

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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ADHD and Age at School Enrollment

According to an analysis of data from a large national insurance database, rates of ADHD diagnosis and treatment are higher among children with a birthday in the month before the age cutoff for kindergarten than in their older peers. This finding implies that behavioral symptoms may be attributed to ADHD in the younger children, rather than being recognized as associated with their younger age.

Methods: The investigators analyzed data from a large claims database that covers all 50 U.S. states and includes commercial payers but not Medicaid claims. The nearly 408,000 children in the study cohort were born between 2007 and 2009 and had completed ≥ 1 year of elementary school by 2015, the end of the study. In the 18 states that enrolled children with a birthday cutoff of September 1, rates of ADHD diagnosis and treatment were compared between children born in August ($n=36,319$), the youngest in their class, and children born in September ($n=35,353$), the oldest. The analysis was repeated in other consecutive birth-month cohorts of school-aged children and in children aged <4 years (before school entry) with August and September birthdays.

Results: Among the school-aged children in states with a September 1 kindergarten entry cutoff, ADHD was diagnosed at a 34% higher rate in children born in August than in those born in September (85 vs 64 per 10,000 children, respectively). In states with the cutoff, the gap in ADHD diagnosis between the 2 ends of the cohort was larger in boys and smaller, lacking statistical significance, in girls. Children born in August also had a 32% higher rate of treatment with a stimulant (53 vs 40 per 10,000 children). Among those receiving medication, August-born children received an average of 120 more days of medication than those born in September.

When the analysis was repeated in states that did not have a September 1 cutoff, the differences between August- and September-born children were smaller and not statistically significant. There were also no significant differences in diagnosis or treatment rates between any other consecutive pairs of months or in August versus September birth groups before school-entry age.

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Discussion: These observations emphasize the importance of the context of other children's behavior in influencing teachers' identification of ADHD. Considering the age of a child relative to their peers may help clinicians assess whether behaviors reported by teachers and parents are indicative of ADHD.

Layton T, Barnett M, Hicks T, Jena A, et al: Attention deficit-hyperactivity disorder and month of school enrollment. *NEJM* 2018;379 (November 29):2122–2130. doi 10.1056/NEJMoa1806828. From Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIH. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

TBI and Neurodevelopmental Disorders

Traumatic brain injury in early childhood was associated with subsequent development of ADHD, autism spectrum disorder, and developmental delay in a large cohort study.

Background: Previous studies of TBI and ADHD have focused on school-aged children and adolescents. Because a diagnosis of ADHD is usually made in children aged 3–6 years, the likely sequence of events was previously unresolved. Theoretically, ADHD increases the risk of accidents and accompanying injury. No large-scale epidemiologic study of the incidence of autism following TBI was previously available. Although studies of the causes of autism have focused on genetics, environmental factors such as TBI should not be ignored.

Methods: The analysis was based on Taiwan's National Health Insurance Research Database. The TBI cohort consisted of all children aged <3 years who had a TBI diagnosed clinically or by brain imaging in 1998–2008 and who had no previous diagnosis of ADHD, autism, or developmental delay. Members of the cohort were age- and gender-matched with 4 controls who had not experienced a TBI and had no neurodevelopmental disorder. Children were followed through 2011.

Results: About 7800 children were included in the TBI cohort. The injuries occurred at an average age of 1.5 years and were mild in 94% of cases. TBI was associated with significantly increased incidence of each type of neurodevelopmental disorder. The incidence of ADHD during follow-up was 6.2% in the TBI cohort and 4.0% in controls ($p < 0.001$). Similar trends were observed for autism spectrum disorders (incidence, 0.8% vs 0.4%; $p < 0.001$) and developmental delay (incidence, 2.9% vs 1.1%; $p < 0.001$). Neurodevelopmental disorders were identified at a significantly earlier age in the TBI cohort than in the control group, on average about 1–1.5 years. After adjustment for potential confounding factors—demographic data and comorbid perinatal conditions such as infections, birth trauma, and birth asphyxia—risk for each of the diagnoses was significantly elevated in children who had experienced a TBI, compared with controls, with hazard ratios* of 1.59 for ADHD, 2.06 for autism spectrum disorders, and 2.61 for developmental delay.

Children injured before age 1 year had a higher incidence of each of the 3 disorders than children injured when they were older. Repeated TBI increased risk of ADHD and developmental delay to a larger extent than a single TBI. A longitudinal analysis showed that children whose TBI occurred before the age of 3 years continued to have higher cumulative incidence of the 3 disorders throughout the subsequent ≥ 10 years.

Discussion: The mechanism underlying the association between TBI and neurodevelopmental disorders is unclear. However, MRI studies have shown alterations in cortical thickness and activation following brain injury. In addition, brain injury may impair theory of mind, which develops at an early age and has been suggested to play a role in neurodevelopmental disorders.

Chang H-K, Hsu J-W, Wu J-C, Hunag K-L, et al: Traumatic brain injury in early childhood and risk of attention-deficit/hyperactivity disorder and autism spectrum disorder: a nationwide longitudinal study. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11857. From Taipei Veterans General Hospital, Taiwan; and other institutions. **Funded by Taipei Veterans General Hospital. The authors declared no competing interests.**

*See Reference Guide.

Youth Trauma and Early Adult Psychotic Experiences

Trauma during childhood or adolescence was associated with the occurrence of psychotic experiences in early adulthood, according to the results of a longitudinal study. The results support the idea that trauma has a causal relationship with psychotic experiences.

Background: Research has suggested that childhood trauma is associated with increased risk of psychosis, but the causality of the association has remained unclear and few studies have compared the roles of different trauma types. Studies examining whether there is a critical period of risk have had inconsistent results. The present study was undertaken to clarify the effects of trauma type, developmental age, exposure frequency, and confounding variables on the association between childhood trauma and later psychotic experiences.

Methods: The study was based on data from the Avon (U.K.) Longitudinal Study of Parents and Children. Members of the cohort were born in 1991–1992 and followed until 2017. Psychotic-like symptoms were assessed when cohort members were aged 12 years and again at 18 years, using the psychosis-like symptoms semi-structured interview. Children were asked whether they had any of 12 specific psychotic experiences (e.g., hallucinations, delusions, experiences of thought interference) during the previous 6 months. As 18-year-olds, they were questioned about onset of psychosis-like symptoms since age 12 years. Trauma variables were obtained from questionnaires completed by parents or self-reported by participants. The questionnaire items were grouped into 6 different trauma types (i.e., physical, sexual or emotional abuse, emotional neglect, domestic violence, bullying), and exposures were grouped by the age at which they occurred: early childhood (through age 4 years), middle childhood (5–10 years), and adolescence (11–17 years).

Results: The sample consisted of 4433 individuals, 9.3% of whom were rated as having an actual or suspected psychotic experience by age 18 years. Of many potential confounding factors assessed, several were significant mediators of the relationship between trauma and psychotic experiences: gender, parental drug use, living in crowded conditions, low family income, and maternal education status. After adjustment for these factors, participants who had psychotic experiences were more frequently exposed to trauma than those with no psychosis. (See table.) No specific type of trauma was significantly more strongly associated than others with risk of a psychotic experience.

Association Between Trauma Types and Later Psychotic Experiences		
Trauma type	Proportion of patients affected	Adjusted odds ratio (OR)* in exposed patients [‡]
Any	64.5%	2.91
Physical abuse	23.1%	1.69
Emotional abuse	23.7%	1.81
Bullying	32.9%	2.05
Sexual abuse	11.0%	2.50
Domestic violence	21.9%	1.79
Emotional neglect	7.8%	1.89

[‡]All ORs are statistically significant ($p < 0.001$).

Risk of psychotic experiences increased with the number of different types of trauma experienced, from 1 (OR, 1.94) to ≥ 3 (OR, 5.19). Exposure to trauma during any of the age periods was associated with risk, but the association was strongest for exposures during adolescence.

Discussion: These results support a causal association between childhood trauma and later psychosis. Although the mechanism that underlies the association is unclear, it appears to be dependent on the severity, chronicity, and possibly recency of exposure.

Croft J, Heron J, Teufel C, Cannon M, et al: Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.3155. From the University of Bristol, U.K.; and other institutions. **Funded by the U.K.'s Medical Research Council; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Individualizing Methylphenidate

A wide array of modified-release methylphenidate products designed for once-daily dosing are now available, each characterized by a distinctive exposure time course. The previous standard of care, immediate-release (IR) methylphenidate, with its relatively short half-life requiring twice- or thrice-daily dosing, has been largely replaced by these newer agents. The modified-release agents differ in the proportion of immediate-release (IR) methylphenidate they contain and in their formulation technology. Their availability allows the prescriber to tailor daily methylphenidate exposure to each patient's needs, using such considerations as the length of the school day, homework load, domestic harmony, or an adult's workday demands.

Three key features distinguish the available modified-release methylphenidate products: the percentage of the dose formulated as IR, allowing for patient-specific needs in the rate of onset of action; early exposure, defined as the proportion of active ingredient released within the first 3 hours after administration; and the time to peak concentration (T_{max}), which is a surrogate for the duration of drug effects. (See table for an overview of pharmacokinetic data obtained from each product's FDA-approved labeling for healthy adults in a fasting state.)

Current methylphenidate products			
Common trade names	% IR	% released in 0–3 hours	T_{max} (hours)
Short-acting (approximately 4 hours)			
<i>Ritalin, Focalin</i>	100%	33–39%	2–2.4
Intermediate-acting (approximately 6–8 hours)			
<i>Metadate ER</i>	0%	17%	4.1
<i>Metadate CD, Quillichew ER, Quillivant XR, Cotempla XR-ODT</i>	15–30%	13–15%	4–5
Long-acting (approximately 10–12 hours)			
<i>Concerta</i>	22%	16%	6
<i>Aptensio</i>	37%	17%	2–8
<i>Ritalin LA</i>	50%	30%	1.8/6.1 [±]
<i>Focalin XR</i>	50%	21%	1.5/6.5 [±]
<i>Daytrana</i> (transdermal)	0%	—	10

[±]For low and high doses, respectively

Oral clearance of methylphenidate is lower, and pharmacokinetics are more variable in children. Food can delay T_{max} values and may increase total exposure to the drug. In addition to the estimates in the table here, each product's labeling contains curves showing the unique exposure time course properties of each product, which can be matched with the individual needs of patients. Within products, the dose-proportional nature of methylphenidate activity can enable product-specific titration to an optimal maintenance dose.

In recent developments, following a large number of reports of reduced efficacy especially later in the day, 2 generic products have lost their "AB" designation as bioequivalent to OROS methylphenidate. They are now designated as "BX"—i.e., no longer substitutable for the innovator OROS methylphenidate (*Concerta*). A triple-layer dexamethylphenidate formulation, mimicking the old standard of practice of thrice-daily dosing, is in development. A recently approved evening-dose formulation (*Jornay PM*) is designed to delay the first pulse of drug release until 12 hours after ingestion, followed by extended release during the day. Also in the pipeline are a new prodrug form of methylphenidate with an even longer duration of action and other methylphenidate homologues with more specificity for target mechanisms and an even longer duration of action.

Patrick K, Radke J, Raymond J, Koller L, et al: Drug regimen individualization for attention-deficit/hyperactivity disorder: guidance for methylphenidate and dexamethylphenidate formulations. *Pharmacotherapy* 2018; doi 10.1002/phar.2190. From the Medical University of South Carolina, Charleston; and the University of Tennessee College of Pharmacy, Memphis. **Source of funding not stated. The authors declared no competing interests.**

Sugar Consumption and ADHD

In a population-based cohort study, high sucrose consumption was associated with an increased prevalence of ADHD in 6-year-old boys. However, associations were not found in girls or with ADHD onset in later childhood.

Methods: Subjects in this ongoing cohort study were enrolled at birth, in 2004 or later. The present analysis was based on evaluations when the children were aged 6 and 11 years. ADHD was identified in 6 and 11 year olds using the ADHD module of the Development and Well-Being Assessment, a 31-item parent questionnaire based on DSM criteria. At both evaluations, mothers or caregivers were administered a food frequency questionnaire with a 1-year recall. About 10 foods were identified as contributors of sucrose to the children's food intake, with sucrose content of foods estimated from USDA data. Sucrose consumption was divided into tertiles, and then combined to create 5 categories based on the pattern between the 2 evaluations: always low, always medium, always high, increasing, and decreasing.

Results: The analysis included 3721 6 year olds, of whom 3497 also provided follow-up data at age 11 years. The mean sucrose consumption was higher in children with ADHD than in those without, at both ages 6 and 11. (See table). Because mean sucrose consumption differed significantly between boys and girls, the genders were analyzed separately. At age 6 years, after adjustment for multiple other factors, sucrose intake was significantly associated with ADHD in boys (1.8% in the lowest tertile, 2.8% in the middle, 5.8% in the highest; $p=0.02$). ADHD prevalence was not associated with sucrose consumption in 11-year-old boys or in girls at either age. The 5 different temporal patterns of sugar intake were not linked with ADHD onset between the ages of 6 and 11 in either boys or girls.

Mean sucrose consumption (cross-sectional) in children with/without ADHD			
	ADHD	No ADHD	Significance
Age 6 years	131 g/day	108 g/day	$p=0.003$
Age 11 years	187 g/day	148 g/day	$p<0.001$

Discussion: In this study population, sugar accounted for about 30% of all calories consumed by children, far above the World Health Organization's recommended 10% limit. An association between sucrose intake and ADHD is biologically plausible. However, it is also possible that higher sugar consumption in children with ADHD is a consequence of the disorder rather than a cause.

Del-Ponte B, Anselmi L, Assunção M, Tovo-Rodrigues L, et al: Sugar consumption and attention-deficit/hyperactivity disorder (ADHD): a birth cohort study. *Journal of Affective Disorders* 2019;243 (January):290–296. doi 10.1016/j.jad.2018.09.051. From the Federal University of Pelotas, Brazil; and other institutions. **Funded by the Brazilian Public Health Association; and other sources. The authors declared no competing interests.**

Electronic Device Use and Psychological Distress

According to a series of national polls of U.S. adolescents, elevated use of electronic devices has a dose-related association with psychological distress. Although the study could not determine the causal direction of the association or whether it is reciprocal, it is likely due at least in part to the displacement hypothesis—i.e., elevated use of electronic devices deprives the individual of opportunities for constructive social or physical activity.

Methods: The authors analyzed data from the national Youth Risk Behavior Survey, which samples representative groups of U.S. high-school students in biannual waves. This analysis was based on 5 waves of questionnaire data obtained between 2009 and 2017, with sample sizes of about 15,000 students per year. Elevated use was defined as use of a computer, smartphone, gaming device, or other electronic device for non-school-related purposes for ≥ 3 hours per weekday. The outcome variable, psychological distress, was a composite of 3 items: sadness or hopelessness leading to discontinuation of usual activities, serious suicidal ideation, and a suicide plan. To reduce selection bias, pairs of adolescents with and without elevated use were propensity score matched* on the basis of age, gender, race, body weight status, bullying victimization, smoking, alcohol use, physical activity, and insufficient sleep.

Results: The prevalence of elevated electronics use increased from about 25% in 2009 to a plateau of 41% in 2013, probably reflecting market saturation of smartphones. Device use for ≥ 3 hours/day was more prevalent in boys until 2011, after which there was no difference between genders. The proportion of adolescents reporting ≥ 1 of the 3 mental health issues also increased, from 32% in 2009 to 36% in 2017 ($p < 0.001$). During the last survey year, depression or sadness was present in 32% of adolescents, suicidal ideation in 17%, and a suicide plan in 14%. The proportion of adolescents with elevated electronic use was associated in a dose-related fashion with the number of mental health issues in each survey year ($p < 0.001$).

Discussion: Although it is possible that psychological distress drives increased screen time as a coping mechanism for low mood or loneliness, it is at least equally likely that excessive screen use negatively affects mood. In addition to the displacement hypothesis, the causal explanation may include sleep deprivation and cyberbullying.

Wang C, Li K, Kim M, Lee S, et al: Association between psychological distress and elevated use of electronic devices among U.S. adolescents: results from the youth risk behavior surveillance 2009-2017. *Addictive Behaviors* 201;90 (March):112-118. doi 10.1016/j.addbeh.2018.10.037. From Western Washington University, Bellingham; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Odds Ratio: A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio > 1 indicates that the event is more likely to occur in that group than in the comparison group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

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