A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP13966.

Invited Perspective: Long-Term Effects of Gestational PFAS Exposures on Adiposity—Time for Solutions

Jessie P. Buckley[1] *and Joseph M. Braun*[2]

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[2]Department of Epidemiology, Brown University, Providence, Rhode Island, USA

https://doi.org/10.1289/EHP13966

Refers to https://doi.org/10.1289/EHP12597

Barker and colleagues' studies on the developmental origins of health and disease demonstrated that fetal undernutrition can lead to poor cardiovascular and metabolic health decades later.[1] Prenatal environmental exposures are also linked to fetal growth restriction and adverse childhood cardiometabolic outcomes; however, few studies have characterized the long-term effects of prenatal exposure to per- and polyfluoroalkyl substances (PFAS).

In this issue of *Environmental Health Perspectives*, Zhang et al. assess relationships between concentrations of six PFAS and their mixture measured during early pregnancy and multiple measures of body composition in late adolescence (age: 16–20 years old) in the Project Viva cohort.[2] The authors found that higher concentrations of PFAS, particularly perfluorooctane sulfonate (PFOS), and the PFAS mixture were associated with greater body mass index (BMI), risk of obesity, and accelerated growth in the first 20 years of life. Consistent with the Barker hypothesis, a prior study from the same cohort found that prenatal PFOS concentrations were associated with lower birth weight.[3] Zhang et al.'s report suggests PFAS may belong to a group of established developmental toxicants, including diethylstibesterol[4] and tobacco smoke,[5] that have long-term impacts on health.

Notably, the results from this and other studies of PFAS and anthropometry in Project Viva were robust to adjustment for maternal hemodynamics (plasma albumin) and renal function (serum creatinine), which can influence both PFAS excretion and birth weight.[6] The links of prenatal hemodynamics and renal function with later-life body composition are largely unknown and worthy of further exploration. However, the findings from Zhang et al. suggest these factors may not be major confounders when examining prenatal PFAS and later-life anthropometry.

A key strength of the Project Viva analysis is the availability of multiple modes of body composition assessment that go beyond BMI to distinguish between general adiposity, central adiposity, and lean mass. Interestingly, associations of PFOS with BMI-based measures did not appear to be driven by overall or central adiposity; in fact, PFOS was weakly positively associated with all body composition measures, and several PFAS were significantly associated with higher lean mass index among males.[2] These findings underscore that "obesogenic" associations based on BMI measures may not always be due to increased fat and—although mechanisms are unclear—indicate lean mass as an understudied aspect of body composition that may be affected by developmental chemical exposures.

Pregnancy levels of some PFAS in the Project Viva cohort (enrolled in 1999–2002) are higher than those in contemporary general populations[2] but are representative of PFAS exposures experienced by millions of Americans for decades.[7] Moreover, PFAS exposures continue to be widespread in the United States,[8] with thousands of locations estimated to have PFAS contamination.[9] Furthermore, these "forever chemicals" are not going away given their persistence in the environment[10] and human tissues.[11] Studies like that by Zhang et al. leave the environmental health research community with an uncertain message for individuals who have already been exposed to PFAS. Short of inventing a time machine, what can parents and adolescents do to mitigate effects of exposures that have already occurred?

Recent studies provide some clues, suggesting that certain factors known to protect against obesity may also mitigate the adverse effects of PFAS exposures. In the Health Outcomes and Measures of the Environment Study, we found associations of maternal gestational perfluorooctanoic acid (PFOA) concentrations with higher visceral fat area among children with lower physical activity scores, but not higher scores, at 12 years of age.[12] A cross-sectional study of Canadian adults reported adverse associations of PFOA with the liver function biomarker gamma-glutamyltransferase among those with low physical activity but not among those meeting Canada's physical activity guidelines.[13] Similar results have been reported in the Diabetes Prevention Program, a randomized trial of a lifestyle intervention consisting of modified diet, physical activity, and behavior among adults at high risk of diabetes.[14] Associations of baseline PFAS concentrations with incident diabetes,[15] adiposity,[16] cholesterol and triglycerides,[17] and blood pressure[18] at follow-up were stronger among individuals randomized to placebo compared to the intervention group, suggesting that lifestyle intervention protected against PFAS toxicity. Although these studies serve as the basis for research to determine if such lifestyle modifications can meaningfully reduce adverse effects of PFAS exposures, the emphasis should be on systems-level changes that prevent or mitigate PFAS effects without placing an additional burden on individuals.

PFAS are a major public health challenge linked to a myriad of health effects.[9] Although evidence from long-term studies like that of Zhang et al. is necessary to demonstrate implications of early life exposures, we further encourage solution-oriented research to identify strategies to counter these effects. Producing actionable results is critically important to empower affected individuals, communities, health care providers, and public health agencies grappling with how to respond to PFAS exposures.

Acknowledgments

This work was funded by grants from the National Institute of Environmental Health Sciences (R01 ES030078, R01 ES033252, R21 ES034187, and R01 ES032836). The content is solely the

Address correspondence to Jessie P. Buckley, 2106-B McGavran-Greenberg Hall CB#7435, Chapel Hill, NC 27599-7435 USA. Email: jessie.buckley@unc.edu

J.M.B. was compensated for serving as an expert witness for plaintiffs involved in litigation related to PFAS-contaminated drinking water. J.P.B. declares nothing to disclose.

Received 9 September 2023; Revised 23 October 2023; Accepted 24 October 2023; Published 6 December 2023.

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to 508 standards due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehpsubmissions@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Barker DJ. 2004. The developmental origins of adult disease. J Am Coll Nutr 23(6 Suppl):588S–595S, PMID: 15640511, https://doi.org/10.1080/07315724.2004.10719428.
2. Zhang M, Rifas-Shiman SL, Aris IM, Fleisch AF, Lin PD, Nichols AR, et al. 2023. Associations of prenatal per- and polyfluoroalkyl substance (PFAS) exposures with offspring adiposity and body composition at age 16–20 years: project viva. Environ Health Perspect 131(12):127002, https://doi.org/10.1289/EHP12597.
3. Sagiv SK, Rifas-Shiman SL, Fleisch AF, Webster TF, Calafat AM, Ye X, et al. 2018. Early-pregnancy plasma concentrations of perfluoroalkyl substances and birth outcomes in project viva: confounded by pregnancy hemodynamics? Am J Epidemiol 187(4):793–802, PMID: 29155920, https://doi.org/10.1093/aje/kwx332.
4. Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, et al. 2011. Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med 365(14):1304–1314, PMID: 21991952, https://doi.org/10.1056/NEJMoa1013961.
5. Albers L, Sobotzki C, Kuß O, Ajslev T, Batista RF, Bettiol H, et al. 2018. Maternal smoking during pregnancy and offspring overweight: is there a dose-response relationship? An individual patient data meta-analysis. Int J Obes (Lond) 42(7):1249–1264, PMID: 29717267, https://doi.org/10.1038/s41366-018-0050-0.
6. Verner M-A, Loccisano AE, Morken N-H, Yoon M, Wu H, McDougall R, et al. 2015. Associations of perfluoroalkyl substances (PFAS) with lower birth weight: an evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK). Environ Health Perspect 123(12):1317–1324, PMID: 26008903, https://doi.org/10.1289/ehp.1408837.
7. Calafat AM, Wong LY, Kuklenyik Z, Reidy JA, Needham LL. 2007. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ Health Perspect 115(11):1596–1602, PMID: 18007991, https://doi.org/10.1289/ehp.10598.
8. Centers for Disease Control and Prevention. U.S. Department of Health and Human Services. 2022. *National Report on Human Exposure to Environmental Chemicals*. http://www.cdc.gov/exposurereport/ [accessed 1 September 2023].
9. National Academies of Sciences, Engineering, and Medicine. 2022. *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up*. Bethesda, MD: National Institutes of Health.
10. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, et al. 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag 7(4):513–541, PMID: 21793199, https://doi.org/10.1002/ieam.258.
11. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115(9):1298–1305, PMID: 17805419, https://doi.org/10.1289/ehp.10009.
12. Braun JM, Papandonatos GD, Li N, Sears CG, Buckley JP, Cecil KM, et al. 2022. Physical activity modifies the relation between gestational perfluorooctanoic acid exposure and adolescent cardiometabolic risk. Environ Res 214(pt 3):114021, PMID: 35952751, https://doi.org/10.1016/j.envres.2022.114021.
13. Borghese MM, Liang CL, Owen J, Fisher M. 2022. Individual and mixture associations of perfluoroalkyl substances on liver function biomarkers in the Canadian health measures survey. Environ Health 21(1):85, PMID: 36104725, https://doi.org/10.1186/s12940-022-00892-6.
14. The Diabetes Prevention Program Research Group. 1999. The diabetes prevention program. Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care 22(4):623–634, PMID: 10189543, https://doi.org/10.2337/diacare.22.4.623.
15. Cardenas A, Hivert M-F, Gold DR, Hauser R, Kleinman KP, Lin P-ID, et al. 2019. Associations of perfluoroalkyl and polyfluoroalkyl substances with incident diabetes and microvascular disease. Diabetes Care 42(9):1824–1832, PMID: 31296647, https://doi.org/10.2337/dc18-2254.
16. Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert M-F, Fleisch AF, et al. 2018. Association of perfluoroalkyl and polyfluoroalkyl substances with adiposity. JAMA Netw Open 1(4):e181493, PMID: 30646133, https://doi.org/10.1001/jamanetworkopen.2018.1493.
17. Lin P-ID, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert M-F, et al. 2019. Per- and polyfluoroalkyl substances and blood lipid levels in pre-diabetic adults-longitudinal analysis of the diabetes prevention program outcomes study. Environ Int 129:343–353, PMID: 31150976, https://doi.org/10.1016/j.envint.2019.05.027.
18. Lin P-ID, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert M-F, et al. 2020. Per- and polyfluoroalkyl substances and blood pressure in pre-diabetic adults-cross-sectional and longitudinal analyses of the diabetes prevention program outcomes study. Environ Int 137:105573, PMID: 32088543, https://doi.org/10.1016/j.envint.2020.105573.