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Invited Perspective: PFAS and the Childhood Obesity Phenotype—Challenges and Opportunities

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Childhood obesity represents a public health crisis with serious long-term consequences.[1] The "metabolism-disrupting chemical" hypothesis postulates that environmental chemicals with endocrine-disrupting ability have the potential to alter the body's metabolic systems, especially when exposure occurs during sensitive developmental periods, and to increase susceptibility to higher adiposity.[2] In line with this hypothesis, per- and polyfluoroalkyl substances (PFAS), a group of manmade chemicals, have received increased attention for their potential obesogenic effects. These chemicals have been widely used in various industrial and commercial applications,[3] and owing to their perfluorinated carbon moieties, they are characterized by physical stability, chemical resistance, and environmental persistence. Detectable blood levels have been reported in population studies around the world.[4–7] Given that exposures are chronic and widespread across the general population, even modest increases in the relative risk of adverse health effects can translate into a large number of cases of obesity and other related metabolic complications at the population level.

In their new study, Liu et al.[8] relied on the Environmental influences on Child Health Outcomes (ECHO) consortium to examine associations between prenatal exposure to PFAS (assessed through maternal serum or plasma concentrations) and childhood obesity. Although not the first to report on this subject, the new study addresses key elements that previous work did not delve into,[9] including assessment of sex-specific effects and examination of PFAS exposures as a mixture. The authors found that higher gestational exposure to PFAS was associated with a slightly higher risk of overweight or obesity in children 2–5 years of age, with no evidence of sex specificity. As expected, measured PFAS concentrations were significantly correlated. This probably reflects common exposure sources and provides evidence in favor of the notion that PFAS should be examined and managed as a class.[10]

Liu et al.[8] make an important contribution to the field by pooling data across eight prospective cohorts from various locations in the United States (Georgia, Colorado, Massachusetts, California, New Hampshire, New York, and Illinois), even though the overall sample size achieved through this pooling is still relatively small. The researchers assessed body mass index (BMI) and defined overweight/obesity as BMI $\geq$85th percentile for age and sex. Approximately one in every five children included in this study had overweight or obesity—a prevalence estimate that is not only worrying but also very similar to that reported previously in U.S. and European youth.[11,12]

Obesity, traditionally defined as an excess of body fat causing prejudice to health, is usually assessed in epidemiological research by BMI given its simplicity as a tool. However, it is now well accepted that a high BMI is a heterogeneous entity, because it cannot distinguish between lean and fat mass or accompanying cardiometabolic complications.[13] If PFAS do not affect BMI per se, underestimation of risk in population subgroups may occur. For instance, studies have shown that individuals with a normal or high BMI are at higher risk for cardiovascular complications if they have an excess of visceral adipose tissue, increased ectopic fat accumulation (e.g., in the liver), higher triglyceride levels, or elevated blood pressure.[13–15] Several studies in experimental models have demonstrated the ability of PFAS to interfere with key metabolic and endocrine systems, and to affect a multitude of obesity-related outcomes, including liver fat accumulation and lipidemia.[16] Future epidemiological research should focus on a more detailed characterization of obesity phenotype(s) by using direct measurements of body fat distribution and mass (e.g., through imaging) and by assessing markers of adiposity-related metabolic complications, including inflammation (e.g., interleukin-6, C-reactive protein), liver injury (e.g., alanine aminotransferase, hepatic fat fraction), blood pressure, lipids (e.g., triglycerides, high-density lipoprotein cholesterol), and blood glucose and insulin levels. Such efforts will inform evaluations of PFAS toxicity and ultimately provide a clearer picture of the metabolic disruption associated with this class of pervasive chemicals.

Liu et al.[8] assessed exposure to seven long-chain PFAS [including perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA)]. However, PFAS constitute a group of thousands of chemicals. Accumulating knowledge on their high mobility in the environment, bioaccumulation in living organisms, and deleterious health effects led to the monitoring of several PFAS, particularly the long-chain compounds (>6 fluorinated carbons), and their phasing out. Following this, several other compounds, including the short-chain PFAS and the so-called "PFAS alternatives" (e.g., GenX), have been adopted as alternatives and are now increasingly being detected in the environment and in humans.[17] Animal studies suggest that these chemicals also have the potential to interact with peroxisome proliferator-activated receptor pathways and affect body weight.[18] Evidence of the toxic effects of the emerging PFAS homologs is largely lacking in humans. This is problematic because, in communities with high exposure to these PFAS, the magnitude of potential health impacts has not been quantified, and such information is necessary to engage in risk mitigation actions. Thus, to prevent the extensive production and use of similarly bioavailable PFAS in the future, it

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is imperative to accelerate research on the potential health effects of the emerging compounds, both individually and as mixtures.

Many cohorts worldwide have measured PFAS in biological samples collected during pregnancy and have followed up with anthropometric measurements and, less frequently, adiposity-related biomarkers in children. Liu et al.[8] make an important contribution by showing that it is possible to set up multi-cohort collaborations with access to individual data. The experiences gained by the ECHO Program and similar ongoing initiatives in Europe—which include the harmonization of data on PFAS, other environmental chemicals, and health outcomes [e.g., projects LifeCycle and Advancing Tools for Human Early Lifecourse Exposome Research and Translation (ATHLETE)][19,20]—provide the opportunity for large collaborative efforts to analyze individual data from similar cohorts across continents and populations. Beyond achieving larger sample sizes, such collaborations would allow the comparison of results across diverse study populations and the in-depth exploration of potential sources of heterogeneity, including exposure sources and sociodemographic and lifestyle characteristics. This type of collaboration would provide a clear advantage over literature-based meta-analyses.

Unfortunately, the pace of our research is inadequate to address the rapidly changing chemical landscape and the emerging concerns of affected populations. People living in communities with high exposures to PFAS want to know what can be done to protect their health and the health of their children. The analysis by Liu et al.[8] underlines the urgent need for further research and for immediate public health action.

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