

Developmental time as a design principle for maternal and child exposomics

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Received 16 September 2026; Revised 17 September 2026; Accepted 17 September 2026; Published 29 September 2026

<https://doi.org/10.55092/ijee20260015>

Abstract: Maternal and child exposomics can characterize complex exposure profiles, but measurement remains uneven across the developmental continuum. Although prospective preconception cohorts and studies of minipuberty demonstrate the feasibility of early enrollment and infant hormone phenotyping, these windows are not routinely harmonized across cohort designs. We propose developmental-event-guided exposomics, combining core pregnancy and birth assessments with targeted preconception recruitment and infant sampling during biologically defined windows. Sampling frequency and specimen type should reflect chemical toxicokinetics, with paired external and internal measurements used to calibrate exposure estimates. Computational models should quantify uncertainty rather than obscure unobserved developmental states. Standardizing a limited set of sentinel windows could reveal modifiable sources while biological responses remain measurable, providing a stronger basis for timely exposure reduction before critical opportunities for prevention are lost.

Keywords: exposome; preconception exposure; minipuberty; biomonitoring; temporal exposure assessment

Maternal and child exposomics can now characterize hundreds of chemicals and exposure-related features from small biospecimens. Yet the timing of measurement remains uneven across the developmental continuum. Since 2004, the EARTH Study has enrolled women and men before conception and followed through pregnancy [1]. This precedent establishes feasibility, but recruitment through a fertility clinic limits population representativeness. Beyond such selected cohorts, a recent review found that preconception evidence remains geographically concentrated and seldom includes parental exposure [2]. Influential early-life exposome projects have likewise concentrated biospecimen collection during pregnancy and at birth, with detailed child phenotyping conducted later [3]. The problem is therefore not the absence of precedents. It is that preconception and early infancy have not become standardized, harmonized windows across cohorts.

Early infancy deserves particular attention because exposure routes and host physiology change simultaneously. Placental transfer ends, while lactation, feeding, indoor air, dust and hand-to-mouth behavior create direct postnatal routes of infant exposure. Minipuberty makes this temporal problem concrete. In boys, gonadotropins and testosterone peak at about one to three months and decline toward childhood levels by about six months; gonadotropin activity may persist longer in girls [4]. This rapid activation illustrates

how the endocrine context for interpreting exposure-related effects can change within a narrow developmental window, while maturing metabolism and excretion also alter how exposure biomarkers should be interpreted. In the Odense Child Cohort, hormones were measured in 479 infants at three months and linked to maternal prenatal phthalate biomarkers, demonstrating that minipuberty can be phenotyped within a cohort and can yield exposure-associated signals in boys [5]. Because phthalates were measured prenatally, however, this study does not substitute for biomonitoring during infancy. What remains limited is replication using harmonized measurements of exposure and biological state within the same postnatal window. Whether postnatal exposure during the window has independent effects on reproductive development remains an open question.

We propose developmental-event-guided exposomics as a tiered design principle, not a requirement for maximal sampling from every family. A large pregnancy cohort could retain common pregnancy and birth assessments. A parallel preconception arm could recruit both prospective parents through fertility services, primary care and pregnancy-planning platforms, with selection and transportability assessed explicitly. An intensive infant panel could collect biospecimens near one and three months and at weaning, replacing lower-priority visits rather than simply adding collections. Short sampling bursts could follow prespecified



events, including exposure events such as renovation, wildfire smoke or a change in infant feeding, and events that alter physiology or metabolism, such as infection or medication use. Because these observation times partly depend on exposure-related events, triggers and missed collections should be recorded and addressed using inverse-intensity weighting or joint modeling.

Sampling also matches chemical toxicokinetics. Archived newborn dried blood spots can provide a molecular anchor at birth, as shown by metabolomic signatures associated with prenatal per- and polyfluoroalkyl substance exposure [6], but they cannot characterize exposures emerging during minipuberty. Persistent chemicals have long half-lives, so their internal levels integrate long-term exposure and, may also reflect lactational transfer in infants. In contrast, for rapidly eliminated chemicals such as phthalates, a single spot urine sample largely reflects recent exposure. Evidence from pregnancy indicates that repeated or pooled urine specimens improve characterization of average exposure over a target window [7]. Infant protocols require separate validation, including prescreening collection materials and using field blanks to detect contamination. Longitudinal personal monitoring has revealed substantial variation in airborne exposures across individuals and over time [8]. In infants, however, caregiver-worn devices remain proxies whose agreement with infant exposure requires validation. External (environmental or wearable) and internal (biospecimen) measurements should therefore be paired according to chemical half-lives and expected toxicokinetic delays.

With sparse sampling, computational models can integrate paired external and internal measurements with chemical half-lives to estimate exposure between samples and identify informative times for additional sampling. Brief exposure peaks or transient physiological changes may still go undetected. Reconstructed trajectories should therefore be reported with their uncertainty and interpreted as estimates rather than continuous observations.

Mechanistic studies should preserve the same temporal and mixture logic, because infants are exposed to chemical mixtures, use mixture rather than single compounds. A mixture reconstructed from pregnancy-cohort data has already been tested at human-relevant concentrations in human brain organoids and vertebrate models, providing a concrete precedent for linking epidemiological mixture profiles with experimental systems [9]. Extending this strategy to minipuberty is more difficult because no single experimental system reproduces the coordinated human endocrine transition. Experiments using cohort-derived mixture ratios, human-relevant internal concentrations and window-matched durations could identify convergent responses across complementary systems. Such concordance would strengthen biological plausibility and prioritize pathways

for further validation, but it would not alone establish causation or long-term developmental benefit.

Actionability must also be prespecified. Because most exposome biomarkers lack clinical thresholds, individual results should not automatically prompt family advice. Whether and how individual results are returned to participants should be specified in advance with ethics oversight. Where a source is credible and modifiable, a registered exposure-reduction sub-study could provide product substitution, ventilation support or filtration without shifting costs to families. Repeat biomonitoring and hormonal assessment could then test whether source reduction changes internal dose and proximal biology.

Temporal design is not the only priority for maternal and child exposomics, but it is one that cannot be repaired after data collection. Standardizing a small number of biologically defined windows across cohorts would improve comparability and allow investigators to test whether reducing a modifiable source changes internal exposure while the relevant physiology is still unfolding. The public health value of exposomics depends not only on identifying what families encounter, but on measuring it when the evidence can still guide prevention.

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