

# The worldwide prevalence of ADHD in preterm born children and adolescents

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## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorders in Western countries. ADHD is characterized by symptoms of inattention and/or impulsivity and hyperactivity which can significantly impact on many aspects of behaviour and performance and effect on the quality of life of affected individuals and their families both at school and at home. According to the CDC, about 9.5% children in the USA have been diagnosed with ADHD [1], whereas research based in Europe shows 5-7% of diagnosed with ADHD [2].

Several studies have shown that preterm born children and adolescents have a higher incidence of ADHD. Preterm birth is when a baby is born too early, before 37weeks of pregnancy have been completed. The incidence of the worldwide prevalence of preterm births (<37weeks gestation) was estimated at 11.1% and significant amount of these were born very preterm and extremely preterm [3].

Children who were born very preterm (<33 weeks of gestation) have a 2- to 3- fold increased risk of being diagnosed with ADHD compared to their term born (4-fold risk in those born at < 26weeks) [4].

With the increase in births and survival rates of prematurity, many places in each country are studying about an increased risk for negative long-term outcomes [5]. Specially, children and adolescents born preterm have a great risk of cognitive neurophysiological impairments often associated with Attention- deficit/hyperactivity disorder (ADHD), including attention, inhibitory control, and arousal regulation difficulties. Yet, the underlying risk pathways from preterm birth to ADHD remain poorly understood.

Past studies have given the impression that ADHD is largely predominant disorder in the United States of America (USA) and much less prevalent elsewhere. Because ADHD is related with social and cultural factors of USA. Nevertheless, ADHD is a behavioral disorder common to children of many different races and societies worldwide.

In this study, we investigate the neurocognitive correlates of ADHD symptoms in a high-risk sample of preterm born children and adolescents and present the available data to comparison ADHD prevalence in them of many countries.

## Material and methods

Studies included in systematic review were cross-sectional, prospective, or retrospective studies of subjects diagnosed with ADHD or dimensional symptoms and who were preterm born children or adolescents. The bibliographic search included Medline and PubMed for the term ADHD or attention deficit/hyperactivity disorder and

prevalence and prematurity or preterm, combined with identified papers. Then, we checked to ascertain the population studied and the diagnostic criteria used.

Preterm is defined as babies born alive before 37 completed weeks of gestation. There are sub-categories of preterm birth, based on gestational age; extremely preterm (less than 28weeks) very preterm (28 to 32 weeks) moderate to late preterm (32 to 37weeks).

## Screening tools-procedures

Studies using diagnostic evaluations are required to provide definitive evidence of increased prevalence of disorders in preterm born children or adolescents.

Parents and teacher's questionnaire through checklist and interview or child behavior checklist and clinical assessment were used to confirm the ADHD.

## Main diagnostic criteria in current use for ADHD

Diagnostic and Statistical Manual of Mental Disorders; DSM-IV; or DSM-5 criteria [6]. In diagnostic criteria comprised of 36 questions in three subtests related to the three core symptoms of ADHD: hyperactivity, impulsivity, and inattention. Teacher's questionnaire comprised of 50 items, evaluating auditory comprehension, verbal language, orientation, general behavior, motor behavior, attention, hyperactivity-impulsivity, and academic performance, etc. People with ADHD show a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. In the DSM-5 diagnostic guidelines, they require 6 or more symptoms that appear before age 12, symptoms cause impairment in more than one setting (e.g., home and school), and more and one type of person observes and reports on the child's symptoms (e.g., parent and teacher)

International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 criteria [7]. In the ICD-9 or ICD 10, ADHD is actually referred to under Hyperkinetic disorders, which characterized by the following: "an early onset(usually in the first five years of life), lack of persistence in activities that require cognitive involvement, and a tendency to move from one activity to another without completing any one, together with disorganized, ill- regulated, and excessive activity,"10

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ADHD can be found in the ICD-10 under the code F90.0, Disturbance of Activity and Attention, and "attention deficit" can be defined as one of the following: attention deficit disorder with hyperactivity, attention deficit hyperactivity disorder, or attention deficit syndrome with hyperactivity.

### Two main diagnostic criteria are in current use for ADHD: ICD-10 and DSM-IV

Child Symptom Inventory-4<sup>th</sup> edition (CSI-4) [8]. The research diagnosis in a DSM-IV- referenced rating scale that screens for 13 emotional and behavioral symptoms of childhood. Parent checklist contains 97 items that screen for 15 emotional and behavioral disorders and teacher checklist contains 77 items that screen for 13 emotional and behavioral disorders.

Development and Well-being Assessment interview (DAWBA) [9]. DAWBA is a novel package of questionnaires, interviews, and rating techniques designed to generate ICD- 10 and DSM-IV or DSM-5 psychiatric diagnoses.

Woodcock Johnson-III Tests of Achievement (WJ-III-Ach) [10]. The WJ-III-Ach has 22 tests measuring five academic areas: reading, mathematics, written language, oral language, and academic knowledge and are typical of curricular areas emphasized in the school setting in children and adolescents.

### Diagnostic Interview for ADHD

Conners' Parent Rating scale [11]. Inattentive and hyperactive-impulsive symptoms were measured using the Long Version of Conners' Parent Rating Scale. Summing the scores on the 9-item hyperactive-impulsive and 9-item inattentive DSM IV symptoms subscales forms a total DSM IV ADHD symptoms subscale. There must be six counted behaviors with a score of 2 or 3 out of the nine questions for inattention or hyperactivity to meet DSM-5's criteria for ADHD.

Barkley Functional Impairment Scale (BFIS)-Children and teens [12]. BFIS-CA is designed to obtain parent reports on possible impairment in 15 different domains of everyday activities for children and teens. And included is follow-up parent interview form for obtaining more information about specific problem areas. The scales can provide highly useful information concerning the functional ineffectiveness of individuals in the 15 domains of major life activities assessed by each scale. The scale is usefully employed not only in initial evaluations of individuals but also in the assessment of change in their impairment status over time.

We collected the information from each selected study; first author; country in which the sample was collected; place (i.e., hospital, school, or study sample name) study design; information source (ie, parents or teacher); mean age(weeks); severity of prematurity or range of gestational age; the sample size, male in sampling (%) and prevalence of ADHD. Prevalence effect sizes were calculated as percentage or odds ratio (OR) with 95% confidence intervals for categorical data according to the number of ADHD and non- ADHD subjects among preterm subjects and controls. The characteristics and prevalence of preterm infants diagnosed with ADHD in Europe, America, Asia, and Oceania were suggested with tables and the prevalence rates were compared by continent with studies that accurately presented the prevalence rates. These studies cover a period from 2010 to 2020 published.

Exclusion criteria of all groups were IQ of <70, general learning difficulties, cerebral palsy or any other medical condition that affects

motor disability including epilepsy, as well as brain disorders, any genetic or medical disorder and psychotic disorders, mood, anxiety and personality disorders and mental retardation that might mimic ADHD. Also, they don't have congenital malformations, chromosomal abnormalities or mendelian disorders potentially affecting growth.

### Results

This study investigated the worldwide studies and prevalence of ADHD in children or adolescents born prematurity. A total of 20 studies were identified in a MEDLINE and PubMed® search for ADHD, or attention deficit/hyperactivity disorder and preterm or prematurity. The prevalence rates have been summed from 2010 to 2020. We reviewed the country of residence, authors, published year, assessment method, mean age or ranges of diagnosed with ADHD, gestational range of preterm born child or adolescents, male proportion, and prevalence.

11 were studies of Europe populations and 4 were of America. And 5 were studies of Asia and Oceania. Table 1 shows the characteristics of studies assessing categorical and prevalence of ADHD diagnosis in Europe children and adolescents born prematurity. Although there are some differences between studies, the prevalence of ADHD in preterm born children was higher in patients with ADHD than in full-term born children in this study.

Table 2 shows the characteristics of studies assessing categorical and prevalence of ADHD diagnosis in USA children and adolescents born prematurity. The preterm groups have significantly higher ADHD than the control groups. The study of Table 2, Malinda et al. reported the ADHD in late preterm infants with a population-based birth cohort. They focused on the comparison of subjects in late preterm group (34 to 37weeks) and term (37 to 42 weeks). By 19 years, they found no statistically significant differences in the incidence of ADHD between the late preterm versus term groups (7.7% vs. 7.2%, P=0.84). And there is a significant difference in prevalence between the studies of Megan et al. and Malinda et al. This suggests that the birth age was extremely prematurity in Megan's study and late preterm in Malinda's study.

Table 3 shows the characteristics of studies assessing categorical and prevalence of ADHD diagnosis in Asia and Oceania children and adolescents born prematurity. These preterm groups also have significantly higher ADHD than the control groups. The prevalence of ADHD in these group at least higher than ADHD in term born USA children and adolescents.

And we compared the prevalence range for ADHD in preterm born children and adolescents of Europe, America, Asia, and Oceania in Table 4.

### Discussion

Preterm birth has been associated with an increased risk of ADHD like symptoms and cognitive impairments similar to those seen in ADHD, including attention and inhibitory control difficulties even after accounting for genetic and environmental factors. As survival rate of preterm infants increases, studies of the association of preterm birth and ADHD are increasing on a small or large scale. A meta-analysis demonstrated that preterm-born children (n=1,556) were at heightened risk (relative risk [RR]=2.64) for developing attention-deficit/hyperactivity disorder (ADHD) relative to controls (n=1,720) [13]. A population-based study of Norwegian adults further reported a 1.3- and 5-fold increased risk for ADHD in adults born preterm (<37 weeks) and extremely preterm (<28 weeks), respectively [14].

**Table 1.** Characteristics of Studies assessing Categorical and Prevalence of ADHD Diagnosis in Europe children and adolescents born prematurity.

Country	Author (s),y	Sample	Assessment method	Age mean (range,years)	Gestational range, wk (mean or range)	Sample size	Males in sample (%)	Prevalence (%)
United Kingdom	Rommel et al, 2017	school	Rating scale, Interview	14.9 (11.0-20.0)	24-36	186	54.3	significant elevated rate (p<0.05)
Sweden	Karolina et al, 2011	hospital	ADHD medication	6.0-19.0	24-36	682	67.6	OR =1.6 (p<0.05)
Finland	Kati et al,2010	hospital	Rating scale	4.7	34	172	57.6	OR =1.13,(p<0.05)
United Kingdom	Anita et al,2020	hospital	Rating scale	4.5	25-32	119	54.0	36.2
Germany	Breeman et al. 2016	hospital	Rating scale	6.0-8.0	30.6	260	53.0	OR=1.81,(p<.001), 95%CI=1.27-2.59
Ireland	McNicolas et al, 2015	hospital	Rating scale, Interview	11.6	30.0	64	37.5	significant elevated rate (p<0.05)
United Kingdom, Ireland	Samantha et al, 2010	EPICure Study	Rating scale,	11	<26	307	NS	OR=1.5 (p<0.05)
Netherlands	De Koevoet et al, 2012	school	Rating scale, Interview	7.5	29.3	66	50.0	significant elevated rate (p=0.22)
Norway	Indredavik et al, 2010	hospital	Rating scale	14.0	29.0	65	54.0	significant elevated rate (p<0.05)
Norway	Helga et al,2018	MoBa	Rating scale	5.0, 8.0	24-36	2365	55.4	OR=1.55,OR=1.85
Norway	Grunewaldt et al, 2014	Hospital	Rating scale	10.2	29.7	31	48.0	significant elevated rate (p<0.05)

OR (Odds ratio), CI (confidence interval), NS: not stated, MoBa: Norwegian Mother and Child Cohort Study (MoBa)

**Table 2.** Characteristics of Studies assessing Categorical and Prevalence of ADHD Diagnosis in USA children and adolescents born prematurity.

Country	Author (s),y	Sample	Assessment method	Age mean (range, years)	Gestational range (wk)	Sample size	Males in sample (%)	Prevalence(%)
USA	Megan et al, 2017	school	Rating scale, Interview	10.0	23-28	634	65.3	40.4
USA	Scott et al,2012	Hospital	Rating scale, Interview	6.0	26	148	NS	OR=2.5, (p=0.004)
USA	Malinda et al, 2013	Hospital school	Rating scale, Interview	19	34-36	256	49.6	7.7
USA	Samantha et al, 2010	Hospital	Rating scale	6,11	<26	219	NS	OR=4.3, 95%CI=1.5-13.0

USA: united states of America, OR (Odds ratio), CI (confidence interval), NS: not stated

**Table 3.** Characteristics of Studies assessing Categorical, and Prevalence of ADHD Diagnosis in Asia and Oceania children and adolescents born prematurity.

Country	Author (s), y	Sample	Assessment method	Age mean (range, years)	Gestational range (wk)	Sample size	Males in sample (%)	Prevalence (%)
New Zealand	Woodward et al, 2017	Hospital	Rating scale, Interview	9.0	27.8	223	51.0	OR =3.04, 95%CI=2.19 - 4.21
Japan	Michiko et al, 2020	Hospital	Rating scale	9	Birth weight <1,500	224	NS	12
Taiwan	Shih- Ming et al, 2012	Hospital	Rating scale	6-12	27-43	195	NS	18.5
South Korea	Ju Hyun et al, 2020	Hospital	Rating scale	7-19	32~36	37	59.5	11.6
Australia	Anderson et al, 2011	Hospital	Rating scale	8.1	26.5	189	51	significant elevated rate (p<0.05)

OR (Odds ratio), CI (confidence interval), NS: not stated

**Table 4.** Prevalence range comparison for ADHD in preterm born children and adolescents for Europe, America, Asia and Oceania.

	N	Approximate range for mean age (years)	Prevalence range
Europe	11	4.5-19.0	36.2(n=1) OR =1.6(p<0.05), OR =1.13, (p<0.05), OR=1.81, (p<.001), 95%CI=1.27-2.59 OR=1.5(p<0.05), R=1.55/OR=1.85(n=5)
America	4	6.0-10.0	7.7, 40.4(n=2) OR =2.5, p=0.004, OR=4.3, 95%CI=1.5-13.0 (n=2)
Asia and Oceania	5(3)	6.0-19.0	11.0~18.5(n=3) OR =3.04, 95%CI=2.19-4.21(n=1)

Several perinatal complications of preterm infants are known to associated with an increased risk for long-term neurological sequelae. Perinatal asphyxia may cause hypoxic-ischemic encephalopathy in the neonate with widespread brain injuries and periventricular hemorrhage is a well-known risk factor for cerebral palsy in preterm infants. ADHD

However, the study of Anita Montagna et al suggests that higher inattentive ADHD symptom scores were associated with higher perinatal clinical risk especially more days on mechanical ventilation and more days on parenteral nutrition. And higher hyperactive ADHD symptom scores were associated with lower socioeconomic status [15].

A variety of environmental factors and genetic factors (specific genes have not been identified.) are influential in ADHD. Especially, fetal exposure perinatal medication or toxic substances such as lead, alcohol have been reported to increase the risk of ADHD. The psychosocial environment such as maltreatment or unfavourable socioeconomic conditions also associated with an increased risk of ADHD.

ADHD symptoms in preterm children exhibit specific cognitive correlates that are not observed in term born children with ADHD, and behavioral symptoms of inattention in very preterm children could be completely accounted for by slow responses and impairments

in visuo-spatial working memory [16]. And preterm children with ADHD do not show the typical pattern of very higher prevalence in males compared to females, and they tend not to have co-occurring conduct disorder [17].

Moreover, preterm brain injury is associated with an increased risk of neurodevelopmental disorders, such as ADHD and autism spectrum disorder. The mechanism of gray matter injury in preterm born children is unclear and multifactorial, but inflammation, a high predictor of poor outcome in preterm infants, has been associated with disrupted interneuron maturation in many animal models. Interneurons are important role for regulating brain development and affect the etiology of neurodevelopmental disorders. They are primarily derived from the medial and lateral ganglionic eminence during embryonic development and migrate to the cortex during the early postnatal period, where they mature over the first few weeks of life in mice study, equivalent to early childhood in humans [18]. This maturation process includes maturation of dendritic arbors, and synapses, as well as changes in synaptic activity, and contacts, and transient networks [19]. Specifically in preterm born infants with diffuse white matter injury had reduced number of calretinin interneurons in the cortex and altered arborization of other interneuron populations [20].

Nevertheless, little is known about the physiologic and neurologic pathways of preterm children with ADHD. More studies are therefore required to further investigate these associations. They should include quantitative measures of brain structure and function to further characterize the association between clinical risk and brain development to better understand possible causative pathways leading to ADHD in preterm born children or adolescents.

Here, we compared worldwide characters and prevalence of ADHD in preterm- born children and adolescents. In all but one study, children or adolescents born prematurity had a higher risk of ADHD than full-term born children or adolescents. The study of Table 2, Malinda et al. [21], they found that the prevalence of ADHD in late preterm born children is higher than term born children but no statistically significant differences in the incidence of ADHD between the late preterm versus term groups. It is already well recognized that former preterm infants (those born at gestational age <34 weeks) are at significantly increased risk for neurodevelopmental, learning, and behavioral problem. It is presumed that this increased incidence of neurodevelopmental disability results from medical complications of preterm infants that negatively impact on brain development. Late preterm infants mostly do not experience the range of medical complications and have more short-term morbidity.

In the study of Samantha et al., the correlates and comorbidities of ADHD in preterm children are different clinical presentations than for children born at term. The male predominance in ADHD in the general population is typically not observed in preterm populations and there is no significant increase in conduct disorders in preterm populations [22,23].

Multiple criteria mostly with DSM-IV diagnosis, they suggest that the prevalence of ADHD is at least as high in many non-EU children as in EU children. Certain populations in Asia are known to have an increased odds ratio for ADHD medications as the degree of immaturity at birth increases, and studies have shown a higher prevalence of ADHD symptoms.

There are limitations to this study. ADHD is a difficult to define because all suspected patients are not conducting tests and the criteria built into existing diagnostic classifications are subjective and context

sensitive. In addition, it is necessary to conduct follow-up study on premature infants for a long period of time. In many studies, it is difficult to know exact prevalence by finding a suitable control group.

## Conclusion and perspectives

In conclusion, this study demonstrates that preterm born children are at increased risk of ADHD symptoms in worldwide. And preterm and early term birth increases the risk of ADHD by degree of immaturity. Future opportunities for research, prospective and large-scale, studies with full term born control group cohort for comparison are needed for the study of preterm born children or adolescents. Moreover, research such as functional MRI and diffusion tensor imaging lead to understanding cognitive deficits and behavioral disorders during brain development.

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