



# Child psychiatry cannot afford not to properly study differences by sex

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The current issue of ECAP covers relevant, yet understudied, topics for child and adolescent psychiatry practice. Among others, it covers differences by sex in clinical presentation, response, and outcome of psychiatric disorders, the impact of potentially preventable factors on cognition and mental health, and the inclusion of users' views on treatment evaluation.

Two articles focus on clinical differences between girls and boys with autism spectrum disorder (ASD). Sanchez et al. [1] assessed differences in internalizing and externalizing behaviors in 85 boys and girls (8–16 years) diagnosed with ASD and with a Full Scale IQ > 64. They report the surprising finding that, using the Externalizing and Internalizing composite scales of the Behavior Assessment System for Children, Second Edition (BASC-2), girls showed higher externalizing scores, more problems with Anger Control, higher scores in Bullying Others, Emotional Control than boys, and no differences on Internalizing scores. The sexes did not differ on Awareness, Cognition, Communication, Mannerisms, Motivation as measured by the Social Communication Scale (SRS) subscales. The authors claim that the higher proportion of externalizing behaviors in girls in this sample may imply a referral bias towards girls with higher behavioral difficulties and reflect under-referrals of girls with different clinical presentations. Meanwhile, Bourson and colleagues performed a literature review of 19 studies to describe the characteristics of restricted interests in girls with ASD [2]. Despite the higher source of bias depending on the instruments and the different ways to administer them, their results show fewer restricted interests in girls than in boys and indicate that girls' interest differed also qualitatively: they are closer to neurotypical girls

than to boys with ASD. Although many questions remain, such as the role of age or IQ on phenotypic sex-differences, this review points at the need to gather more data on how ASD manifests in girls, particularly at younger ages, and how it compares with neurotypical controls, instead of relying solely on sex comparisons between people with ASD diagnosis.

Van Meter et al. [3] evaluated the course and outcome of attention deficit hyperactivity disorder (ADHD) in participants of the Longitudinal Assessment of Manic Symptoms (LAMS) with childhood onset ADHD at baseline and at least 2 follow-ups ( $N=431$ ). They found that half had a consistent course of ADHD, nearly 40% a remitting course, and the remaining participants a fluctuating course. Although not designed to find sex-related differences in ADHD course, this study revealed sex differential trends in symptom stability, with boys having persistent or fluctuating courses more frequently than girls and girls being more likely to have remitting courses, and differences in symptom presentation, with boys reporting more symptoms of hyperactivity than girls ( $t=2.09$ ,  $p=0.038$ ).

Differences in the impact of puberty's between both sexes is another relevant aspect in need of study. Rosenthal et al. [4] compared pubertal timing between girls with and without ADHD and between females with ADHD differing by history of stimulant use during childhood from the Berkeley Girls with ADHD Longitudinal Study, a prospective investigation following 140 girls with ADHD and 88 age-matched neurotypical peers from childhood into adulthood (209 in adolescent follow-up). Pubertal timing showed no differences between girls with and without ADHD. However, among females with ADHD, those who had received stimulant medication during childhood menstruated significantly later (12.39 years ( $SD=1.16$ )) than those without (11.87 years ( $SD=0.99$ )), with medium to low effect size (Cohen's  $d=0.48$ , 95% CI [0.06, 0.89]).

Researchers have seldom explored the biological correlates of sex differences on resilience. Now Pan et al. [5] used structural magnetic resonance imaging to estimate brain gray matter volume in 231 healthy adolescents (52% females)

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and found a differential association by sex. They report a positive correlation among males and a negative correlation among females between psychological resilience and gray matter volume in the left ventrolateral prefrontal cortex (a brain region engaged in emotion regulation and cognitive control), and the anterior insula, which modulates stress-related affective and behavioral responses. The authors suggest that these associations may be linked to sex differences in the hypothalamic–pituitary–adrenal axis and brain maturation during adolescence, but also point at differences between both sexes in stress response strategies. Results from these studies [1–5] call for a more thorough investigation of sex differences in child psychiatry, particularly in disorders whose prevalence varies by sex, such as neurodevelopmental disorders.

The impact of external factors on child and adolescent mental health is another matter this ECAP issue explores. Hrdlicka et al. [6] studied the association between age at diagnosis of ASD and demographic variables such as socioeconomic status, parental education level, age of parents, Autism Diagnostic Observation Schedule (ADOS) scores, and intellectual disabilities in a cohort of 324 children aged 2 to 16 years. This study used multiple regression analysis and the classification tree method, a person-centered approach, on the same data. The classification tree scheme showed that symptom severity, but also paternal age and maternal education, influenced time at diagnosis, with youngest age at diagnosis in children with higher communication and social domain scores and paternal age at delivery  $\geq 29$  years, and oldest age at diagnosis in those with lower clinical scores and with maternal education at the elementary school level. In a cohort of preschool children ( $n=2509$ , mean age =  $24.2 \pm 1.3$  months), Luo et al. [7] showed that around 1 in 5 children this age had psychosocial problems and that their appearance and maintenance were associated with lower socioeconomic status as reflected by lower maternal education level, single-parent families, and financial difficulties.

Using a data-driven approach including 8-year follow-up data of a representative Chinese national sample of children, Wang et al. [8] developed an environment-wide association study aimed at identifying potentially modifiable factors associated with childhood cognitive performance. The study supported negative associations between cognitive performance and factors such as family size and the percentage of children and of poverty in the community, and positive associations with parental involvement on education and with still less studied factors such as paternal happiness and mobile Internet use. Descarpentry et al. [9] also explored the relationship between technology use and psychopathology. Using data from the French EpiCov cohort study, an online interview of parents of children 3 to 14 years old ( $N=1,089$ ,

51.5% girls), they assessed the association of persistent high screen use in the first year of the COVID-19 pandemic and internalizing and externalizing behaviors [9]. In this study, high screen time was not associated with internalizing behaviors or emotional symptoms, but showed weak associations both with a higher risk of peer problems (regardless of age or sex) and, in children 11 to 14 years old, with behavioral problems and externalizing behaviors. Although the results of these studies [8, 9] need to be understood as belonging to specific contexts, they stress the need for further exploring how exposure to technology affects children and adolescents' cognitive development and mental health. This is particularly relevant given the recent sharp rise in the use of the Internet on mobile telephones among children and adolescents, the mixed findings on such use with mental health outcomes, and the design limitations of studies.

Finally, some studies stress the relevance of including patient and families' views in the evaluation of the treatment they receive. Shilton et al. [10] reported on parents' experience of the shared parent–child stay in an inpatient unit. They signaled that joint hospitalization had a positive impact on the process of separation from the child and on building confidence with the treating team, with a positive impact on the child's recovery. Ruprect-Smith et al. interviewed children and young people from minority backgrounds and found a positive impact on outcomes of factors related to perception of personalized treatment such as support and the right therapist, while experiences of inequalities and stigma had the opposite effect [11].

As detailed above, this issue of ECAP deals with important transdiagnostic aspects for child and adolescent psychiatry. Among them, one of the most relevant aspects that is still understudied is the influence of sex in clinical presentation and its translation in clinical practice. Sex is a biological determinant that adds more complexity to the evolving clinical presentation of developing children and adolescents. Some of the standard practices in research to address this complexity are using sex as a covariate in combined analyses or excluding the minority sex, such as girls with neurodevelopmental disorders, from studies. However, not considering sex as a relevant determinant and to plan sex-related outcomes already at the design phase of studies, makes it more difficult to properly diagnose and treat a sizeable proportion of the population. Given the current trends towards developing precision psychiatry approaches in child psychiatry [12], including sex and sex-related outcomes in research that informs child and adolescent mental health clinical practice should be standard practice.

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