Bone Accrual During Adolescence: Do Endocrine-Disrupting Chemicals Play a Role?

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Abbreviations: aBMD, areal bone mineral density; NHANES, National Health and Nutrition Examination Survey; PFAS, perfluoroalkyl and polyfluoroalkyl substances.

In a new study, Carwile et al (1) investigate the link between adolescent bone health and 2 classes of endocrine-disrupting chemicals: perfluoroalkyl and polyfluoroalkyl substances (PFAS) and phthalates. These synthetic chemicals are used in a myriad of consumer products and have been found in the bodies of nearly every American (2). PFAS have been dubbed “forever chemicals” given their resistance to degradation in the environment and long biological half-lives in humans, while phthalates are known as “everywhere chemicals” because of their extensive uses in plastics, personal care products, building materials, and many other everyday items. Decades of research indicates that PFAS and phthalates affect a wide range of endocrine-sensitive end points, particularly when exposures occur during critical periods of development (3). Findings from Carwile et al support the emerging hypothesis that these chemicals may also act as bone toxicants with implications for reduced bone mass accrual during adolescence.

Carwile et al conducted a cross-sectional study using data from the 2011 to 2016 National Health and Nutrition Examination Survey (NHANES) to examine relationships between biomarkers of exposure to PFAS and phthalates and total body less head areal bone mineral density (aBMD) Z scores among adolescents aged 12 to 19 years (1). The authors found that higher concentrations of several PFAS and phthalate biomarkers were associated with lower total body less head aBMD Z scores in males, while there were modest positive associations with aBMD for some chemicals among females. Similar to prior epidemiologic studies examining prenatal (4, 5) or childhood (6, 7) PFAS exposures, Carwile and colleagues found the strongest magnitude of association for exposure to perfluorooctanoate.

A novel feature of the Carwile et al study is assessment of the combined effects of multiple PFAS and phthalates. Evaluating chemical mixtures is a priority of the National Institute for Environmental Health Sciences given that individuals are simultaneously exposed to many environmental chemicals that may have synergistic effects on health (8). Using Bayesian kernel machine regression, an advanced statistical technique developed to assess mixture effects, the authors estimated that higher combined exposure to all PFAS and phthalate biomarkers was associated with lower total body less head aBMD among males but not females (1). This study is the first to examine bone health in relation to mixtures across chemical classes and supports the importance of evaluating effects of real-world combined exposures.

Because PFAS have long half-lives in serum, cross-sectional associations may reflect effects of cumulative PFAS exposure on bone over time. In contrast, phthalates are metabolized and eliminated in urine within hours of exposure and therefore urinary biomarkers quantify recent exposures, are subject to measurement error, and may not represent exposures at the relevant time period for bone mineral accrual. Therefore, prospective studies of phthalate exposures in adolescence are needed to disentangle temporal ordering of exposure and bone outcomes.

The Carwile et al results expand on prior studies by demonstrating that adolescence may be a critical period of susceptibility to environmental bone toxicants. Owing to the cross-sectional study design and lack of clinical end points, additional longitudinal studies with long-term follow-up are needed to determine whether bone deficits persist and relate to greater risk of fractures and osteoporosis in adulthood. Likewise, mechanisms for effects of PFAS and phthalates remain to be elucidated but may involve inflammatory pathways, peroxisome proliferator–activated receptor gamma agonism, or androgen antagonism (1). The latter pathway may explain stronger relations of chemicals with lower aBMD among males compared with females, though differences in pubertal stage may also play a role in observed sex differences. Because PFAS and phthalates may influence pubertal timing and body composition, future research in longitudinal cohorts will be necessary to determine whether these characteristics mediate associations with aBMD.
Both PFAS and phthalates have been the target of policy actions and market-based campaigns to reduce human exposures from consumer products. However, chemicals are often replaced with alternatives that have similar structure and biological activity and may be “regrettable replacements” for their predecessors. Furthermore, national biomonitoring in NHANES includes only about 350 of the more than 40,000 chemicals currently allowed for use in the United States. Gaps in our understanding of chemical exposures reinforces the need for further research to elucidate the effect on bone accrual of not only the PFAS and phthalates studied by Carwile and colleagues but also their replacements and other contemporary endocrine-disrupting chemicals.

Given the ubiquity of chemical exposures in the United States and around the world, even small decrements in bone mass accrual could have large effects on population-level bone health. Although long-term and clinical implications remain to be elucidated, emerging research by Carwile et al and others suggest that reducing early-life chemical exposures may be a promising new avenue for optimizing early-life bone accrual and potentially lifelong bone health.

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**Disclosures**

The author has nothing to disclose.

**Data Availability**

Data sharing is not applicable to this article because no data sets were generated or analyzed.

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