participants at age 11 was also assessed with the Development and Well-Being Assessment (DAWBA), a semi-structured interview that generates DSM-IV diagnoses – including ADHD-PI. In this subsample, 24% of the ADHD cases were of ADHD-PI, 40% of which were not detected by the screening instrument. Therefore, we can conclude that 10% (40% of 24%) of the childhood ADHD cases were not included in the childhood ADHD group.

Extrapolating for the entire sample at 11 years of age, the scenario suggests that the 393 cases in childhood represent 90% of the real ADHD cases and the ADHD-PI that were not diagnosed by the instrument would count up 44 new cases. It is important to note that this mathematical reasoning addresses only the issue related to ADHD-PI. It does not take in to account the performance of the screening for other subtypes of ADHD.

Although the ADHD combined type seems to be the most persistent subtype,[4] let us assume conservatively that all these ADHD-PI cases in childhood would continue to present ADHD in young adulthood. This assumption would increase the proportion of young adults with ADHD with childhood history of ADHD symptoms from 13% (reported in the manuscript) to 21%.

Thus, we cannot throw the baby out with the bath water! We were also surprised with our findings and explored our data from diverse angles to assess potential flaws. Others did the same.[5] The main message continues to be that the great majority of young adults with the ADHD phenotype do not have a childhood history of significant ADHD symptoms.

Finally, we are in complete agreement with Dr. Solanto's proposal that the translation of data from population-based to clinical studies is challenging and that more studies are needed to understand the reasons for this surprising rate of adult-onset ADHD cases in population samples. Indeed, a group of researchers interested in this controversial issue has begun to work on numerous data-driven hypotheses.[6]

Word-count: 490

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Conflicts of interest: Dr. Rohde reports receiving honoraria for serving on the speakers' bureau/advisory board, and/or acting as a consultant for Eli-Lilly, Janssen-Cilag, Novartis, and Shire in the last 3 years; receiving authorship royalties from Oxford Press and ArtMed; and receiving travel awards for participating in the 2014 American Psychiatric Association and 2015 World Federation of ADHD annual meetings from Shire. The ADHD and juvenile bipolar disorder outpatient programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. The other authors report no further disclosures of interest.
Data access and analysis: Arthur Caye states that he had full access to the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
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Appendix #2

Published in the American Journal of Psychiatry.

Late-Onset ADHD Reconsidered With Comprehensive Repeated Assessments Between Ages 10 and 25

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Clinical trials number: NCT00000388, Multimodal Treatment Study of Children with Attention Deficit and Hyperactivity Disorder (MTA) (https://clinicaltrials.gov/ct2/show/NCT00000388).

Attention Deficit Hyperactivity Disorder, Diagnosis And Classification

Objective: Adolescents and young adults without childhood attention deficit hyperactivity disorder (ADHD) often present to clinics seeking stimulant medication for late-onset ADHD symptoms. Recent birth-cohort studies support the notion of late-onset ADHD, but these investigations are limited by relying on screening instruments to assess ADHD, not considering alternative causes of symptoms, or failing to obtain complete psychiatric histories. The authors

address these limitations by examining psychiatric assessments administered longitudinally to the local normative comparison group of the Multimodal Treatment Study of ADHD.

Method: Individuals without childhood ADHD (N=239) were administered eight assessments from comparison baseline (mean age=9.89 years) to young adulthood (mean age=24.40 years). Diagnostic procedures utilized parent, teacher, and self-reports of ADHD symptoms, impairment, substance use, and other mental disorders, with consideration of symptom context and timing.

Results: Approximately 95% of individuals who initially screened positive on symptom checklists were excluded from late-onset ADHD diagnosis. Among individuals with impairing late-onset ADHD symptoms, the most common reason for diagnostic exclusion was symptoms or impairment occurring exclusively in the context of heavy substance use. Most late-onset cases displayed onset in adolescence and an adolescence-limited presentation. There was no evidence for adult-onset ADHD independent of a complex psychiatric history.

Conclusions: Individuals seeking treatment for late-onset ADHD may be valid cases; however, more commonly, symptoms represent nonimpairing cognitive fluctuations, a comorbid disorder, or the cognitive effects of substance use. False positive late-onset ADHD cases are common without careful assessment. Clinicians should carefully assess impairment, psychiatric history, and substance use before treating potential late-onset cases.

In recent years, an influx of adolescents and young adults without documented childhood attention deficit hyperactivity disorder (ADHD) have presented to clinics with complaints of inattention and/or hyperactivity/impulsivity symptoms, often inquiring about stimulant medication (1–3). It remains unclear whether this trend is driven by typically developing individuals seeking stimulant medication for cognitive enhancement or by individuals with late-onset ADHD that warrants medical treatment. Recent birth cohort studies support the phenomenon of late-onset ADHD, reporting a 2.5%□10.7% prevalence for a form of ADHD that first emerges in adolescence or adulthood (4–7). These studies claim that most adult ADHD cases (67.5%□90.0%) do not involve the experience of symptom onset in childhood. This claim is contrary to decades of research characterizing ADHD as a chronic neurodevelopmental disorder with symptoms that appear before age 12 (8–11). The authors speculate that late-onset ADHD may appear spontaneously, but critics suggest that these cases may also represent individuals with undetected childhood symptoms (i.e., late-identified rather than late-onset) (12–14).

Critics also suggest that late-onset ADHD prevalence may be inflated by methodological artifacts, such as reliance on ADHD screening instruments, inability to detect symptoms that emerged in long gaps between assessments, a false-positive paradox, and failure to consider other mental disorders, health problems, or substance abuse as the source of symptoms (12–14). If many late-onset cases are false positives, this may misinform the field's understanding of ADHD as a chronic disorder and overstate its prevalence. On the other hand, true late-onset ADHD may partially explain the uptick in adolescents and young adults seeking first-time treatment for newly reported difficulties (4–7).

The present study investigates late-onset ADHD in the local normative comparison group of the Multimodal Treatment Study of ADHD, which was designed to carefully assess ADHD symptoms over time (15, 16). For 14 years from childhood to adulthood, comparison participants underwent comprehensive psychiatric evaluations with multi-informant assessment of ADHD symptoms and impairments (17, 18). Due to the frequency (eight time points) and

comprehensiveness of these assessments, ADHD symptom onset, other mental disorders, impairments, and substance use can be isolated temporally and considered when determining the history and nature of potential late-onset cases. Through careful review of multi-informant, longitudinal psychiatric data using a stepped diagnostic procedure that pinpoints symptom origins, we aimed to 1) understand what proportion of individuals with reported late-onset ADHD symptoms represent true cases of the disorder and 2) provide detailed clinical profiles for identified late-onset ADHD cases. Our procedure complements the epidemiological population studies by exploring the nature of late-onset ADHD after addressing previously noted methodological confounds and illustrating how late-onset ADHD might emerge over time (12–14).

Method

The Multimodal Treatment Study of ADHD compared effects of 14 months of pharmacological and psychosocial treatments for children (7.0–9.9 years old) with ADHD, combined type (15). Two years after baseline, 289 classmates were recruited for the local normative comparison group. The Multimodal Treatment Study of ADHD continued with prospective follow-up until 16 years after baseline (15–18). Informed consent was obtained in childhood and adulthood.

Participants

We identified a comparison group subsample (N=239) (Table 1) who did not meet diagnostic criteria for ADHD during childhood baseline assessment and who had at least one assessment in adolescence (ages 12–17) and adulthood (aged 18 years or older). Of the 289 originally recruited comparison participants, we excluded 31 individuals with a baseline Diagnostic Interview Schedule for Children diagnosis of ADHD (17–19) and 19 participants with insufficient follow-up data. This subsample (N=239) was recruited between 8.19 and 13.85 years of age (mean=9.89 years [SD=1.22]), and the average age at the final adult assessment was 24.40 years (SD=1.36).

Procedures

Comparison group recruitment was designed to reflect the local population from which the ADHD sample was drawn. Classes in the schools of the ADHD participants were randomly selected. After obtaining consent from more than 50% of the classmates in the selected classroom, individuals were selected randomly and group-matched for sex. ADHD diagnosis was neither inclusionary nor exclusionary for the comparison group. Study assessments were administered to comparison participants upon recruitment (comparison baseline; 2 years after ADHD baseline) and at 3, 6, 8, 10, 12, 14, and 16 years after initial baseline by Bachelor's-level staff who were trained to be objective.

Measures

ADHD symptoms.

Symptoms in childhood and adolescence were measured using the SNAP [Swanson, Nolan and Pelham] Rating Scale completed by parents, teachers, and adolescents (20, 21). Symptoms in adulthood were measured using the Conners' Adult ADHD Rating Scale completed by participants and parents (22). The SNAP and Conners' scales both list DSM-IV-TR ADHD symptoms. Respondents indicated the extent to which participants displayed each symptom on a scale from 0 "not at all" to 3 "very much." Scores of 2 and 3 indicated symptom presence, as is standard practice when using these scales to detect clinically meaningful ADHD symptoms (23).

Impairment.

In adolescence, impairment was measured using the parent version of the Columbia Impairment Scale (24). Because the Columbia Impairment Scale assesses impairment across multiple domains, including several that are unrelated to ADHD (e.g., feeling nervous/afraid), we examined impairment scores for four central domains of ADHD-related impairment: "getting along with kids own age," "schoolwork," "behavior at home," and "behavior at school." The scale utilizes a 0–4 severity range, and a score □3 in at least one of the four domains was considered sufficient to meet the impairment threshold (25). In adulthood, parent- and self-versions of the Impairment Rating Scale were used to measure impairment globally and in 11 domains of functioning (26). Response options ranged from 0 ("no problem") to 6 ("extreme problem"). The Impairment Rating Scale is a measure of general impairment and has strong psychometric properties for identifying ADHD-related impairment. An empirically validated cutoff score >3 on any item was used to define clinically significant impairment (26).

Substance use.

Heavy substance use was measured using the Diagnostic Interview Schedule for Children and Substance Use Questionnaire (19, 27, 28). Substance use disorders reported on the Diagnostic Interview Schedule for Children by either the parent or participant were considered when determining late-onset ADHD. Self-reported marijuana or other drug use on the Substance Use Questionnaire more than twice per week was classified as heavy substance use.

Mental disorders.

On the Diagnostic Interview Schedule for Children (19), parent- or self-report that indicated the presence of a mental disorder that better accounted for ADHD symptoms was exclusionary for a late-onset ADHD diagnosis. All disorders assessed using the Diagnostic Interview Schedule for Children were considered (see the data supplement accompanying the online version of this article). Eight experienced, licensed clinicians (three psychiatrists, five clinical psychologists) reviewed onset and chronicity of all mental symptoms, and each voted whether a case should be excluded based on ADHD symptoms or impairment being attributable to another disorder (e.g., effects of anxiety symptoms on concentration). A case was excluded if agreed upon by a majority. Most decisions were unanimous (see the online data supplement).

Analytic Plan

There is a considerable risk for both false negative and false positive ADHD diagnoses in adolescents and adults (29). Regarding false negatives, there is established underreporting of ADHD symptoms in non-self-referred children, adolescents, and adults, concern that informants do not fully observe the functioning of adolescents and adults, and evidence that wording of some DSM ADHD symptoms may not be developmentally relevant for adolescents and adults (21, 29–32). Regarding false positives, normative variations in attention can be mistaken for ADHD symptoms, and ADHD symptoms often overlap with features of other disorders (33). To optimize sensitivity and specificity, our strategy to assess adolescent- and adult-onset ADHD took the stepped approach outlined by Sibley et al. (34), which first casts an intentionally wide net for ADHD symptoms to protect against false negatives (using a version of an "or rule" that allows all reported symptoms to be considered). The second step protects against false positives by carefully assessing and requiring meaningful impairment, establishing symptoms across settings, and ruling out substance abuse or other mental disorders as the source of ADHD-like symptoms.

Symptom criteria.

At each assessment, ratings on the SNAP (parent, teacher, and adolescent) or Conners' (parent and adult) scale were combined at the item-level using an "or rule," such that if a symptom was endorsed by any rater, it was deemed present. Symptom count was determined separately for inattention and hyperactivity/impulsivity. After calculating combined symptom count, DSM-5 symptom thresholds were applied considering current age (six symptoms for participants ages 12–16; five symptoms for participants aged 17 and over) for either inattention or hyperactivity/impulsivity (35).

Impairment.

Next, parent- and self-ratings from the Impairment Rating Scale were combined at the item level using an "or" rule to designate clinically significant impairment. If a participant who met symptom threshold for ADHD also had clinically significant impairment according to the parent Columbia Impairment Scale (adolescents) or combined Impairment Rating Scale (adults), he or she was retained as a potential case of late-onset ADHD.

Onset.

We examined SNAP symptom data at all assessments for those cases with symptoms and impairment in adolescence (ages 12–17) or adulthood (aged 18 or older). If a case subject was younger than 12 years old when symptom criteria for ADHD were first met, the individual was not considered to be late-onset.

Substance use.

All retained cases were examined to determine whether heavy substance use was a probable source of ADHD symptoms. If ADHD symptoms occurred exclusively in the context of heavy substance use, we designated substance use to be the source of ADHD symptoms.

Other mental disorders.

Next, retained cases were examined to determine whether ADHD symptoms or impairments were better explained by another mental disorder. Cases with comorbidities were retained as potential cases of late-onset ADHD if there was low likelihood that the comorbid disorder could account for ADHD symptoms or impairments.

Cross-situational symptoms.

DSM-5 ADHD diagnosis requires several symptoms to be present in two or more settings (35). Therefore, cross-situational symptoms were required at the time DSM-5 symptom thresholds were met. Cross-situational symptoms were defined as 1) at least two symptoms reported, each by the parent and teacher, or 2) at least two symptoms endorsed, each by the case subject (self-report) and another informant. Because symptoms endorsed on self-reports might occur in the same setting as parent or teacher reports, we consulted interview questions about symptom setting to ensure self-reported symptoms represented a second context.

Onset and chronicity.

Among case subjects who met criteria for late-onset ADHD, we calculated the average age at onset and examined chronicity by plotting ADHD symptoms by rater at each assessment point. To consider whether included case subjects were late-onset compared with late-identified, we compared childhood ADHD symptom severity for included cases to sample (N=239) means at baseline in childhood (see Table 1).

Results

Adolescent-Onset ADHD

An outline of the multistep assessment process and display of the proportion of case subjects included in each step are provided in Table 2.

Symptom criteria.

Of the 239 comparison case subjects without ADHD at baseline, 96 (40.2%) met DSM-5 symptom threshold for ADHD based on combined parent, teacher, and self-reports using an item level "or rule" during at least one adolescent follow-up assessment. (If a stricter "or rule" was applied requiring a single rater to endorse symptoms above the DSM-5 threshold, 93 adolescents met DSM-5 ADHD symptom count.)

Impairment.

Of the 96 case subjects who met symptom criteria for ADHD in adolescence, 32 (33.3%) experienced clinically significant impairment at the time they met the DSM-5 symptom count. In total, 13.4% of the 239 comparison case subjects without ADHD at baseline met both symptom and impairment criteria for ADHD at an adolescent follow-up assessment.

Adolescent-onset.

Among these 32 cases, 11 were under age 12 when they first met DSM ADHD symptom count according to at least one source and were considered childhood-onset cases. Thus, only 21 case subjects actually had onset during adolescence.

Ruling out substance use.

Among the 21 case subjects who showed adolescent-onset ADHD symptoms and impairment, three had a marijuana use disorder that better accounted for the ADHD symptoms. In total, 18 cases of adolescent-onset ADHD with significant impairment were not attributable to heavy substance use.

Ruling out other disorders.

Of these 18 case subjects, nine had a history of pre-existing or concurrent mental disorders and were reviewed by the clinical panel. The panel voted to exclude five based on evidence that symptoms better reflected another mental disorder (see the online data supplement). Thus, 13 case subjects appeared to have onset of elevated ADHD symptoms and impairment in adolescence that was not attributable to other mental disorders.

Cross-situational symptoms.

Of the 13 case subjects who had onset of elevated ADHD symptoms and impairment in adolescence, six had symptoms that were only reported by a teacher. One had symptoms that were reported by the teacher and the participant (self-report), but self-reported symptoms occurred only in the classroom. Thus, six case subjects (2.5% of the comparison subjects without ADHD at baseline) appeared to have an onset of elevated ADHD symptoms and impairment in adolescence that were present in more than one setting (see Table 2).

Onset and chronicity.

The average age at onset among the six adolescent-onset cases of ADHD was 14.22 years (SD=1.50; range: 12.09–16.08). The chronicity of ADHD across assessment points for all adolescent-onset ADHD cases is shown in Figures 1 and 2. Four of these six met symptom criteria only during the teenage years. These four remitting case subjects did not receive any medication or behavioral treatments for ADHD during the follow-up period. Two had symptoms

that persisted into their 20s. Five of the six adolescent-onset case subjects (83.3%) had childhood ADHD symptoms that exceeded sample baseline means (see Table 1 and Figures 1 and 2). The average number of childhood symptoms among the six included case subjects was 2.5 for inattention (range=0–5; SD=2.26; Cohen's d=0.31) and 1.67 for hyperactivity/impulsivity (range=0–3; SD=1.21; Cohen's d=0.33).

Adult-Onset ADHD

Symptom criteria.

Of 239 comparison case subjects without ADHD at baseline, 19.7% (N=47) met DSM-5 symptom criteria for ADHD during at least one adult assessment based on combined parent and self-report using an item-level "or rule." (If a stricter "or rule" was applied requiring a single rater to endorse symptoms above the DSM-5 threshold, 43 adults met DSM-5 ADHD symptom criteria.)

Impairment.

Among 47 case subjects who met symptom criteria, 40 (85.1%) experienced clinically significant impairment. In total, 16.7% of the 239 comparison cases without ADHD at baseline met both symptom and impairment criteria for ADHD during at least one adult assessment.

Adult onset.

Of the 40 case subjects with both ADHD symptoms and impairment in adulthood, 12 showed symptom onset during childhood, 18 during adolescence, and 10 during adulthood. Four were previously deemed adolescent-onset cases. Thus, 24 of 239 case subjects first met impairment criteria for ADHD in adulthood, although 14 had initial symptom onset in adolescence and 10 had initial symptom onset in adulthood.

Ruling out substance use.

Of the 24 case subjects meeting symptom and impairment criteria, 14 had impairing symptoms exclusively in the context of heavy substance use (see the online data supplement). In total, 10 adult-onset ADHD cases were not attributable to heavy substance use.

Ruling out other mental disorders.

Of the 10 remaining case subjects, five were excluded because symptoms or impairment were attributable to another mental health disorder. Two did not possess Diagnostic Interview Schedule for Children data for adulthood, and these cases were deemed inconclusive. Thus, three case subjects appeared to have onset of elevated ADHD symptoms and impairment in adolescence that was not attributable to other mental disorders. One of the included adult case subjects was excluded in adolescence due to anxiety and mania but included in adulthood because comorbid disorders had remitted when ADHD symptoms returned (see Figure 3).

Cross-situational symptoms.

One of the three remaining adult-onset ADHD case subjects possessed symptoms in only one setting. Thus, of 239 comparison case subjects without ADHD at baseline, only two (0.8%) showed evidence of adult-onset ADHD (see Table 2).

Onset and chronicity.

The adult-onset case subjects reported onset at ages 21.05 and 27.45, respectively. Both met criteria for ADHD at only one adult assessment. One subject's childhood symptoms (inattention,

N=0; hyperactivity/impulsivity, N=1) were below the baseline sample average. The other was first assessed at age 12, reporting one inattention symptom and two hyperactivity/impulsivity symptoms at that time (see Figure 3).

Characteristics of case subjects with late-onset ADHD symptoms and impairment who were excluded from diagnosis are summarized in the online data supplement.

Discussion

The local normative comparison group of the Multimodal Treatment Study of ADHD provided a unique opportunity to study detailed fluctuations in ADHD symptoms over time in adolescents and young adults without a childhood history of ADHD. After using a stepped diagnostic procedure that carefully considered multi-informant data, longitudinal symptom patterns from childhood to adulthood, impairment, co-occurring mental disorders, and substance use, approximately 95% of case subjects who initially screened positive for late-onset ADHD were excluded from diagnosis (Table 2). These data indicate that when assessing adolescents and young adults for first-time ADHD diagnoses, clinicians should obtain a thorough psychiatric history and assessment of current functioning. Furthermore, 53% of adolescents and 83% of adults who met all symptom, impairment, and late-onset criteria for ADHD were excluded because symptoms or impairment were better explained by heavy substance use or another mental disorder (Table 2) (also see the online data supplement). Therefore, previously reported late-onset ADHD prevalence rates (2.5%–10.7%) may be overestimated due to limited ability to consult multi-informant data, track symptoms in extended gaps between assessment points, and review detailed patterns of substance use and comorbidity over time when determining diagnosis (4–7).

Six adolescent-onset ADHD case subjects appeared in the comparison group. One form of adolescent-onset ADHD (N=4) was adolescence-limited (Figure 1) and characterized by above-average childhood symptoms, borderline to average intelligence, and symptom remission by age 19. In all four of these cases, the preponderance of symptoms was reported by teachers, although corroborated by parents and the adolescents. One explanation for this pattern is developmental misfit that mimics or facilitates inattention symptoms. Mounting environmental demands in adolescence may temporarily exacerbate above-average but subthreshold childhood ADHD symptoms (Figure 1) or create cognitive overload for adolescents with slower developing prefrontal regions (36, 37). In absence of mature executive functions, some adolescents may also display deficient self-control in socially or emotionally salient contexts, leading to adolescence-limited behavior problems that may be perceived as hyperactive/impulsive symptoms by raters (38). Further work is needed to better understand this adolescence-limited presentation and the influence of cognitive development on ADHD-like symptoms in adolescents without childhood ADHD.

A second adolescent-onset ADHD presentation was characterized by above-average childhood ADHD symptoms and superior intellect (Figure 2). Two male subjects with superior IQs exhibited a persistent form of late-onset ADHD with slowly escalating symptoms from childhood through young adulthood. This profile echoes previous findings that childhood ADHD symptoms may be masked in individuals with cognitive strengths, delaying initial ADHD diagnosis (1). Since symptoms were likely present but mitigated in childhood, these individuals might better be characterized as late-identified, rather than late-onset, ADHD cases (39).

The Multimodal Treatment Study of ADHD comparison group did not support adult-onset ADHD independent of a complex psychiatric history. The two case subjects identified as adult-onset both possessed a variety of past or current mental health symptoms (Figure 3). In both

cases, it was difficult to disentangle the etiology of these individuals' symptoms, and thus the panel conservatively voted to retain the cases. In line with the false-positive paradox (8), the vast majority of case subjects who initially met late-onset symptom and impairment criteria were excluded from diagnosis because of clear evidence that heavy substance use or another mental disorder better accounted for symptoms or impairment (Table 2). In fact, the majority of impairing late-onset ADHD symptoms in young adulthood could be traced to heavy substance use (Table 2) (also see the online data supplement). There are still other potential causes of late-onset symptoms, such as brain injury, illness, or trauma, that should also be considered in future investigations. Without clear exclusionary guidelines for ADHD in adolescents and adults, there is risk that ADHD may become a catchall diagnosis for executive dysfunction stemming from any source. It is unclear whether ADHD-like presentations stemming from nontraditional sources should be differentiated from a chronic form of ADHD with developmental origins, although treatment may be similar (40). Despite many strengths to birth-cohort samples, they are limited because they do not possess the detailed and frequent data collection required to carefully follow psychiatric functioning over time. One of the studies also did not perform full childhood diagnostic assessments, which may have led to missed childhood symptoms in some cases (5). Of course, the average age at comparison baseline was approximately 10 years old, limiting our study's ability to consider detailed symptom records before this assessment.

The comparison group was drawn from the same local school, sex, and age/grade pool as the ADHD sample, which may over-represent certain characteristics, such as male sex or slightly above-average family income. During adolescence, impairment ratings were only available from parents. Some case subjects may have met impairment criteria in adolescence if teacher or self-ratings had been available. We assessed case subjects only to the mid-to-late 20s. New late-onset cases might appear later in development. We also did not collect comprehensive data on physical health or personality disorders with impulsive features that may better explain late-onset cases. Because only eight late-onset cases were detected, we were insufficiently powered to conduct analyses comparing late-onset cases with other subgroups.

Conclusions

Some adolescents and young adults who present for first-time ADHD diagnoses may represent valid late-onset cases. However, the most common source of impairing late-onset ADHD symptoms in adolescence and young adulthood was substance use. Prior to diagnosing or treating ADHD in late-onset cases, clinicians should carefully assess and treat substance use and comorbid mental health disorders as a potential source of symptoms. The majority of adolescent-onset cases possessed transient symptoms. Thus, it may be appropriate to give provisional first-time ADHD diagnoses in adolescence and to monitor symptoms over time, as remission may occur within a few years. Further research is needed to understand how cognitive immaturity or adolescent neurocognitive changes might mimic or facilitate emerging ADHD symptoms.

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TABLE 1. Baseline Characteristics of the Comparison Subsample (N=239)a

Characteristic		
	N	%
Male sex	191	79.9
Race/ethnicity	239	
White	159	66.5
Black	27	11.3
Hispanic	31	12.9
Other	22	9.3
	Mean	SD
Age at baseline (years)	9.89	1.22
Intelligence scoreb	109.82	18.65
SNAP Rating Scale scorec		
Baseline inattention symptoms count	1.70	2.61
Baseline hyperactivity/impulsivity symptom count	1.03	1.92

a The median household income of the comparison subsample was $55,000.
b Determined using the WISC-III.
c SNAP=Swanson, Nolan and Pelham Rating Scale.

TABLE 2. Results of Stepped Procedure for Evaluating the Validity of Late-Onset ADHD Casesa

Result	Adolescent-Onset		Adult-Onset	
	N	%	N	%
Meets DSM-5 ADHD symptom criteria	96	40.2	47	19.7
Clinically significant impairment	32	13.4	40	16.7
Late-onset	21	8.8	24	10.0
Not due to substance abuse	18	7.5	10	4.1
Not attributable to other mental disorder	13	5.4	3	1.3
Cross-situational symptoms	6	2.5	2	0.8
Absence of subthreshold childhood symptoms (less than	3	1.3	2b	0.8

three childhood symptoms of inattention and hyperactivity/impulsivity)				

a Symptom criteria were counted using an "or rule" that considered information from all available informants (e.g., parent, self, teacher); the designated period was either adolescence or adulthood; cross-situationality was inferred from multiple raters and consulting interview questions about context as needed.
b One case subjects was first assessed at age 12, at which point there were not subthreshold symptoms.

Appendix #3

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Treatment strategies for ADHD: an evidence-based guide to select optimal treatment.

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing disorder affecting children, adolescents and adults. Several treatment strategies are available that can

successfully ameliorate symptoms, ranging from pharmacological to dietary interventions. Due to the increasing range of available options, an informed selection or prioritization of treatments is becoming harder for clinicians. This review aims to provide an evidence-based appraisal of the literature on ADHD treatment, supplemented by expert opinion on plausibility. We outline proposed mechanisms of action of established pharmacologic and non-pharmacologic treatments, and we review targets of novel treatments. The most relevant evidence supporting efficacy and safety of each treatment strategy is discussed. We review the individualized features of the patient that should guide the selection of treatments in a shared decision-making continuum. We provide guidance for optimizing initiation of treatment and follow-up of patients in clinical settings.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity[1]. The disorder affects around 5% of children and adolescents[2] and 2.5% of adults[3] worldwide. Decades of research consistently report strong links between ADHD and adverse life outcomes[4-6]. Children with ADHD show an increased risk of accidental injuries[7], poor relationship with peers[8] and parents[9], worse quality of life[10], and impaired school performance[11]. Adolescents with ADHD show more school refusal and grade retention[11], earlier and more frequent use of marijuana, tobacco and other drugs[12, 13], earlier sexual engagement[14] and more frequent teenage pregnancy[15, 16]. Prospective studies of adults with child-onset show that individuals with persistent ADHD (but not remitting ADHD) have lower education attainment, reduced job performance, and increased emotional problems[17-19], and studies of adult onset ADHD show increased risk of traffic accidents[20], criminality[21], unemployment[22] and substance abuse[23]. A common denominator throughout the life cycle is increased mortality by external and accidental causes[24]. Overall, the estimated incremental economic burden imposed by ADHD ranges from $143 to $266 billion dollars in the United States alone, most of which is a consequence of lost productivity [25].

The evidence documenting the individual and social impact of ADHD is the most important justification for treatment. Accordingly, there is agreement between clinical guidelines from Pediatrics, Psychiatry, and Primary care bodies that health professionals should be identifying, diagnosing and treating individuals with ADHD[26-30]. Furthermore, numerous meta-analyses published in the last few years have assessed the efficacy of pharmacological, non-pharmacological and combined treatment for managing ADHD[31-42]. Evidence clearly supports short-term efficacy of pharmacological treatments, but evidence for long-term efficacy is less clear. Non-pharmacological interventions such as cognitive training and neurofeedback are probably not efficacious, and more research is needed to support or refute the role of behavioral therapies on ADHD treatment. Interestingly, health professionals are often given differing and sometimes contradictory advice about how to best interpret this evidence and prioritize the various treatment approaches for their patients. In this review, we examine the evidence of efficacy, safety, and tolerance of available interventions, and propose a balanced hierarchical approach to treatment selection and optimization.

PHARMACOLOGICAL TREATMENT

Pharmacological treatment remains the mainstay of ADHD treatment in most clinical settings and guidelines[26-30]. In some settings, around 90% of children with ADHD eventually receive medication as treatment[43]. The most widely used medications are two psychostimulants, methylphenidate (MPH) and the Amphetamines (AMP). Second-line medications include atomoxetine (ATX), guanfacine (GFC) and clonidine (CLO), usually prescribed after lack of response, intolerance or contraindication to the psychostimulants. Other unlicensed medication options include bupropion, modafinil, and tricyclic antidepressants.

MECHANISMS OF ACTION OF MEDICATIONS FOR ADHD TREATMENT

A comprehensive discussion on mechanism of action of all drugs used for ADHD treatment is beyond the scope of this paper; however most medications for ADHD are thought to act primarily on catecholamine pathways[44] (Figure 1). At the synaptic level, these drugs seem to be catecholamine agonists, increasing availability of dopamine or norepinephrine (e.g., by blocking reuptake). However, there is controversy about the density of dopamine transporters in individuals with ADHD and the impact of this on catecholamine levels. Some studies suggest increased transporter density with rapid recycling of synaptic dopamine resulting in a dopamine deficit[45-47]. Others[48, 49] suggest a dopamine deficit associated with low dopamine release, which in untreated cases is associated with low transporter density. Recent PET imaging studies indicate that transporter density increases and becomes high after chronic treatment with stimulants[50, 51].

There are differences in the specific mechanism of action for each medication. The psychostimulants (MPH and AMP) inhibit dopamine and norepinephrine transporters. They work as reuptake inhibitors increasing neurotransmission, primarily in the striatum and prefrontal cortex [52]. Atomoxetine inhibits the norepinephrine transporter 1 (NET 1). It prevents the reuptake and therefore increases neurotransmission of norepinephrine in all regions of the brain[53] and of dopamine specifically in the prefrontal cortex, where there are very few dopamine transporters[53]. The alpha-2 receptor agonists (clonidine and guanfacine) stimulate alpha-2 noradrenaline receptors in the central nervous system. The mechanism of action in ADHD symptoms is mediated by the increased noradrenergic tone in the prefrontal cortex and an indirect input of noradrenaline from the locus coeruleus[54]. Bupropion is converted into two main metabolites (hydroxybupropion and threohydrobupropion) that are potent norepinephrine enhancers by transporter inhibition[55]. Tricyclic antidepressants (TCAs) primarily act by blockade of the serotonin and norepinephrine transporters, which enhances neurotransmission[56]. There is little effect on dopamine transporters[52]. Modafinil has been shown to induce an atypical conformational change in the DAT compared to traditional psychostimulants[57].

The simplified mechanisms of action described are useful for an initial discussion of the expected therapeutic and adverse effects of these medications. Nonetheless, we acknowledge

that this is a reductionist and incomplete perspective. For example, although these medications may have different mechanisms of action, the ultimate effects may be similar, since they all appear to increase the availability of dopamine and/or noradrenaline. This in turn modulates neurotransmission of a wide range of brain circuits (primarily GABAergic and glutamatergic) that control a range of cognitive functions including executive functioning, response to reward, memory and timing[58-61] (Figure 1 – inferior left panel). These immediate effects on dopaminergic and noradrenergic neurotransmission do not fully explain other aspects of treatment, such as differences in the latency for onset and offset in efficacy, which are short (hours to days) for stimulants and longer (weeks to months) for non-stimulants [62-65]. One plausible albeit speculative hypothesis is that some ADHD medications may promote long-term alterations in the brain through the regulation of genes and proteins involved in neurite outgrowth and configuration of receptors and transporters of neurotransmitters[66-68] (Figure 1 – inferior right panel). If this hypothesis is correct, long-term stimulant treatment could even normalize the trajectory of cortical development and other structural brain changes [69]. However, these changes are also consistent with the development of long-term tolerance through up-regulation of monoamine transporters[70].

PHARMACOGENOMICS OF MEDICATION FOR ADHD

Although pharmacological treatment with psychostimulants for ADHD are among the most effective interventions available in Psychiatry[71], a considerable proportion of patients - roughly a third - do not respond adequately to and/or tolerate stimulant treatment[72, 73]. This heterogeneity in individual response and adverse events could be due to genetic factors, which has been investigated in dozens of ADHD pharmacogenomic studies in the last decades, with most studies focusing on methylphenidate[74].

Most reports describe candidate-gene approaches with catecholamine receptor genes. A recent meta-analysis reviewed all pharmacogenomic studies with methylphenidate and suggested associations of single nucleotide polymorphisms (SNPs) at ADRA2A, COMT, SLC6A2 and variable number of tandem repeats (VNTRs) in DRD4 and SLC6A3[75] with response to treatment. Authors suggested that future studies might propose a multivariable approach to combine small effects of individual genes into one valuable clinical tool, but current clinical use is not yet recommended.

Another promising field of research in ADHD pharmacogenomics relates to genes involved in the metabolism of the medications. Studies investigating the role of the human carboxylesterase 1 gene (CES1), that encodes an enzyme that metabolizes MPH[76], have shown that CES1 variants are associated with the total dose needed and the effect side profile in children medicated with MPH[77, 78]. Likewise, different alleles of the cytochrome p450 2D6 (CYP2D6) gene confer to individuals the feature of poor to extensive metabolizers of Atomoxetine, which has been shown to significantly affect clinical response and effect side profile[79, 80].

Lately, more sophisticated designs have been applied to the study of ADHD pharmacogenomics. Two genome-wide studies have been conducted, failing to find specific genetic variants associated with response to treatment or adverse effects[81, 82]. A study which combined GWAS, functional annotation, pathway enrichment analyses and expression quantitative trait loci strategies, provided promising evidence for potential gene candidates that mediate methylphenidate response in adult patients. A meta-analysis conducted within this study identified 15 positive signals. The phosphatidyelathanolamine binding protein 4 (PEBP4), which is involved in cell proliferation and survival, was the top hit (Pagerols et. al, final review). The underlying mechanisms that mediate these findings through clinical effects are yet to be clarified.

Several companies offer extensive genetic testing with a promise of optimizing pharmacological selection for ADHD[83-85]. We reviewed the information on the websites, which we find to be insufficient for the claims made. We and others do not believe that routinely use of these genetic tests to guide ADHD treatment is currently supported by evidence and that they should not be recommended[74, 86]. However, special cases, such as patients with clear indication to atomoxetine but refractory to treatment, might benefit from dose adjustments based on their classification between slow and fast metabolizers through CYP2D6 genotyping.

EVIDENCE OF EFFICACY

Psychostimulants

Psychostimulants are the most studied medications used for ADHD. Hundreds of randomized clinical trials have been conducted to study short-term efficacy and safety of psychostimulants for the treatment of ADHD in children, adolescents, and adults and have been summarized in many meta-analyses[32, 33, 38, 39, 87-105]. The overall conclusion is that psychostimulants are the most effective available treatment for ADHD, at least in the short-term[87, 89, 106], with clear acute benefits (typically within an hour after an adequate dose) that continue until the drug is metabolized (which depends on pharmacokinetic properties of the drug and method of drug delivery used). If medication is continued, these acute benefits persist for at least a year (although dose increases may be necessary to maintain full efficacy). The evidence also suggests that stimulants are safe and well-tolerated[37, 107].

A recent Cochrane review and meta-analysis questioned the quality of available data on the efficacy of methylphenidate [33]. Authors confirmed the previously observed substantial effect sizes for symptom reduction and the absence of major adverse effects in randomized clinical trials of methylphenidate for children and adolescents with ADHD. However, they classified all 185 included trials as being at high risk of bias. This review has been criticized by experts in the field due to methodological choices of bias assessment[108-110]. For instance, randomized clinical trials funded by government or independent funding agencies were labeled as biased if any one of multiple authors had disclosed a financial connection to the pharmaceutical industry.

A network meta-analysis including 190 randomized clinical trials of ADHD treatments supported psychostimulants as the most efficacious treatment available for ADHD considering pharmacological and nonpharmacological options[32]. This review also found no differences in acceptability between psychostimulants and other pharmacological options. Summarized estimates of efficacy and tolerability reported in this meta-analysis are presented in Table 1. However, the overall quality of the studies ranged from low to very low according to the GRADE system. A second network meta-analysis of pharmacological treatments including 73 studies and 15,025 participants used a ranking strategy to stratify medications according to efficacy and tolerability[111]. Authors concluded that Lisdexamfetamine and Methylphenidate had the best overall ranking scores. It is important to note that some methodological aspects in these meta-analyses like the heterogeneity among studies, the different number of studies included for each comparison, and the quality of some studies included provide results that need to be checked in future studies.

Atomoxetine

Atomoxetine is considered an important pharmacological treatment for ADHD in clinical guidelines[26-30], particularly when psychostimulants are contraindicated or not tolerated. In addition, it might be considered in some special situations e.g. when ADHD is comorbid with Bipolar Disorder and the risk of mood destabilization is high with stimulants, substance abuse/dependence or Tourette Syndrome[26-30].

Randomized clinical trials and several meta-analyses have consistently suggested that atomoxetine has acceptable efficacy and tolerability, but the observed effect size is smaller than that for psychostimulants[32, 38, 87]. Importantly, clinical trials have been conducted in children and adults with common comorbidities, like Anxiety disorders. In these patients, atomoxetine was effective in reducing ADHD symptoms while not exacerbating and in some cases reducing symptoms of comorbid disorders[112-115].

Alpha-2 Agonists

The effectiveness of immediate release clonidine was demonstrated in several early randomized clinical trials[116]. An early meta-analysis reported a moderate effect size for the reduction of ADHD symptoms, particularly hyperactivity[117], although not as big as that for stimulants. However, due to a short duration of action and adverse effects such as somnolence and hypotension [118-120], it is relatively infrequently prescribed as a standalone treatment. In some countries, it is used as an add-on treatment with psychostimulants[26-28, 32]. An extended-release formulation of clonidine has been approved for ADHD in some countries.

Guanfacine is a more selective alpha 2 agonist with less sedating and cardiovascular effects. An extended-release preparation of guanfacine (GFC) was approved by the FDA for the treatment of ADHD in 2010. Seven randomized clinical trials in children and adolescents, support efficacy compared to placebo. Meta-analyses suggest that the effect size is lower than for psychostimulants and comparable to atomoxetine[32, 87, 116]. While one small clinical trial in adults

reported a large effect[121], the actual effect size is still uncertain. There is evidence that guanfacine is useful as an adjunctive treatment to psychostimulants, being more effective than placebo when both are compared as an add-on treatment[122-124].

Antidepressants

The effectiveness of bupropion as a treatment for ADHD has been studied in six clinical trials for children and adolescents and six clinical trials for adults. Results were summarized recently in two systematic reviews both of which concluded that the overall effect is small to moderate and quality of the evidence is poor[125, 126]. Comparative evidence seems to suggest that bupropion efficacy is inferior to that of psychostimulants and probably similar or inferior to that of atomoxetine[127, 128].

Tricyclics, and in particular desipramine, have been studied in six randomized clinical trials for children and adolescents including 216 participants summarized in a Cochrane meta-analysis[129]. There are even fewer studies in adults and no meta-analysis is available[121, 130, 131]. The evidence seems to support the efficacy of these medications in reducing ADHD symptoms. However, tricyclics are usually considered a third or fourth-line option in the treatment of ADHD[26-30], because of the small number of studies and the overall low quality of evidence, as well as their adverse effect profiles.

Modafinil

Evidence describing the efficacy of modafinil for ADHD symptom reduction is still emerging. The results of five short-term randomized clinical trials in children and adolescents have been summarized in a meta-analysis[132]. Modafinil appeared to have a moderate effect in reducing ADHD symptoms and a dropout rate due to side effects similar to placebo. Prominent adverse effects were insomnia and decreased appetite. Studies on adults are less conclusive with contradictory results[121]. Clinical trials and post-surveillance reports have associated Modafinil with serious skin reactions, which led to FDA's request of more data for the approval of the drug for ADHD[133, 134].

New drugs on the ADHD portfolio

Nearly all of drugs in development for ADHD continue to focus on enhancing dopamine and norepinephrine (e.g., HLD200, Dasotraline, Viloxazine, and Mazindol)[135-138]. These drugs are being successfully tested in phase II and III trials and are likely to enter the market soon. However, because of the very similar mechanisms of action, their side effect profile and counter indications are likely to overlap with the drugs already available.

Nevertheless, clinical trials registers and patent applications indicate that novel targets are being considered in preclinical studies. Amiloride is a sodium channel blocker used as an adjunctive treatment for high blood pressure. There is one ongoing clinical trial investigating its

role in ADHD[139]. Fasoracetam is a metabotropic glutamate agonist that is approved for stroke and vascular dementia. Phase II and III trials have been completed with adolescents, but no results have been published so far[140]. Metadoxine is a GABA modulator approved for acute alcohol intoxication. It was being tested for ADHD, but it failed phase III trials and the company halted its development[141]. Molindone, an antipsychotic drug that antagonizes dopamine receptors, is being testes as an add-on treatment for aggressive behavior in children and adolescents with ADHD[142]. Vortioxetine is an atypical antidepressant that inhibits the reuptake of serotonine, and is being tested in a phase II trial with adults with ADHD [143]. While these have very different mechanisms of action to current ADHD medications, it should be noted that they are likely to be acting on the same brain circuits but downstream of the dopamine and noradrenaline modulation.

In summary, the field should not expect significant revolutions in drug resources for ADHD in the next few years. Most of the new developments are focused on changing the mechanisms of drug delivery, especially by increasing their half-lives to cover wider intervals of the day.

NONPHARMACOLOGICAL TREATMENTS

Behavioral and psychosocial treatments

Behavior parent training and social skills training are the primary recommended alternatives to medication management of ADHD[26-28] They are usually regarded as first-line treatments for very young children or those with mild to moderate ADHD[26-28]. They are also the standard add-on to medication treatment for severe presentations at any age[26-28]. In summary, most guidelines recommend behavioral interventions for ADHD in any situation, either alone or in combination with medication treatment[26-28] and these are the most frequently used nonpharmacological treatment among children and adolescents[43].

However, the evidence is mixed and complex, making a definitive interpretation difficult. A seminal study was the Multimodal Treatment study for ADHD (MTA)[144]. In this 14-month randomized clinical trial, children were randomized to receive methylphenidate plus behavioral treatment (a combination of previously suggested strategies of parent-training, child-focused and school-based behavioral therapies), medication only, behavioral treatment only, or referred to usual care within a community setting. The authors and others have noted[145] that there was no statistical difference between combined treatment and medication alone at the end of the treatment-by-protocol (primary analyses). This led to the conclusion that intensive behavioral treatment did not add to the efficacy of well-managed treatment with medication.

Subsequent to the MTA, additional studies have provided evidence of efficiency for behavioral treatments. For example, (a) Charach and colleagues reviewed the efficacy of behavioral and pharmacological treatment for preschool children with ADHD[94]. For this age group, the evidence for benefits of behavioral treatment was strong, but the evidence for pharmacological treatment was not, and (b) sequencing of behavioral and pharmacological treatment revealed

that starting with behavioral treatment and adding medication resulted in better outcome (at a lower dose) than starting with medication and adding behavioral treatment[146].

Current appraisals of the available evidence do not agree on whether the balance of evidence supports or refutes the efficacy of psychosocial treatments for ADHD. One meta-analysis concluded that behavioral treatments were highly effective for ADHD[147], and a review for the Agency for Health Care Research and Quality concluded that the evidence for positive effects of behavioral treatment on preschool children was strong enough to guide clinical practice[94]. However, a Cochrane systematic review and meta-analysis of randomized trials concluded that while BPT may have a positive effect on the behavior of children and adolescents with ADHD, the evidence is not strong enough to guide clinical practice[41]. A separate Cochrane meta-analysis concluded that the evidence was insufficient to support social skills training for adolescents[42]. Several clinical guidelines have recommended both BPT and social skills as behavioral treatments[26-28]. Some of these discrepancies may be explained by the type of rater considered by reviews. Two recent meta-analyses identified a moderate and statistically significant pooled effect size for behavioral therapies on ADHD symptoms when all probably unblinded raters were included but that this effect was not maintained when considering only probably blinded raters.[36, 148]. The same group did however confirm that behavioral therapies were effective in improving positive parenting and conduct problems of children with ADHD, even on blinded ratings.

The evidence for psychological therapies in adults is also conflicting. A carefully conducted randomized clinical trial compared the effect of adding a highly structured cognitive behavioral therapy (CBT) or relaxation with educational support to standard medication treatment. The main finding was a greater improvement in ADHD symptoms in the CBT group[149]. Another important study compared group CBT with individual clinical management either in combination with MPH or placebo, finding no difference in core symptom reduction but better outcomes in the Clinical Global Impression Scale[150]. Meta-analyses conclude that the overall effect of cognitive-behavioral therapies is small to moderate compared to active control groups for adults with ADHD[151, 152].

In summary, the evidence for behavioral interventions is difficult to integrate and summarize. Several different protocols are available and it is likely that not all patients are suitable for receiving each of the behavioral interventions. This may explain some of the controversial findings in the literature. Meanwhile, behavioral interventions are supposedly free from adverse effects and are strongly preferred over medication by some patients and caregivers[153-155]. Considering the evidence from blinded studies, we conclude that we need more high-quality studies before we can support the effectiveness of behavioral interventions on core ADHD symptoms. For now, well controlled studies suggest that they are effective at improving parenting, parent child relationships and oppositional behaviors that are common in children with ADHD and their families. Positive effects are more likely to be seen in favorable clinical settings where patient and/or caregiver are willing to engage in therapy, and a suitable protocol is readily available. Also, the combination of behavioral intervention with medication may result in a clinical dose that is lower than for treatment with medication alone. However, more

studies are needed to unequivocally prove or refute the effectiveness of behavioral interventions in either reducing symptoms or improve overall functioning of patients with ADHD.

Cognitive training

Cognitive training strategies aim to reduce ADHD symptoms by improving performance in specific neuropsychological functions associated with ADHD (e.g.: attention, inhibitory control and working memory)[31, 156]. Cognitive training programs are usually delivered through electronic interfaces such as computers or mobile phones, and are designed to be appealing to the user (i.e. resembling videogames). Performance is continually reassessed so that training is adaptive[157-159].

A recent meta-analysis evaluated the effects, across sixteen randomized clinical trials, for probably blinded and potentially un-blinded raters separately [35]. The conclusions match those of previous meta-analyses[40, 148], indicating moderate efficacy in improving the neuropsychological functions targeted by the intervention but a less clear effect on symptoms. The effect size for total ADHD symptoms and inattentive symptoms was moderate and significant when rated by a potentially un-blinded rater. The estimates decreased when outcomes were rated by a probably blinded rater. Of note, the effect size was much larger for programs that included multiple process training (i.e., targeting more than one executive functioning) compared to those that focused on just on cognitive process. However, for the multiple process studies only potentially unblinded ratings were available. In summary evidence so far available suggests that cognitive training has no effect on core ADHD symptoms or other functional outcomes for ADHD patients.

Neurofeedback

In neurofeedback, the patient is trained to improve self-control over brain activity patterns, which is most often monitored through simultaneously collected electroencephalogram (EEG) data[160, 161]. Its use in ADHD stems from the knowledge that patients with ADHD exhibit distinct EEG patterns compared to their non-affected peers[162, 163]. Current neurofeedback protocols focus predominantly on decreasing *theta* waves (low-frequency waves related to decreased vigilance) and/or increasing *beta* waves (high-frequency waves related to concentration and neuronal excitability). This is achieved by measuring EEG activity while the patient is engaged in a task, often a simple computer game, and modulates performance and reward according to specific changes in EEG pattern. It is estimated that in the United States around 10% of children and adolescents with ADHD have received neurofeedback interventions [43].

While preliminary evidence from open-label trials suggested moderate to large effect for ADHD symptoms,[164, 165] the latest meta-analyses concluded that the effects are moderate to large when proximal, potentially unblinded, raters were considered, but reduced by half and lost statistical significance when pooling estimates from probably blinded raters[34, 148]. However, the aggregated measures included both trials with standard and non-standard protocols. An

exploratory analysis revealed that, considering only 3 trials with both probably blinded raters and a standard protocol, the effect was moderate and significant, albeit with a large confidence interval.

Although neurofeedback may have few adverse effects, it is a specialized intervention which usually requires 20 to 40 sessions, and as a consequence it is often expensive for the end user. Future research may identify more effective methods for using neurofeedback in ADHD. For instance, new protocols are using simultaneous functional magnetic resonance imaging as the therapy target of the intervention (i.e., the parameter that patients are induced to improve)[166, 167]. On the other hand, feasibility also requires less expensive and complex equipment requirements. The evidence available indicates that neurofeedback is not effective for core ADHD symptoms and more high-quality studies should be performed before we can support the effectiveness of neurofeedback on core ADHD symptoms. Future trials should focus on standard protocols and effectively blinded raters.

Dietary modifications

The hypothesis that dietary factors might play a role in the etiology of ADHD was first proposed over forty years ago, and it remains a controversial topic until the present day. The main restrictive strategies are to remove artificial food colors from diet continuously (AFC) or to restrict several foods in a rapid course of 9 to 28 days – the 'few foods approach' (FFD). Supplementation with poly-unsaturated fatty acids (PUFAs) is also a commonly proposed strategy, based on the possible neuroprotective effect of those substances.

The observed effect of dietary modification strategies for ADHD varies considerably depending on methodological aspects, including whether assessments are made by blinded or unblinded raters. A recent systematic reviewed data from 6 out of 14 available meta-analyses on this subject and concluded that the estimated effect size of PUFAs for ADHD is too small to be considered a tangible contribution. The estimated effect of AFC exceeds that of PUFAs, but, while it is not so small to dismiss, neither is it large enough nor secure enough to make conclusive recommendations for implementation. The effect sizes for FFD were medium to large, and authors consider that the results might justify its administration in children with ADHD. However, they also note that the complete implementation of this treatment, which encompasses several courses of intense food restriction to identify the individual ideal scheme, might be unfeasible in many cases. Authors of the trials with the largest effect sizes have not made the protocols for their interventions public and it is therefore not yet possible to implement these outside of the original research setting. An overall appraisal of the evidence seems to suggest that the FFD and AFC diets have significant, although clinically small, effects on ADHD symptoms while having few adverse effects.

Other promising nonpharmacological therapies

New nonpharmacological options and strategies are being developed and tested for ADHD. Coaching programs designed to help an individual cope with the demands of the environment

usually focus on improving executive functions such as time management, prioritization and effort sustainment over time. Initial empirical studies have shown promising results[168, 169], but these trials are small naturalistic studies that need to be confirmed by randomized clinical trials. The Supporting Teens' Autonomy Daily (STAND) program targets adolescents with ADHD and uses motivational interviewing to enhance adherence. A randomized clinical trial showed promising acute and long-term (six months after treatment ceased) effects on ADHD symptoms, parental stress and executive functioning skills[170]. Mindfulness is the act of self-regulating attention towards the current moment and the self. Mindful-based therapies are rooted in ancient Buddhist practices, and have recently gained popularity in western cultures to promote general well being and treat psychiatric disorders[171]. Some investigators suggest that mindfulness therapies are especially well suited to address the deficits associated with ADHD, as it involves intensive training of attentional and emotional regulation. A recent systematic suggested that the observed effect is moderate to large for children with ADHD, but the overall quality of the studies is very low[172]. The only randomized clinical trial reported negative results, as did two out of only three trials that had a control group. At the moment, more well-designed studies are needed.

IMPACT OF TREATMENT IN REAL-LIFE OUTCOMES

The extent to which reduction of ADHD symptoms leads to better real-life outcomes is studied. A systematic review of long-term clinical studies suggested that patients with ADHD who received treatment (by any modality) had better long-term outcomes than their non-treated counterparts across most studied domains, and the effect was higher for combined pharmacological and nonpharmacological treatment than for either of those alone[173]. Evidence from randomized clinical trials supports the conclusion that treatment for ADHD improves the quality of life of patients[174-177].

Medical registries from large-scale observational studies have been used to investigate outcomes within the same individuals by comparing periods on and off medication. Those studies showed that medication periods were associated with improved performance on higher education test exams[178], reduced vehicle motor crashes[179], reduced criminality[21], reduced emergency room admission related to substance abuse[23] and reduced risk of trauma and brain injuries[180-182]. Some limitations of these studies need to be highlighted. The within-subject design controls for between-subject and time independent within subject factors but not for time dependent factors that might influence on patient´s decision to start or stop medication. Furthermore, the nature of this design (based on frequent starting and stopping of medication) evaluates effects over short periods of time, limiting the evaluation of long-term effects of medication.

In line with this reasoning, prospective follow-up studies of childhood-onset ADHD have documented clear beneficial effects of starting medication, but have not detected long-term benefits in adulthood associated with typical long-term patterns of treatment (either residual effects of inconsistent treatment associated with stopping medication in childhood or adolescence or consistent treatment into adulthood that occurs in less than 10% of the

cases)[183-185]. An important complicating factor might be the age-related decrease in symptom-severity and remission of ADHD in many affected children, which is associated with improved real-life outcomes, regardless of treatment.

Overall, the evidence suggests that treating ADHD can improve several important functional outcomes. Likewise, cost-effectiveness studies consistently show that treatment benefits significantly outweigh its costs[186-188]. The critical question for clinicians is how to prioritize among available treatments for individual patients.

SELECTION OF TREATMENT

Among the available efficacious treatments for ADHD, the main differences relate to modality (i.e., pharmacological and nonpharmacological), age of the patient, financial cost, patient and caregiver time demand, expected effectiveness on symptom reduction, adverse effects, safety and tolerability. Selection should be a shared decision-making process with input from the clinician and the patient and their caregivers. To engage in this process, patients and their families need to be adequately and accurately informed about the evidence and the choices[189]. The first major decision will be to consider whether pharmacological and/or non-pharmacological interventions will be used, and if both how they will be sequenced.

The Clinician Input

The clinician's input is a technical appraisal of the patient's characteristics that takes evidence into account to favor some treatment options above others. Major considerations include: 1) age of the patient; 2) severity of the disorder; 3) comorbidities (Table 2).

Age is a major factor in the recommendations of ADHD clinical guidelines. For instance, most guidelines do not usually recommend pharmacological therapy for preschool children (under age 6)[26-28]. Although this partially relates to the fact that these medications are generally not licensed for use in those under six years of age, it is also true that the efficacy and safety of medication treatments is much less studied in this age range.[190] When studied, the benefits are smaller and the side effects are greater than in older children[191]. Behavioral therapy has more evidence of efficacy than medication for preschoolers[94]. Furthermore, the targets of treatment may be different since the academic demands are less for preschool than school-aged children. With increasing patient's age, there will be a tendency to favor medication due to increased evidence for efficacy and safety and as increasing academic and social demands are less likely to be met with nonpharmacological interventions alone. For school-aged children, pharmacological treatment is usually the first choice. Likewise, the technical appraisal of evidence is balanced towards pharmacological treatment for adult patients, as effectiveness is less clear for nonpharmacological interventions[192]. In adulthood, findings on the effectiveness of combined treatments (i.e., CBT interventions + stimulants)[149, 150] are more controversial.

The severity is another important clinical consideration. As addressed here and elsewhere[32, 87, 106], the effectiveness of ADHD treatments are on a continuum beginning with

nonpharmacological treatment showing small to moderate effect sizes; non-stimulant pharmacological treatment with moderate to large effect sizes; and stimulant treatment with large to very large effect sizes. Combined treatments (medication plus cognitive behavioral therapy or stimulant plus non-stimulant) has often been assumed to be the most effective strategy, although the evidence supporting superiority to psychostimulants alone remains controversial. We recommend that severity should be matched with the expected effectiveness of the treatment: (a) for low severity, nonpharmacological interventions; (b) for moderate severity, pharmacological interventions; (c) for high severity, combined intervention.

Simple and uncomplicated ADHD is not common. In most cases ADHD co-occurs with other psychiatric and developmental disorders, and these comorbidities also have implications for the treatment required (see Table 2). For example, Oppositional Defiant Disorder and Conduct Disorder are the most common co-occurring disorders, and only pharmacological treatment has been shown to reduce these comorbid symptoms with large effect sizes[39]. Tics or tic disorders also co-occur with ADHD, and although psychostimulants might not exacerbate these comorbid symptoms in general[193], tic worsening might occur in some patients[194]. Co-occurrence with Substance Use Disorders (SUDs) is also common in adolescence and adulthood. In patients who have both ADHD and SUDs[195], the evidence suggests that psychostimulants are effective in reducing ADHD symptoms, but not in improving substance abstinence. Also, many clinicians are apprehensive to prescribe these medications for these comorbid cases because of their potential for abuse, although available evidence does not fully support this view[196]. Thus, non-stimulants like atomoxetine and the alpha 2 agonists, which have a much lower liability of abuse than the stimulants, or nonpharmacological treatment might be preferred for treatment of some ADHD patients with comorbid SUDs[197]. If stimulants are recommended, methylphenidate and extended-release formulations (which may have less abuse potential) should be preferred over amphetamine derivatives and immediate-release formulations[198]. It was usually believed that Atomoxetine was the preferred option when ADHD was comorbid with Anxiety Disorders, due to its positive effect in Anxiety symptoms, while psychostimulants might have a negative effect[114, 199]. Particular co-occurring disorders might cause or exacerbate ADHD symptoms while being hierarchically prioritized in the treatment decision. These include mood disorders such as depression and bipolar disorder, and psychotic disorders in the schizophrenia spectrum. Even if the clinician judges that the criterion E of the DSM is met (i.e., symptoms are not explained by the co-occurring disorder), we recommend prioritizing treatment of the comorbid disorder. The clinical assessment of ADHD to select treatment should focus on symptoms that remain after stabilization of a major mood or psychotic disorder.

The Patient/Caregiver Input

The patient/caregiver input involves an analysis of personal aspects that, considering the clinician's recommendations, will give more or less weight to a given set of suggested treatment options. This is highly variable and depends on complex sociocultural aspects and their interactions. The most important aspects are: 1) preferences around treatment modality; 2)

expectations of efficacy; 3) feasibility considering financial and time demands; 4) age of the patient.

Among the most important individual aspect to consider is the acceptance of the proposed treatment by the patient/caregiver. Studies suggest that the likelihood of preferring medication treatment as a first-line approach for ADHD is somewhat idiosyncratic but highly dependent on social and cultural characteristics[153, 154]. For instance, parents with higher education more frequently conceptualize ADHD as a biomedical illness, which in turn increases their likelihood of accepting medication[183, 200]. However, these preconceived conceptualizations should not be considered a closed topic and an adequate understanding of the disorder by patients and parents should be one of the goals of the therapeutic process. Furthermore, discrepancies between child and parent preferences are common. A trial on medication is usually sought by the parent, and children are frequently reluctant to or refuse to take medication due to complex factors such as social stigma, side effects or simply not appreciating the benefits of treatment[201, 202]. In those cases, particular characteristics of the family such as the extent of autonomy that parents give to the child play an important role in treatment choice. In summary, patient and caregivers usually exhibit preconceived treatment preferences closely related to their sociocultural context.

They also have different expectations about treatment effectiveness. These expectations should be carefully assessed by the clinician, as they should be matched with actual treatment efficacy/safety. Unrealistic expectations should be discussed and patients properly informed. A young adult attending college with severe ADHD causing failure to thrive academically probably expects more from the treatment than another young adult with less attentional demand and a milder disorder. The former would have his/her expectations frustrated by treatments with small to moderate effect sizes; the latter may not find the benefit to risk and cost ratios of the most effective treatments favorable. Accordingly, the degree of symptom control was the most important factor taken into account by parents who selected stimulant treatment in a study of six European countries[154].

Finally, the gap between the ideal world and clinical practice also impacts the final decision on treatment selection for ADHD. Effective nonpharmacological strategies such as behavioral therapies, neurofeedback or cognitive training are more expensive, time-consuming, and less available outside central urban areas of developed countries than pharmacological alternatives. There are also differences in the cost of medications that need to be considered in countries where patients pay with out of the pocket money.

SELECTION OF THE FIRST MEDICATION

Many cases that present to clinical practice will require and ADHD medication. Several factors need to be considered for the selection of the first medication, mainly to decide between stimulants versus non-stimulants. These are summarized in Table 3.

MONITORING, FOLLOW UP AND CONTINUED CARE

There is evidence that monitoring patient improvement through the use of rating symptom scales in each visit increases positive clinical outcomes and chance of remission in Psychiatry[203]. There is also now emerging evidence that implementing a carefully constructed medication protocol with routine measure of standardized outcomes can result in significant improvements in clinical outcomes and that these can be sustained over long periods of time[204]. We recommend assessing the intensity of ADHD symptoms before and after treatment at each appointment using validated rating scales[205, 206] and adjusting treatment in order to optimize outcomes (see the MTA medication algorithm[207] and Dundee ADHD Clinical Care Pathway protocol[204] for possible strategies). Alongside with symptom monitoring, clinicians should also assess real-life measurable parameters of functional benefits accompanying from symptom control. They need to combine their subjective impressions with such objective measures to guide dosage adjustments, treatment switch or add-on therapy. Likewise, adverse effects should be actively asked about in a "review of systems" manner and in the physical exam, focusing on the most likely adverse effects of each medication. After stabilization of symptoms, clinicians should reassess treatment response and adherence, vital signs and adverse effects at least once a year[26].

The question ‘how long should a patient be treated?’ is an incompletely answered question. ADHD is regarded as a chronic disorder: in long-term clinical follow up studies (i.e., six years or more), about 50% of the child-onset cases are reported to have persisting ADHD impairing symptoms[208, 209]. Adverse outcomes also continue to occur more frequently in those with ADHD for many years after the initial diagnosis, even for those who symptoms remit[210]. Although some meta-analyses suggest that treatment improves the majority of long-term ADHD outcomes and combined treatment seems to be associated with larger effects sizes for these improvements[173], long-term benefits of ADHD treatment is yet a controversial area. After treatment cessation, the associated benefits tend to reduce until they are no longer discernable.

This suggests that in routine clinical practice patients and caregivers should be informed about the heterogeneous course of ADHD symptoms throughout life, and that desistence is seen in many of childhood-onset cases. Several childhood factors increase the risk of long-term syndrome persistence. These include increase ADHD severity and comorbidity with disruptive disorders and major depression[211]. Also, self-selection will result in stopping medication in many cases from whom ADHD is recognized and treatment is initiated in childhood. In some cases, shared treatment decisions will result in carefully medication tapering (or to reduce the intensity of non-pharmacological treatments gradually) over time as an individual matures. This may be used to evaluate syndrome remission, preferable in a period of stable relatively lower demands from the environment. Alternatively, in some cases, the symptoms may emerge when some individuals encounter higher demands in adolescence or adulthood[212], and previously treated cases may require re-starting medication (or previous unrecognized and untreated cases may require a trial on medication).

CONCLUSIONS

Patients with ADHD benefit from a wide variety of available efficacious treatments that target and alleviate the disorder symptoms, impairment and poor functioning. They encompass different classes of medication, several protocols of therapy, computerized training, dietary modification, and their combinations. New strategies, such as coaching and mindfulness, are being developed and tested. Facing this wealth of options, the clinician may find it hard to hierarchize treatments in an effective, evidence-based manner.

We conclude that all ADHD medications, while differing in their synaptic mechanisms, eventually act on broader neuro-cognitive networks in the short-term. Psychostimulants are highly effective, when compared to other psychiatric medications. Non-stimulants while less effective options should be considered in special situations. Psychosocial interventions are especially useful for very young children or mild disorders, or as an add-on treatment to medication to improve efficacy or reduce required dosage. Treatment selection should rely on a shared decision-making process between the clinician and his or her patient. The main aspects to be considered by the clinician are age of the patient, severity of the disorder and comorbidities. Patients should be routinely followed to assess response to treatment and adverse events, as well as disorder persistence or remission.

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Table 1. Efficacy and tolerability of treatments approved for ADHD

	Efficacy		Tolerability	
	Magnitude	**# trials**	**Magnitude**	**# trials**
Methylphenidate	++++	40	+++	55
Amphetamine derivatives	++++	9	++++	8
Atomoxetine	+++	27	++++	37
Clonidine	+++	4	++	6
Guanfacine	+++	10	++++	9
Modafinil	++++	5	+++	6
Bupropion	++	1	+++	3
Behavioral therapies	+++	15	+++	25
Cognitive training	+/-	2	++++	10
Neurofeedback	++/-	4	+++	10
Poly-unsaturated fatty acids	++/-	3	++++	9
Stimulants + behavioral	++++	8	+++	13
Non-stimulants + behavioral	++++	4	++++	3
Stimulants + non-stimulants	++++	4	+++	7

Efficacy and tolerability estimates were extracted from a recent network meta-analysis [32]. Odds Ratio against placebo were converted to Cohen'd effect sizes. The higher the number of +, higher are efficacy and tolerability. Tolerability expressed as number of patients discontinuing the protocol.
+ = up to 0.2 | ++ = 0.2 to 0.5 | +++ = 0.5 to 0.8 | ++++ = more than 0.8 | /- = non significant

Please note that the strength of the evidence is not considered (there is large heterogeneity in the overall number of trials available for each intervention). # trials represents the number of high-quality trials (as judged by the authors of the meta-analysis) used to compute the effect estimates.

Estimated effects for non pharmacological interventions stem from studies using unblinded raters.

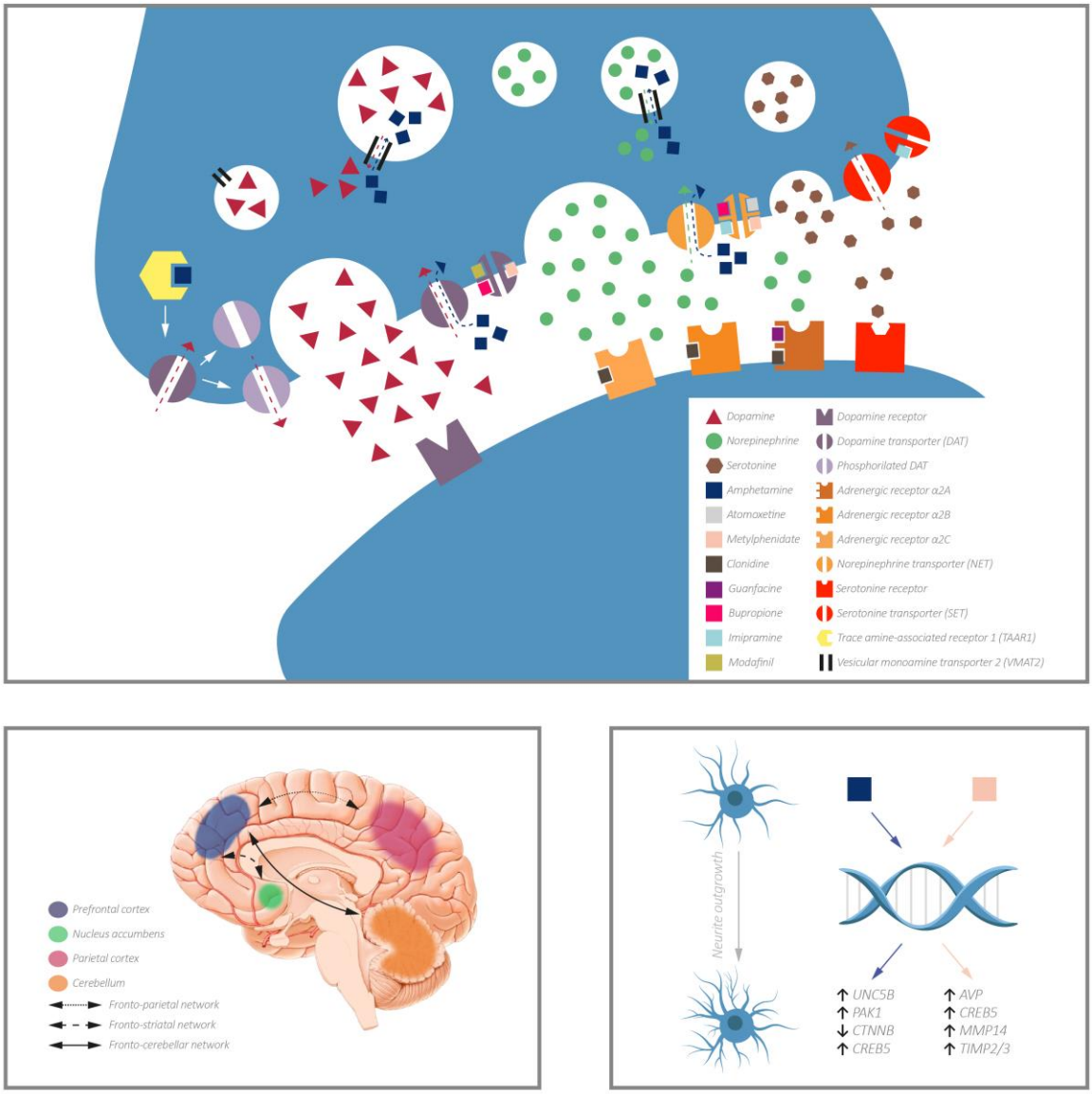
Table 2. Major clinical aspects implicated in the selection of treatment strategies for ADHD

Aspect	Recommendation	Rationale
Patient's age	- Start with behavioral treatment when possible in preschool children - Prefer pharmacological treatment in adults	- Less evidence supporting safety and efficacy and lower benefit : risk ratio for medication in preschool children. - Lower efficacy of nonpharmacological interventions
ADHD severity	- Monotherapy with nonpharmacological treatment for mild disorder - Combination treatment for severe disorder	- Expected efficacy of treatment lies within a continuum: nonpharmacological < non stimulants < stimulants < combination therapy
Comorbidities	- Tic disorders: non-stimulants might be an option in cases where methylphenidate increases tics - Disruptive disorders: prefer stimulants - Substance use disorders: non-stimulants might be an option - Mood and psychotic disorders: prioritize comorbidity treatment	- Psychostimulants might exacerbate symptoms of tic disorders in some cases - Psychostimulants reduce ODD/CD symptoms with large effect sizes - Theoretical potential for abuse of this class of medication - Comorbid conditions may cause or exacerbate ADHD symptoms; their core features are not likely treated with ADHD medication.

Table 3. Factors implied in the selection of the first medication treatment for ADHD

Factor	Evidence	Recommendation
Effectiveness	Stimulants are the most effective class	Prefer stimulants for moderate to severe cases
Adverse effects	Non-stimulants (especially ATX and GFC) have different profile of adverse effects	Prefer non-stimulants in case of intolerance to stimulants or when specific adverse effects are a special concern
Duration of action	Extended release formulations of stimulants last for around 12h; ATX and extended release GFC last for the entire day	Prefer these when the effect is desired for more than one segment of the day
Abuse potential	Stimulants have theoretical abuse liability	Non-stimulants might be an option when abuse is a relevant concern
Time to onset of effect	Stimulants have immediate onset/offset of action	Prefer stimulants when immediate onset/predicted offset is needed
Patient and parental preferences	Patients and parents might have personal opinions on existing options	Consider patient and parent preferences, provide evidence-based information

Figure 1. Proposed mechanisms of action for the medications commonly used to treat ADHD



Pharmacodynamics (superior panel): **Amphetamines** (blue square) have at least three mechanisms of action: 1) they are transported by the monoamine transporters DAT and NET, thus competing with those neurotransmitters and decreasing their reuptake in the synapse; 2) They also cause Trace amine-associated receptor 1 (TAAR1) to phosphorylate DAT. The Phosphorylated DAT is either internalized into the presynaptic neuron and ceases transport or inverses the efflux of dopamine; 3) they enter the presynaptic monoamine vesicle and cause efflux of neurotransmitters off the vesicle, which in turn augments the efflux towards the synapse. These mechanisms are more studied and established for dopamine neurotransmission, but are thought to occur similarly for norepinephrine. **Atomoxetine** (gray square) binds to NET, inhibiting the reuptake of norepinephrine. In the prefrontal cortex, where there is much less expression of DAT, dopamine reuptake by NET is also inhibited by the action of Atomoxetine. **Methylphenidate** binds to NET and DAT, inhibiting the reuptake of norepinephrine and dopamine. **Clonidine** binds to and activates alpha-2 adrenergic receptors. **Guanfacine** binds to and activates specifically alpha-2A adrenergic receptors. **Bupropion** inhibits DAT and NET weakly. **Imipramine** inhibits NET and SET. **Modafinil** inhibits DAT to a weaker extent than other psychostimulants.
Brain network activation (left inferior panel): Pharmacological treatment acutely enhances activation and normalize brain networks involved in attention, cognitive control and working memory in children with ADHD.
Neurodevelopmental signal (right inferior panel): ADHD medications regulate the expression of genes involved in neurite outgrowth. In the panel, for illustration, we provide mechanisms for Methylphenidate and Amphetamines.

Appendix #4

Published in the Molecular Psychiatry.

Response to lithium has a neurobiological signature

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To the editor: A recently published report by the Bipolar Disorder Working Group of the ENIGMA Consortium has analyzed neuroimaging data on 6503 individuals, providing compelling evidence for the existence of a cumulative degenerative effect of Bipolar Disoder (BD) on the cortex of affected patients[1]. Their conclusion, that patients have decreased cortical thickness than unaffected individuals and that this effect is moderated by duration of disease, endorses several previous studies that identified that the disorder is characterized by evident clinical neuroprogression[2].

Nevertheless, the analyses on treatment effects yielded interesting results. Among patients with BD, those on lithium had increased cortical thickness compared to patients not taking lithium, with effect sizes comparable to those observed between patients and controls. On the other hand, antiepileptic treatment was associated with decreased cortical thickness and atypical antipsychotic treatment was associated with decreased surface area among BD patients. The findings of the ENIGMA study concur with previous findings from non-randomized studies that already pointed out that the use lithium is associated with increased or preserved gray matter in bipolar patients, while anticonvulsants and antipsychotics are not[3].

Clinical guidelines usually consider some antiepiIeptics and atypical antipsychotics together with lithium as first-line treatments for acute phase or maintenance of BD[4]. The National Institute For Health and Clinical Excellence, on the other hand, is one of the only main guidelines to suggest lithium as preferred maintenance treatment, while considering other alternatives as second-line options[5]. Lithium prescriptions have been reducing worldwide, while prescription of antiepileptics and atypical antipsychotics have been rising[6]. Therefore, the evidence of a positive effect of lithium against a negative effect of other therapeutic options on neuroimaging markers of cognitive functioning should be given uttermost and careful attention as it could influence clinical practice.

Although we welcome with enthusiasm such interesting findings of the differential effects of BD treatments on cortical thickness and surface area, we suspect that important factors might be confounding the results and should be controlled for. First, there is the case of the distinctive subtype of excellent lithium responders. There is now substantial evidence that about a third of individuals with BD have excellent response to lithium[6]. These patients cluster in families and have a specific genetic signature[7]. More important, they have a significantly better long-term prognosis[8]. As a matter of fact, these singular features have led some authors to understand this subgroup of patients as a separate diagnostic subtype of Bipolar Disorder[9]. Second, there is evidence for an inverse correlation of psychotic symptoms and both cortical thickness and gray matter volume in bipolar patients[10].

In a cross-sectional analysis such as the ENIGMA sample, it is unlikely that excellent lithium responders and their special neurobiological signature are distributed equally among treatment comparisons. It is reasonable to assume that excellent responders to lithium are more frequently taking lithium than other medications. Likewise, patients with psychotic features are more likely

receiving antipsychotics than other patients. Therefore, the differences of cortical thickness and surface found between treatments might have been overestimated by the measure of patient effects, rather than medication effects. We would like to emphasize that controlling for medication use, which was carefully conducted by the authors, does not address this bias entirely. If results hold unchanged even taking into consideration the excellent responder group and the presence of psychotic symptoms, the field will be even more convinced of the existence of a causal relationship between choice of treatment and cortical neurodegeneration. Future longitudinal studies, and especially randomized trials, could help to clarify the issue even further by attempting to identify these groups of patients and taking them into account when comparing neuroimaging data.

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Appendix #5

Published in the Journal of the American Academy of Child and Adolescent Psychiatry

Revisiting the Werther Effect in the 21st Century: Bullying and Suicidality Among Adolescents Who Watched *13 Reasons Why*

Aline Zimerman; Arthur Caye, MD; André Zimerman, MD; Giovanni Salum, MD PhD; Ives Cavalcante Passos, MD PhD; Christian Kieling, MD PhD.

To the Editor:

Unlike most leading causes of death in the US, suicide rates have not declined during the past 50 years.[1] Among young people the situation is even more dramatic, as suicide rates are rising,[2] and suicide is now the second cause of death in 15 to 29-year-olds globally.[3] It has been suggested that descriptions of suicide in the media might impact behavior, and the young may be more vulnerable to this effect.[4]

In the late eighteenth century, the novel *The Sorrows of Young Werther* by Johann Wolfgang von Goethe was blamed for unleashing a suicide epidemic among young men in Europe. There are now real social and scientific concerns on the possible contagion effect of descriptions of suicides in both fictional or nonfictional works.[5,6] The premise that exposure to accounts of suicides may cause predisposed individuals to make attempts is supported by a number of ecological studies;[7,8] however, most research on the topic is outdated, as the relationship between teenagers and the media is rapidly changing.[9] Moreover, ethical and methodological aspects frequently hamper the empirical investigation of this issue.

The success of the Netflix show *13 Reasons Why*[10] was followed by a heated debate on how it approaches the story of an adolescent who commits suicide after being bullied at school.[11] Several experts argued that the show could result in an increase in suicidal thoughts and behaviors,[12,13] which was reinforced by a recently-published article that presented an association between the show release date and suicide-related Google searches.[14] However, to our knowledge, direct evidence on whether the show influences adolescent thinking and behavior is lacking. To address this issue, we assessed adolescents who watched *13 Reasons Why* by asking their perceptions on how it affected them in regard to bullying and suicidal ideation.

METHODS

The study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre, Brazil. We created online surveys in English and in Portuguese with questions related to bullying, depression and suicide prior and after watching *13 Reasons Why*.

We asked respondents whether they had ever been bullied or had bullied someone else before watching the show; for those who answered affirmatively to any of these two questions, we used a 5-points likert scale to assess how much they believed watching the series had changed the way they felt or behaved regarding bullying. For those who had not engaged in bullying before the show, we asked whether they had bullied anyone afterwards.

To measure depressive symptoms, the survey included the Patient Health Questionnaire-2 (PHQ-2),[15] which consists of two questions related to symptoms of depression over the prior two weeks. Scores on the PHQ-2 range from 0-6, in which 0 indicates no cardinal depressive symptoms and 6 indicates feeling depressed and anhedonic practically every day. For this study, the questionnaire asked about the two weeks prior to watching the show. A score equal to or greater than 3 in the PHQ-2 is considered a positive screening for depression.

The last two questions in the survey referred to suicidal ideation. Participants were asked whether, before watching the show, they had ever thought about taking their own life (dichotomic) and how watching the show changed the way they felt about it (5-point likert scale). Answers to this last question were operationalized as decreased (1 and 2), unchanged (3) and increased (4 and 5) suicidal ideation. For the group with no prior suicidal ideation, answers 1 to 3 were merged and considered as no increase in suicidal thoughts (see supplementary material for details).

For the primary analysis, we used Facebook advertising to reach adolescents living in the United States or Brazil who liked pages related to the TV series. Participants included in this analysis were 12 to 19-year-olds, living in the aforementioned countries, who reported having watched all 13 episodes and completed the questionnaire. To address the potential of selection bias by including only participants who liked Facebook pages related to *13 Reasons Why* and may therefore have a more favorable view of the show, we recruited a control group who had liked pages related to Netflix on Facebook but not *13 Reasons Why*. We performed chi-squared tests to compare results between the control and the primary study groups. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 280,973 people viewed the survey links and 26,103 responded. After excluding 2,382 people who did not complete the questionnaire, 2,214 who did not watch all episodes of the show and 445 who were not aged between 12 and 19 years, 21,062 people were included in our sample. Most participants were female, Brazilian residents, and aged 15-17 years (Table 1). Most respondents screened positive for depression (PHQ-2 ≥ 3) in the two weeks before watching *13 Reasons Why* (65.6%), and 64.5% reported a lifetime history of suicidal ideation.

Among this latter group, 16.5% expressed more and 59.2% reported less suicidal ideation after watching the show – 24.2% indicated no change. In the group of participants with no prior history of suicidal ideation, 6.4% reported increase in suicidal thoughts after watching the show. Figure 1 displays the changes in suicidal thinking after watching the show among participants with low (0) and high (6) PHQ-2 scores.

A total of 78.7% of the participants said they had suffered bullying, and, 40.5% of them reported feeling better about it after the show. and A total of 41.3% of the participants stated that they had engaged in bullying before watching the show. A; among those who had not, 97.3% reported unchanged behavior. Among those who had engaged in bullying, 95.5% reported they rethought such behavior after watching the show, and 90.1% of these who reconsidered their attitudes said they began bullying less afterward. mong those who engaged in bullying, 95.5% reported they rethought such behavior after watching the show, and 90.1% of these who reconsidered their attitudes

said they began bullying less afterward. There was no difference in regard to changes in bullying behavior or feelings related to bullying according to PHQ-2 score or history of suicidal ideation in participants who reported bullying or suffering bullying before watching the show (see supplementary Figure S1 for details).

A total of 2,323 people met inclusion criteria for the control group (adolescents who liked Netflix-related pages, but not *13 Reasons Why*). No significant difference was found between results in the primary sample vs. control group regarding decrease in bullying (90.1% vs. 92.1%, p=0.07) and in suicidal ideation (59.2% vs. 60.5%, p=0.31).

DISCUSSION

Our data demonstrate that watching *13 Reasons Why* was associated with decreased rates of self-reported bullying-related attitudes and suicidal ideation among adolescents who took part in our survey. Results related to bullying were well-distributed in the sample, while reductions in suicidal thinking were more pronounced in individuals with no depressive symptoms prior to watching the show.

Regardless of the overall positive effect in this population, it is important to note that a more vulnerable subgroup – participants with depression and/or with prior suicidal ideation – may be more negatively affected by watching the show. These results suggest that while the series has the potential to have positive effects for most of its viewers, it may have negative effects on high-risk individuals. For this reason, the decision on whether to watch the show should be individualized and decided jointly by adolescents, parents and medical authorities,[16] taking into consideration each adolescent's individual characteristics and the impacts of the show observed in this study. Also, although higher rates of suicidal ideation after watching the series were more pronounced in the group with preexisting psychopathology, the rates among those with no depressive symptomatology nor suicidal ideation were non-negligible. It is concerning that 4.7% of adolescents with no prior suicidal thoughts or symptoms of depression (PHQ-2=0) reported they thought more about taking their own life after watching the series.

Despite the advantages of targeting adolescents using social media, there are intrinsic limitations to the method in terms of selection bias, so results here presented might not be generalizable to all teenagers. First, only people who use Facebook were invited to the survey, and only 7.5% of those approached to participate provided valid responses, which may not represent the show's general audience. The respondent sample had a very high prevalence of bullying, depression, and suicidal thoughts. Second, even though a control group showed no differences in the responses compared with the original sample, the survey was primarily targeted at adolescents who had liked pages related to *13 Reasons Why* and, therefore, had a potentially favorable bias towards the show. Third, although it is a common and accepted method of measuring this behavior, self-reporting of bullying might be associated with potential reliability issues. Another important limitation refers to the fact that suicidal thoughts before and after watching the show were both assessed retrospectively. As our survey did not include a question addressing how adolescents perceived specifically the suicide scene, we were not able to assess this controversial issue. It is also noteworthy that, although analyses in this study were focused on bullying, depression and suicide, there may be other potentially relevant unmeasured effects related to watching the show (e.g., related

to the portrayal of help seeking in the series). Finally, because of the retrospective design and lack of a contemporaneous control group that watched a different show that did not address bullying or suicide, it was not possible to identify spontaneous fluctuations or to establish a causal link between watching *13 Reasons Why* and the changes in thinking and behavior we observed.

Public affairs involving emotional issues – such as suicidal behavior induced by a TV show – frequently provoke the spread of emotional opinions and reactions. The present report provides empirical evidence on the potential benefits and risks of the Netflix series *13 Reasons Why* on adolescents' behavior, suggesting a predominant decrease in bullying and suicidality, while also indicating an increased probability of harmful effects to a subgroup of vulnerable youths. Suicide among adolescents is a major public health issue, but one for which preventive strategies are currently available.[17] We hope that further understanding such a complex phenomenon can ultimately help us identify and assist those in need.

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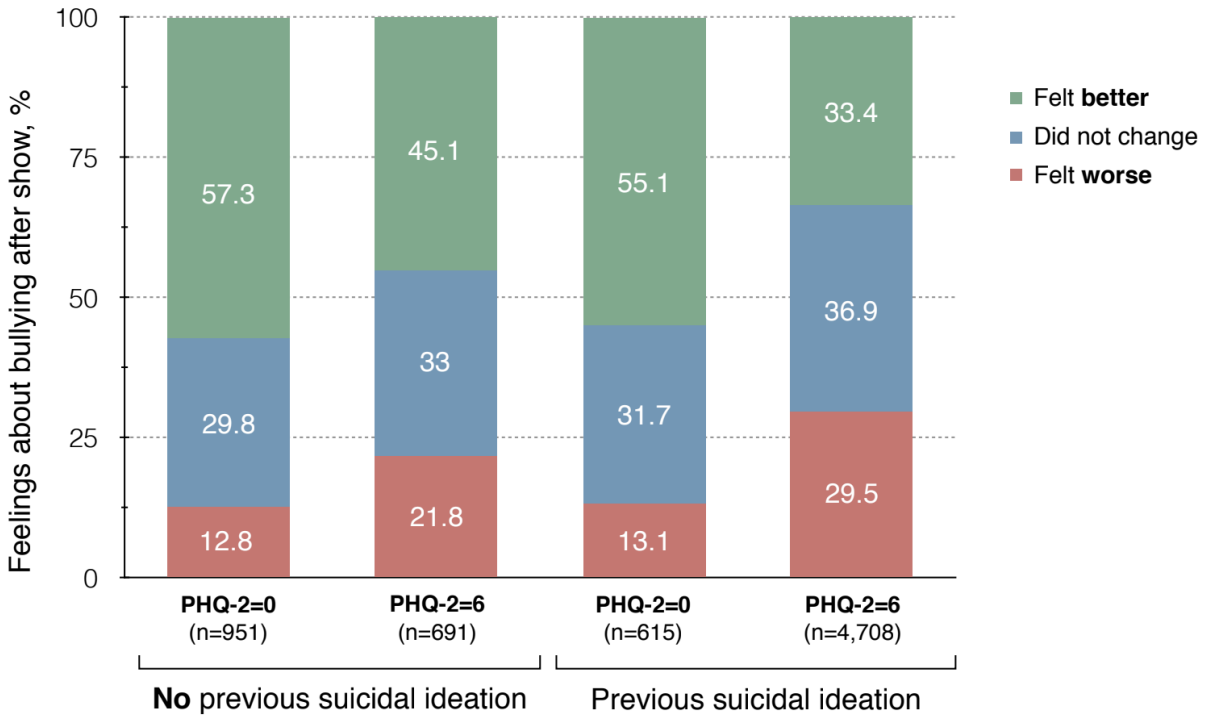
Figure 1. Suicidal Ideation After Watching *13 Reasons Why*



The Patient Health Questionnaire-2 depression scale ranges from 0-6, in which 0 signals no depressive symptoms in the two weeks prior to watching the show and 6 indicates feeling down and anhedonia practically every day during the same period of time.

Appendix #6

Published in the Lancet Psychiatry

Word count: 389 words

Traumatic brain injury and dementia: how strong is the evidence for causality?

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To the editor:

A recent study published on the Lancet Psychiatry found, once again, a prospective association between traumatic brain injuries (TBI) and an increased risk of dementia and Alzheimer's disease[1]. Authors leveraged data from the Danish registries, with hundreds of thousands of cases, allowing interesting analyses, providing a strong case for the association between TBI and Alzheimer's disease. However, previous data has shown that the effect is inconsistent[2] and markedly attenuated by controlling for confounders[3]. What does these data tell us about causality?

One alternative possibility for the study findings is that TBI might occur more frequently in individuals with low cognitive functioning[4], and, therefore, this event might be a risk marker for dementia, but with no causal role. This hypothesis is reinforced by considering the extent to which the association found in the study by Fenn and colleagues is stronger in the first months after the trauma. To address this potential source of bias, authors conducted two sets of supplemental analyses that reinforce TBI's causal role, for which we provide here some new discussion.

First, the study shows that TBI increased the risk of dementia even when it occurred before age 30. Considering the traditional model of Alzheimer's disease, by which affected individuals show normal cognitive functioning during development and early adulthood, reverse causality could be rejected because these young adults performed just like their peers before TBI occurred. However, recent evidence showed that, even in childhood and adolescence, genetic risk for Alzheimer's disease correlates with worse memory performance and lower hippocampal volumes[5]. Therefore, even before the disease becomes self-evident, correlated genetic risk between dementia and TBI might still affect the likelihood of exposure to TBI in subjects with high genetic risk for Alzheimer's disease.

Second, authors argue that the risk of dementia in people with TBI versus those without was almost identical to the risk in people with TBI versus those with non-TBI fractures. However, they do not report if there was an association between non-TBI fractures and dementia. To make this evidence stronger, the authors could provide analyses similar to the ones conducted for TBI considering non-TBI fractures of similar magnitude.

We argue that available data still cannot exclude the hypothesis of reverse causality for the association between TBI and dementia and genetically-informed designs are needed to rule out the role of genetically mediated exposure to environmental factors.

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