

The role of prenatal exposure to serotonin reuptake inhibitor antidepressants, child sex, and serotonin-related genotype on pain-related somatic symptoms and global physical health in young children

Katelynn E. Boerner PhD^{1*}; Melissa Glier PhD³; Ursula Brain BA¹; Amrit Dhariwal PhD²; Ruth E. Grunau PhD¹; Tim F. Oberlander MD^{1,4}

Departments of ¹Pediatrics and ²Psychiatry, University of British Columbia, and BC Children's Hospital Research Institute, Vancouver, Canada; ³Public Health Laboratory, BC Center for Disease Control, Vancouver, Canada; ⁴School of Population and Public Health, University of British Columbia, and BC Children's Hospital Research Institute, Vancouver, Canada

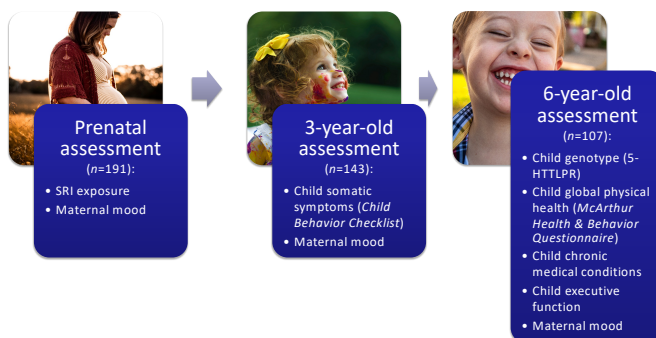
*Corresponding author: katelynn.boerner@bcchr.ca

1. Background

- Somatic symptoms and poor health in childhood may be a precursor to chronic pain [1].
- Little is known about what early life factors predisposes the development of physical symptoms.
- Serotonin is critical to the development of systems that regulate stress and pain-related behaviours.
- Previous studies have shown an impact of prenatal serotonin reuptake inhibitor (SRI) exposure on pain response in human infants [2,3], and animal models have suggested sex-specific impacts of early SRI exposure [4].
- The present study investigated the impact of child sex, prenatal exposure to SRI antidepressants, and serotonin-related genotype on parent-reported childhood health outcomes.

2. Methods

Data from a longitudinal cohort study assessed the following:



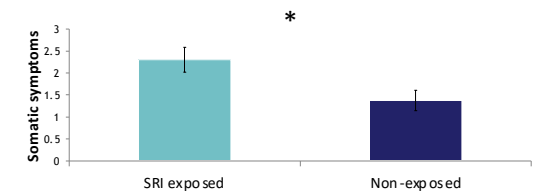
Genotype was coded as "L_AL_A" (carriers homozygous for the long allele, associated with high transcriptional activity) or "S or L_G" (carriers of any functionally similar allele, associated with lower transcription rates). We examined a specific variant, rs25531, which represents an A>G substitution.

3. Results

During the prenatal period 39.8% of children were exposed to SRIs and 44.5% of mothers self-reported a diagnosis of depression. Of the entire sample, children were 52.4% female and 20.9% had the L_AL_A genotype.

Children's somatic symptoms at 3 years old

A three-way analysis of variance (ANOVA) demonstrated a main effect of SRI exposure, $F(1,133) = 5.931, p = .016, \eta_p^2 = .043$; **somatic symptoms were more common amongst children exposed prenatally to SRIs than those who were not.** There was no main effect of child sex or genotype, and no interactions.



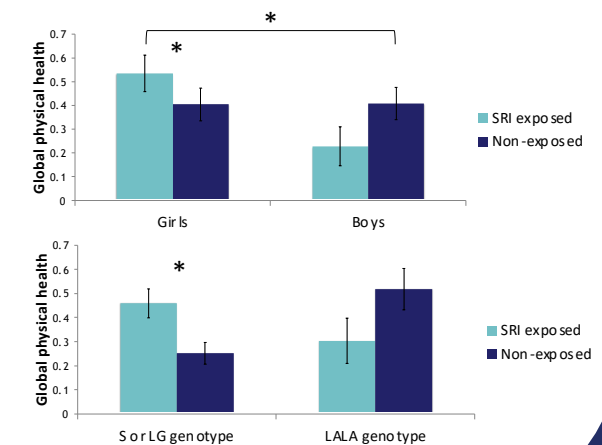
*p < .05. Graph presents estimated marginal means and SEM. Covariates: maternal mood (prenatal and 3-yr)

Children's global physical health at 6 years old

A three-way ANOVA demonstrated a main effect of child sex, $F(1,94) = 4.230, p = .042, \eta_p^2 = .043$, where **worse health was observed in girls compared to boys.**

A SRI exposure by child sex interaction was also observed, $F(1,94) = 4.710, p = .033, \eta_p^2 = .048$, where **SRI-exposed girls had worse health than non-exposed girls.**

There was a significant interaction between SRI exposure and genotype, $F(1,94) = 6.929, p = .010, \eta_p^2 = .069$. **SRI-exposed children with the S or L_G genotype had worse health compared with non-exposed.**



*p < .05. Graphs present estimated marginal means and SEM. Higher scores = more health concerns or impairment. Covariates: maternal mood (prenatal and 6-yr), child somatic symptoms at 3 yrs, child executive function and child chronic medical conditions at 6 yrs.

4. Discussion

- Early changes in serotonin signalling may shape physical health across early childhood, particularly for girls. Genotype appears to be an important vulnerability factor in the impact of prenatal antidepressant exposure.
- These results further our understanding of factors that may be involved in the emergence of sex differences in physical symptoms. There is a need to investigate trajectories of developmental vulnerability for girls and boys from early life.
- Further research is needed to understand how to mitigate these risk factors, e.g., enhanced screening or preventative interventions for girls with prenatal SRI exposure.