

**Title:** Association of gestational age at birth with symptoms of Attention-Deficit/Hyperactivity Disorder in children and adolescents with Down syndrome

**Authors:** Laura del Hoyo Soriano<sup>1</sup>, Tracie Rosser<sup>2</sup>, Debra Hamilton<sup>2</sup>, Taylor Wood<sup>1</sup>, Leonard Abbeduto<sup>1</sup>, Stephanie Sherman<sup>2</sup>.

**Introduction:** Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms are frequently reported in individuals with Down syndrome (DS) (Oxelgren et al., 2017), with up to a 40% meeting diagnostic criteria (Ekstein, Glick, Weill, Kay, & Berger, 2011). Considering the variation in ADHD symptoms in this population, a key challenge is to identify mechanisms underlying this variability. The association between prematurity and ADHD is well established in the euploid population. Indeed, it has been shown that even late preterm children score higher on ADHD symptoms compared to children born at gestational week 40 or later (Ask et al., 2018; Sucksdorff et al., 2015). However, the impact that a low gestational age has on later ADHD is unknown for those with DS, and potentially has implications for targeted early intervention. The current study was designed to investigate the association between gestational age (GA) at birth and symptoms of ADHD in 106 children and adolescents with DS while adjusting for confounder factors such as chronological age CA, sex, and IQ.

**Method:** 105 individuals with DS (49 males and 56 females) between the ages of 6 and 18 years (M=11.1 years, SD= 3.4,) were included in the current study. Participants were drawn from the Down Syndrome Cognition Project. This study had an exclusion criterion of gestational age less than 35 weeks, as well as other exclusion criteria associated with birth trauma. Symptoms of ADHD were assessed using the Conners Parent Rating Scale, Third Edition (Conners-3) (Conners, 2008). For the analyses, we used T-scores for the Inattentive and the Hyperactive-Impulsive subscales, as well as the Global Index T-score. General cognitive level was assessed using the Kaufman Brief Intelligence Test, 2nd Edition (KBIT-2; Kaufman & Kaufman, 2004). Data regarding pregnancy history was obtained through medical records and a phone interview. In order to decide whether our analyses needed to adjust for potential covariates, we first examined the association between GA and ADHD outcomes (i.e., Inattentive T-score, Hyperactive-Impulsive T-score, and Global Index T-score) for each of the following potential covariates: (1) CA of participant with DS at time of ADHD measurement, (2) KBIT-2 composite age-corrected score at time of ADHD measurement, (3) sex of participant with DS, (4) maternal age at birth, (5) maternal level of education and (6) family income. We then examined the contribution of GA to ADHD outcomes (i.e., Inattentive T-score, Hyperactive-Impulsive T-score, and Global Index T-score) in independent linear regression models. Multiple regression models were adjusted, when necessary, for potential covariates.

**Results:** Multiple regression models show that GA is associated with T-scores for the Inattentive and Hyperactive-Impulsive subscales both before and after adjusting for CA of participants with DS at time of ADHD measurement. In addition, GA is associated with the Global Index of the Conners-3, before and after adjusting for CA, and the KBIT-2 composite age-corrected score at time of ADHD measurement.

**Discussion:** Our results are similar to those previously reported in the euploid population, suggesting that lower gestational age may increase ADHD symptoms in children and adolescents with DS. Although much remains to be explored, our findings indicate that variation in gestational age should be addressed when considering ADHD outcomes in children and adolescents with DS. Doing so may guide early behavioral interventions to optimize neurodevelopmental outcomes in this population. Implications of our results will be further discussed.

#### References:

- Achenbach, T. M., Dumenci, L., & Rescorla, L. A. (2003). DSM-Oriented and Empirically Based Approaches to Constructing Scales From the Same Item Pools. *Journal of Clinical Child & Adolescent Psychology*, 32(3), 328–340. [https://doi.org/10.1207/S15374424JCCP3203\\_02](https://doi.org/10.1207/S15374424JCCP3203_02)
- Ask, H., Gustavson, K., Ystrom, E., Havdahl, K. A., Tesli, M., Askeland, R. B., & Reichborn-Kjennerud, T. (2018). Association of Gestational Age at Birth With Symptoms of Attention-Deficit/Hyperactivity Disorder in Children. *JAMA Pediatrics*, 172(8), 749. <https://doi.org/10.1001/jamapediatrics.2018.1315>

Conners, C. K. (2008). *Conners 3rd edition manual*. Toronto, Ontario, Canada: Multi-Health Systems.

Ekstein, S., Glick, B., Weill, M., Kay, B., & Berger, I. (2011). Down syndrome and attention-deficit/hyperactivity disorder (ADHD). *Journal of Child Neurology, 26*(10), 1290–1295. <https://doi.org/10.1177/0883073811405201>

Oxelgren, U. W., Myrelid, Å., Annerén, G., Ekstam, B., Göransson, C., Holmbom, A., ... Fernell, E. (2017). Prevalence of autism and attention-deficit–hyperactivity disorder in Down syndrome: a population-based study. *Developmental Medicine and Child Neurology, 59*(3), 276–283. <https://doi.org/10.1111/dmcn.13217>

Sucksdorff, M., Lehtonen, L., Chudal, R., Suominen, A., Joelsson, P., Gissler, M., & Sourander, A. (2015). Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/Hyperactivity Disorder. *PEDIATRICS, 136*(3), e599–e608. <https://doi.org/10.1542/peds.2015-1043>

<sup>1</sup> UC Davis Mind Institute

<sup>2</sup> Emory University School of Medicine