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PRENATAL DIOXIN EXPOSURE AND NEUROCOGNITIVE FUNCTIONING IN THE SEVESO SECOND GENERATION STUDY

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Introduction:
Prenatal 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure has been shown to alter sexual differentiation of the brain in animal models, impacting pubertal development, behavior, cortical dominance, and cognition.[1-8] Epidemiological evidence also links early life dioxin exposure to impaired neurodevelopment but these effects have been difficult to isolate from neurotoxic co-exposures with PCBs.[9-15] Thus, the specific effects of perinatal TCDD on human neurodevelopment, and its differences by sex, warrant further investigation.

Materials and methods:
The Seveso Women's Health Study (SWHS), initiated in 1996, is a well-characterized cohort of 981 Italian women who lived in proximity to an industrial accident in the summer of 1976 that resulted in the highest residential TCDD exposures on record. In 2014, we began enrolling offspring born after the accident (~1,000 children aged 2-38 years) as part of the Seveso Second Generation Health Study.

Second generation children, aged 7-17 years old, completed a neurocognitive assessment spanning executive function and reverse learning (Wisconsin Card Sorting Test), non-verbal intelligence (Raven's Progressive Matrices), attention and hyperactivity (Connor's Continuous Performance Test), and memory (Rey's Auditory Verbal Learning Test). In utero TCDD exposure was defined as initial TCDD concentration measured by high-resolution mass spectrometry in maternal serum collected soon after the explosion. The associations between maternal 1976 serum TCDD levels and measures of neuropsychological functioning in offspring were modeled with multivariate generalized estimating equations (GEE) to account for correlation among siblings. Because TCDD is suspected to disrupt brain development through altered hormonal signaling and because generally ADHD and other neurological conditions tend to vary in prevalence by sex, we also examined sex as an effect modifier in both stratified regression analyses and with an interaction term.

Results and discussion:
To date, 161 children, averaging 12.5 (±2.8) years and 53% male, have completed the assessment. Geometric mean maternal serum TCDD near the time of the accident was 105 ppt, lipid-adjusted (range: 5.5 – 9,140). In multivariate models, a 10-fold increase in maternal TCDD was not significantly associated with reverse learning (adj-ß=-0.61, 95% CI -2.44, 1.22), working memory (adj-ß=-0.65, 95% CI -0.68, 2.00), or non-verbal intelligence (adj-ß=--0.25, 95% CI -2.40, 1.91). Models using TCDD levels extrapolated to the pregnancy as well as sex-stratified results will be presented.

This is the first study of the exclusive effects of prenatal TCDD exposure on child neurodevelopment across a myriad of neuropsychological domains in a population with well-characterized exposure.

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