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Invited Perspective: PFAS and Pubertal Timing in Girls—A Maturing Literature

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In a downward global trend in timing of maturation, today's children are reaching pubertal milestones earlier than prior generations.[1,2] The average age at onset of breast development (thelarche), for example, has dropped by 3 months per decade since the 1970s,[2] likely owing to higher energy intake and more sedentary lifestyles.[3,4] How do environmental pollutants, particularly those that disrupt the gonadal and adrenal hormone axes that regulate puberty, fit in? Although it may be convenient to speculate that the increasing production of synthetic endocrine-disrupting chemicals (EDCs) around the world has fueled the secular trend in pubertal timing, the reality is, of course, more complicated.[5]

Per- and polyfluoroalkyl substances (PFAS), a class of forever chemicals, are of particular concern in this context given their reproductive and developmental toxicity, their widespread use in industrial applications and consumer products, and their resistance to environmental and biological degradation.[6] Data from the National Health and Nutrition Examination Survey indicate nearly 100% of Americans have measurable blood levels of PFAS, with exposure typically occurring through contaminated water and food, as well as via consumer products.[7,8] To date, results of epidemiological studies examining the impact of PFAS on pubertal outcomes have been inconsistent, likely owing to methodological differences and challenges.[9–12]

Among those challenges is the variable timing of pubertal milestones, leading to mistiming of exposure and outcome assessment in some participants.[9,12] The widespread reliance on self- or parent-reported assessment of pubertal development, rather than gold-standard Tanner staging by a trained professional, can additionally introduce outcome misclassification and obscure true associations.[13,14] Finally, there remains controversy regarding the role of body size as a potential mediator in the association between PFAS and pubertal development; adjustment for body mass index (BMI) as a potential confounder may result in overadjustment bias.

In this issue, Pinney et al.[15] overcome limitations and advance the field through a carefully and intentionally designed longitudinal study developed as part of the larger Breast Cancer and the Environmental Research Program.[16,17] PFAS were measured in middle childhood (6–8 years of age) reducing concerns regarding "late age at entry" that have hindered prior studies. Participants were followed through annual or semiannual visits, including comprehensive assessments of pubertal outcomes by trained examiners using gold-standard methods in addition to measurement of pubertal hormones. Sophisticated statistical approaches were used to estimate ages at thelarche and pubarche (first appearance of pubic hair) based on pubertal changes occurring between regular visits, thereby minimizing error in outcome timing,[18] and mediation analyses were conducted to understand the role of BMI.

These considerable methodological advances make for the most rigorous analysis on this topic to date, and results indicated that girls with higher baseline perfluorooctanoic acid (PFOA) concentrations were significantly less likely to have reached pubarche and menarche (first occurrence of menstruation) by the end of follow-up, with similar patterns observed for perfluorooctane sulfonate (PFOS). PFOA concentrations 6 months prior to thelarche were additionally inversely associated with concentrations of the circulating hormones estrone and dehydroepiandrosterone sulfate, suggesting endocrine pathways through which PFAS exposures may delay puberty. The authors identified a "triangular relationship" between PFAS, BMI, and pubertal timing, moreover, such that PFOA was a significant predictor of lower BMI, as well as of later pubertal milestones, whereas higher BMI independently predicted earlier pubertal milestones. These results both complement and contrast with studies showing that prenatal PFAS exposures were associated with reduced fetal growth and birth weight followed by greater childhood adiposity.[19,20]

Ultimately, the results of the study by Pinney et al. require deep reflection. Concerns about the acceleration of pubertal development in the modern era have been fueled by reports of the negative consequences of early pubertal development, including increased risks of cardiometabolic disease (reviewed by Prentice and Viner[21]) and reproductive cancers,[22–24] as well as mental health and behavioral concerns.[25–27] By contrast, far fewer studies have considered the implications of delayed pubertal development. Although delays in pubertal timing may have benefits in terms of reductions in risks of hormone-sensitive cancers,[28] there may also be adverse impacts on bone density and microstructure.[29] Furthermore, some seemingly protective impacts of delayed maturation may be limited; for instance, one study reported U-shaped associations between age at menarche and risks of coronary heart disease, whereby risks were highest in both early and late maturers.[30]

The work by Pinney et al. improves upon key limitations of the prior literature and provides strong evidence that PFAS exposure in mid to late childhood is associated with delays in pubertal milestones. These compelling results, of course, lead to more questions in urgent need of answers. A clear next step is to query how exposures to mixtures of PFAS—as a class of compounds, as well as in combination with other classes of EDCs—impact pubertal milestones. How do PFAS, moreover, interact with dietary factors that can be both a source of exposure and independent predictors of body size and pubertal development? In addition, the critical and sensitive windows during which PFAS exposures are most impactful remain uncertain, and evaluating the contributions of exposures during multiple critical windows (a so-called "two hit" approach) is warranted.[31,32] Last, the landscape of PFAS contamination is evolving, with average blood levels of legacy PFAS (including PFOA and PFOS) declining even as a new generation of replacement PFAS is on the rise.[33,34]

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Unfortunately, precious little is known about the human health impacts of these newer contaminants. This important study reinforces the urgency of better understanding the impacts of these "forever chemicals" on child and adolescent health.

References

1. Karlberg J. 2002. Secular trends in pubertal development. Horm Res 57(suppl 2):19–30, PMID: 12065922, https://doi.org/10.1159/000058096.
2. Eckert-Lind C, Busch AS, Petersen JH, Biro FM, Butler G, Bräuner EV, et al. 2020. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: a systematic review and meta-analysis. JAMA Pediatr 174(4):e195881, PMID: 32040143, https://doi.org/10.1001/jamapediatrics.2019.5881.
3. Britton JA, Wolff MS, Lapinski R, Forman J, Hochman S, Kabat GC, et al. 2004. Characteristics of pubertal development in a multi-ethnic population of nine-year-old girls. Ann Epidemiol 14(3):179–187, PMID: 15036221, https://doi.org/10.1016/j.annepidem.2002.08.001.
4. Tang J, Xue P, Huang X, Lin C, Liu S. 2022. Diet and nutrients intakes during infancy and childhood in relation to early puberty: a systematic review and meta-analysis. Nutrients 14(23):5004, PMID: 36501034, https://doi.org/10.3390/nu14235004.
5. Uldbjerg CS, Koch T, Lim YH, Gregersen LS, Olesen CS, Andersson AM, et al. 2022. Prenatal and postnatal exposures to endocrine disrupting chemicals and timing of pubertal onset in girls and boys: a systematic review and meta-analysis. Hum Reprod Update 28(5):687–716, PMID: 35466359, https://doi.org/10.1093/humupd/dmac013.
6. 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.
7. Lin PID, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, et al. 2021. Temporal trends of concentrations of per- and polyfluoroalkyl substances among adults with overweight and obesity in the United States: results from the Diabetes Prevention Program and NHANES. Environ Int 157:106789, PMID: 34333293, https://doi.org/10.1016/j.envint.2021.106789.
8. Calafat AM, Kato K, Hubbard K, Jia T, Botelho JC, Wong LY. 2019. Legacy and alternative *per-* and polyfluoroalkyl substances in the U.S. general population: paired serum–urine data from the 2013–2014 National Health and Nutrition Examination Survey. Environ Int 131:105048, PMID: 31376596, https://doi.org/10.1016/j.envint.2019.105048.
9. Lopez-Espinosa MJ, Fletcher T, Armstrong B, Genser B, Dhatariya K, Mondal D, et al. 2011. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant. Environ Sci Technol 45(19):8160–8166, PMID: 21534542, https://doi.org/10.1021/es1038694.
10. Ernst A, Brix N, Lauridsen LLB, Olsen J, Parner ET, Liew Z, et al. 2019. Exposure to perfluoroalkyl substances during fetal life and pubertal development in boys and girls from the Danish National Birth Cohort. Environ Health Perspect 127(1):017004, PMID: 30628845, https://doi.org/10.1289/EHP3567.
11. Kristensen SL, Ramlau-Hansen CH, Ernst E, Olsen SF, Bonde JP, Vested A, et al. 2013. Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. Hum Reprod 28(12):3337–3348, PMID: 24129614, https://doi.org/10.1093/humrep/det382.
12. Marks KJ, Howards PP, Smarr MM, Flanders WD, Northstone K, Daniel JH, et al. 2021. Prenatal exposure to mixtures of persistent endocrine disrupting chemicals and early menarche in a population-based cohort of British girls. Environ Pollut 276:116705, PMID: 33592441, https://doi.org/10.1016/j.envpol.2021.116705.
13. Terry MB, Goldberg M, Schechter S, Houghton LC, White ML, O'Toole K, et al. 2016. Comparison of clinical, maternal, and self pubertal assessments: implications for health studies. Pediatrics 138(1):e20154571, PMID: 27279647, https://doi.org/10.1542/peds.2015-4571.
14. Dorn LD, Sontag-Padilla LM, Pabst S, Tissot A, Susman EJ. 2013. Longitudinal reliability of self-reported age at menarche in adolescent girls: variability across time and setting. Dev Psychol 49(6):1187–1193, PMID: 22889389, https://doi.org/10.1037/a0029424.
15. Pinney SM, Fassler CS, Windham GC, Herrick RL, Xie C, Kushi LH, et al. 2023. Exposure to perfluoroalkyl substances and associations with pubertal onset and serum reproductive hormones in a longitudinal study of young girls in Greater Cincinnati and the San Francisco Bay Area. Environ Health Perspect 131(9):097009, https://doi.org/10.1289/EHP11811.
16. Hiatt RA, Haslam SZ, Osuch J, Breast Cancer and the Environment Research Centers. 2009. The breast cancer and the environment research centers: transdisciplinary research on the role of the environment in breast cancer etiology. Environ Health Perspect 117(12):1814–1822, PMID: 20049199, https://doi.org/10.1289/ehp.0800120.
17. Biro FM, Galvez MP, Greenspan LC, Succop PA, Vangeepuram N, Pinney SM, et al. 2010. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics 126(3):e583–e590, PMID: 20696727, https://doi.org/10.1542/peds.2009-3079.
18. Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, et al. 2013. Onset of breast development in a longitudinal cohort. Pediatrics 132(6):1019–1027, PMID: 24190685, https://doi.org/10.1542/peds.2012-3773.
19. Mora AM, Oken E, Rifas-Shiman SL, Webster TF, Gillman MW, Calafat AM, et al. 2017. Prenatal exposure to perfluoroalkyl substances and adiposity in early and mid-childhood. Environ Health Perspect 125(3):467–473, PMID: 27352404, https://doi.org/10.1289/EHP246.
20. Fleisch AF, Rifas-Shiman SL, Mora AM, Calafat AM, Ye X, Luttmann-Gibson H, et al. 2017. Early-life exposure to perfluoroalkyl substances and childhood metabolic function. Environ Health Perspect 125(3):481–487, PMID: 27586368, https://doi.org/10.1289/EHP303.
21. Prentice P, Viner RM. 2013. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. Int J Obes (Lond) 37(8):1036–1043, PMID: 23164700, https://doi.org/10.1038/ijo.2012.177.
22. Célind J, Bygdell M, Martikainen J, Styrke J, Damber JE, Kindblom JM, et al. 2021. Timing of the pubertal growth spurt and prostate cancer. Cancers (Basel) 13(24):6238, PMID: 34944857, https://doi.org/10.3390/cancers13246238.
23. Day FR, Thompson DJ, Helgason H, Chasman DI, Finucane H, Sulem P, et al. 2017. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. Nat Genet 49(6):834–841, PMID: 28436984, https://doi.org/10.1038/ng.3841.
24. Goldberg M, D'Aloisio AA, O'Brien KM, Zhao S, Sandler DP. 2020. Pubertal timing and breast cancer risk in the Sister Study cohort. Breast Cancer Res 22(1):112, PMID: 33109223, https://doi.org/10.1186/s13058-020-01326-2.
25. Kowalski AJ, Addo OY, Kramer MR, Martorell R, Norris SA, Waford RN, et al. 2021. Longitudinal associations of pubertal timing and tempo with adolescent mental health and risk behavior initiation in urban South Africa. J Adolesc Health 69(1):64–73, PMID: 33431244, https://doi.org/10.1016/j.jadohealth.2020.09.043.
26. Dimler LM, Natsuaki MN. 2015. The effects of pubertal timing on externalizing behaviors in adolescence and early adulthood: a meta-analytic review. J Adolesc 45:160–170, PMID: 26439868, https://doi.org/10.1016/j.adolescence.2015.07.021.
27. Copeland W, Shanahan L, Miller S, Costello EJ, Angold A, Maughan B. 2010. Outcomes of early pubertal timing in young women: a prospective population-based study. Am J Psychiatry 167(10):1218–1225, PMID: 20478880, https://doi.org/10.1176/appi.ajp.2010.09081190.
28. Zhu J, Chan YM. 2017. Adult consequences of self-limited delayed puberty. Pediatrics 139(6):e20163177, PMID: 28562264, https://doi.org/10.1542/peds.2016-3177.
29. Bonjour JP, Chevalley T. 2014. Pubertal timing, bone acquisition, and risk of fracture throughout life. Endocr Rev 35(5):820–847, PMID: 25153348, https://doi.org/10.1210/er.2014-1007.
30. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, et al. 2015. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. Circulation 131(3):237–244, PMID: 25512444, https://doi.org/10.1161/CIRCULATIONAHA.114.010070.
31. Bell MR, Thompson LM, Rodriguez K, Gore AC. 2016. Two-hit exposure to polychlorinated biphenyls at gestational and juvenile life stages: 1. Sexually dimorphic effects on social and anxiety-like behaviors. Horm Behav 78:168–177, PMID: 26592453, https://doi.org/10.1016/j.yhbeh.2015.11.007.
32. Ashrap P, Sánchez BN, Téllez-Rojo MM, Basu N, Tamayo-Ortiz M, Peterson KE, et al. 2019. In utero and peripubertal metals exposure in relation to reproductive hormones and sexual maturation and progression among girls in Mexico City. Environ Res 177:108630, PMID: 31421446, https://doi.org/10.1016/j.envres.2019.108630.
33. Brase RA, Mullin EJ, Spink DC. 2021. Legacy and emerging per- and polyfluoroalkyl substances: analytical techniques, environmental fate, and health effects. Int J Mol Sci 22(3):995, PMID: 33498193, https://doi.org/10.3390/ijms22030995.
34. Mahoney H, Xie Y, Brinkmann M, Giesy JP. 2022. Next generation per- and poly-fluoroalkyl substances: status and trends, aquatic toxicity, and risk assessment. EcoEnviron Health 1(2):117–131, https://doi.org/10.1016/j.eehl.2022.05.002.