A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP3815.

Attention Worthy: Prenatal Phthalate Exposure and Subsequent ADHD Diagnosis

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https://doi.org/10.1289/EHP3815

Exposure to phthalates, a class of endocrine-disrupting chemicals (EDCs) used in plastics manufacture, is ubiquitous.[1] Some research suggests that phthalates may adversely affect neurodevelopment,[2,3,4] potentially increasing the risk of attention deficit/hyperactivity disorder (ADHD).[5,6] A study published in *Environmental Health Perspectives* found that prenatal exposure to certain phthalate metabolites was associated with increased odds of clinically confirmed ADHD in a group of 3-year-old children.[7]

Originally, phthalate research focused on reproductive end points, owing to the similarity between these chemicals and the steroidal hormones that control reproductive tract development and function. However, epidemiological studies have also reported associations between phthalate exposure and behaviors linked to ADHD, although the findings have been inconsistent.[6,8,9,10,11,12]

To clarify the potential association, the authors of the study conducted a population-based case–control analysis of data from the Norwegian Mother and Child Cohort (MoBa). Pregnant women provided blood and urine samples at approximately 17 weeks' gestation. The women also completed questionnaires pertaining to health and lifestyle at gestational weeks 17 and 30, diet at gestational week 22, and child health and development when their children were 6, 18, and 36 months old.

The team used the Norwegian Patient Registry to identify MoBa-enrolled children with clinically confirmed ADHD, randomly selecting 297 cases from that population. An additional 553 children were randomly selected from MoBa as controls. Maternal blood and urine samples underwent testing for concentrations of thyroid hormones and 12 phthalate metabolites, respectively.

The authors initially focused on the relationship between maternal urinary phthalate concentrations and children's ADHD diagnosis. The results indicated that prenatal exposure to the sum of di(2-ethylhexyl) phthalate (DEHP) metabolites was associated with increased likelihood of ADHD. Children in the highest quintile of exposure had an estimated three times the likelihood of having ADHD, in comparison with children in the lowest quintile.

Unlike some earlier studies, the authors found no evidence of an association between other phthalate metabolites and ADHD.

More than 5% of children in the United States have ADHD, a disorder characterized by impaired focus and working memory. Improved diagnosis may partly, but not entirely, explain recent increases in prevalence of the disorder, which appears to have both genetic and environmental underpinnings.[14] Image: © gali estrange/Shutterstock.

They proposed that use of a binary yes or no clinical diagnosis could miss subtle behavioral differences associated with subtypes of ADHD. Additionally, it is possible that certain phthalates are associated only with specific subtypes of ADHD.

The association did not appear to be mediated by maternal thyroid hormone levels, which was previously associated with ADHD symptoms in 8-year-old children.[13] "I cannot exclude the possibility that these associations are mediated by changes in thyroid function, even though we did not detect it in our study," says first author Stephanie Engel, a professor of epidemiology at the Gillings School of Global Public Health, University of North Carolina at Chapel Hill. "Other studies have found relationships between DEHP and thyroid function in adults and pregnant women. And maternal thyroid function is a critical determinant of fetal brain development. So, the biological plausibility of a pathway through thyroid function exists."

The study's strengths include the clinical confirmation of ADHD, adjustment for phthalate coexposures, extensive covariate data, and consideration of potential mediators. The findings may be limited by phthalate and thyroid hormone measurements taken at only a single time point.

Carmen Messerlian, a research scientist at Harvard T.H. Chan School of Public Health, also noted baseline differences between the case and control groups, particularly certain maternal characteristics (education level, smoking status, and reported depression) and the children's birth years. "The fact that the control group [participants] were so different on these very important potential confounders does worry me as far as potential bias in the data," she says.

Nevertheless, Messerlian, who was not involved in the study, notes that the results do point to a possible association. "We're just at the tip of the iceberg of understanding the relationship between environmental chemical exposure in both mothers as well as fathers and neurodevelopment in their children," she says.

Reaching more understanding is an important goal. "Although exposure to DEHP in the population is on the decline," Engel says, "it is still a prevalent exposure, which heightens concern about the potential for developmental impacts."

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