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Prenatal Exposure to Nonpersistent Chemicals and Fetal-to-childhood Growth Trajectories

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Introduction: Prenatal exposure to nonpersistent chemicals, including organophosphate pesticides, phthalates, and bisphenols, is associated with altered fetal and childhood growth. Few studies have examined these associations using longitudinal growth trajectories or considering exposure to chemical mixtures.

Methods: Among 777 participants from the Generation R Study, we used growth mixture models to identify weight and body mass index trajectories using weight and height measures collected from the prenatal period to age 13. We measured exposure biomarkers for organophosphate pesticides, phthalates, and bisphenols in maternal urine at three timepoints during pregnancy. Multinomial logistic regression was used to estimate associations between averaged exposure biomarker concentrations and growth trajectories. We used quantile g-computation to estimate joint associations with growth trajectories.

Results: Phthalic acid (OR = 1.4; 95% CI = 1.01, 1.9) and bisphenol A (OR = 1.5; 95% CI = 1.0, 2.2) were associated with higher odds of a growth trajectory characterized by smaller prenatal and larger childhood weight relative to a referent trajectory of larger prenatal and average childhood weight. Biomarkers of organophosphate pesticides, individually and jointly, were associated with lower odds of a growth trajectory characterized by average prenatal and lower childhood weight.

Conclusions: Exposure to phthalates and bisphenol A was positively associated with a weight trajectory characterized by lower prenatal and higher childhood weight, while exposure to organophosphate pesticides was negatively associated with a trajectory of average prenatal and lower childhood weight. This study is consistent with the hypothesis that nonpersistent chemical exposures disrupt growth trajectories from the prenatal period through childhood.

Keywords: Bisphenols; Growth mixture models; Growth trajectories; Organophosphate pesticides; Phthalates

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The spouse of H.T. is an employee of Eastman Chemical, a company that manufactures substitutes for ortho-phthalate plasticizers. Other authors report no conflicts of interest.

Because of restrictions based on privacy regulations and informed consent of participants, data cannot be made freely available in a public repository. Data can be obtained upon request. Requests should be directed toward the management team of the Generation R Study (secretariaat.genr@erasmusmc.nl), which follows a protocol for approving data requests.

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Robust literature has linked small size at delivery to higher risks of impaired neurodevelopment, cardiometabolic disorders, and mortality.[1–3] In addition to size at birth, the trajectory of growth experienced afterward is associated with later life health, especially for cardiometabolic disorders.[4–6] For example, children who are born small and subsequently experience rapid "catch-up" growth during early life have a higher risk of adverse cardiometabolic outcomes, such as coronary heart disease.[4,6] Given this evidence, growth trajectories may be an important endpoint to consider in population health.

Previous research has demonstrated that the *in-utero* environment, which includes environmental chemicals, influences growth during early life.[7] Like the general population, pregnant people are exposed to a vast array of environmental exposures.[8] These exposures include synthetic chemicals, such as phthalates or bisphenols, which are found commonly in plastics, personal care products, food packaging, and other elements of our indoor environments.[9] Others, such as organophosphate pesticides, are used in pest control and commonly contaminate foodstuffs.[10] While these chemicals may be non-persistent, exposure to them is chronic given their ubiquity in the environment.[9]

Numerous studies have examined prenatal exposure to phthalates, bisphenols, and organophosphate pesticides in relation to altered fetal or childhood growth.[11,12] Relatively fewer have examined associations with longitudinal trajectories of growth,[13–17] and many of these studies are limited to childhood growth and do not examine the trajectory of growth starting before or at birth. Moreover, while organophosphate pesticides have been linked to adverse childhood outcomes,[18] their associations with growth trajectories to our knowledge have not been examined. In addition, investigators have rarely incorporated chemical mixtures into these investigations,[19] even though real-world exposure scenarios occur in the form of complex mixtures.

In this work, we examined associations between exposure to phthalates, bisphenols, and organophosphate pesticides and fetal-to-childhood growth trajectories using data from the Generation R study. We sought to expand upon existing literature in several ways. First, the Generation R study is a large and well-characterized longitudinal cohort with growth data encompassing the prenatal, infant, and childhood periods. Second, we have measures of 19 biomarkers of chemical exposure, including some not frequently studied with respect to childhood growth. Last, we considered the possible joint effects of these chemicals on growth trajectories.

METHODS

Study Design

The Generation R Study is a prospective, population-based cohort located in Rotterdam, Netherlands. The cohort has been described elsewhere.[20,21] Briefly, participants were recruited during pregnancy and provided three urine samples at the time of ultrasound examinations, which occurred at <18 (median: 13 weeks), 18–25 (median: 20 weeks), and >25 weeks (median: 30 weeks) of gestation. Of the 4918 participants recruited between 2002 and 2006, 2083 had a complete set of urine samples available for chemical analysis. Of those participants, 1449 also had childhood follow-up data available at age six. From these participants, 800 were randomly selected for analysis of exposure to all three chemical classes (e.g., organophosphate pesticides, phthalates, and bisphenols). Among the 800 participants, 777 had sufficient sample volume for analyses of all three chemical classes at each timepoint (16% of the Generation R Study participants recruited from 2002 to 2006).[22,23] This sample has been described elsewhere and, briefly, includes participants more likely to be Dutch, have higher educational attainment, and have higher household income than the underlying Generation R Study.[22] Mothers provided written and informed consent at the time of enrollment and at each phase of the study thereafter. Children provided written and informed consent after age 12. The Generation R study design and research aims were approved by the Medical Ethical Committee of Erasmus Medical Center, University Medical Center, Rotterdam, Netherlands (IRB Registration No.: IRB00001482, MEC 198.782.2001.31, MEC 217.595/2002/202, MEC-2007-413, MEC-2012-165).

Exposure Measurement

As described previously, urine samples were collected into polypropylene urine collection containers and kept at −20°C until use for quantification of exposure biomarkers.[24] We measured exposure to organophosphate pesticides through the quantification of six dialkyl phosphates, phthalates through the quantification of 18 phthalate metabolites, and bisphenols through the quantification of eight bisphenols. Methods for their quantification and correction for urine dilution are described in eAppendix 1; http://links.lww.com/EDE/C164. We only included exposures detected in at least 60% of the study population in further analyses, namely, five dialkyl phosphates, 11 phthalate metabolites, and three bisphenols. Subsequently, we calculated the geometric mean (GM) or repeated exposure biomarker concentrations to estimate average exposure during pregnancy.

Fetal and Childhood Growth Measures

During the prenatal period, we used ultrasound scans at the 2nd (18–25 weeks) and 3rd (>25 weeks) prenatal visits to monitor fetal growth.[22,25] We measured head circumference, abdominal circumference, and femur lengths and used them to calculate estimated fetal weights as a summary measure of growth using Hadlock's formula.[26] We converted all estimated fetal weights to gestational-age-adjusted standard deviation scores using a reference growth chart from the full Generation R study population.[25] The chart used to the estimated fetal weight standard deviation score was not standardized for fetal sex because it did not predict fetal growth curves in the Generation R study.[25]

Because no internal growth standards were available, birthweights were collected at delivery and converted into gestational age- and sex-adjusted standard deviation scores based on a Swedish growth reference used previously in this cohort.[27–30]

We measured weight and length (2–24 months) or height (>24 months) during infancy and early childhood at the time of routine health care visits, which occurred at approximately 2, 3, 4, 5–10, 10–13, 13–17, 23–35, 35–44, and 44–56 months of age.[20] After age 5, children were invited to study visits at Erasmus every 3 years and visits occurred at approximately 6, 9, and 13 years of age.[20] We calculated the child's body mass index (BMI) using weight and height. Both child weight and BMI were converted to age- and sex-adjusted standard deviation score using Dutch reference growth curves (Growth Analyzer 3.0, Dutch Growth Research Foundation, Rotterdam, the Netherlands).

We centrally trained study staff required a demonstration of competency in collecting ultrasound and anthropometric measurements.[21] We examined all measurements to check means, standard deviations, outliers, and differences between measures provided by staff members. For ultrasound measures of fetal growth, intra- and inter-observer reproducibility was high.[31]

Growth Mixture Modeling

We used growth mixture models to derive trajectories for the weight standard deviation score from 18 weeks gestation through 13 years of age and BMI standard deviation score from 2 months to 13 years of age.[32] We fit models using 10 replicates with 20 iterations. We considered between 1 and 6 class solutions and explored including a random intercept and fitting age with a linear term, quadratic term, cubic term, or natural cubic splines (2–4 knots). Observations where a participant was missing age and weight or BMI data were excluded from the model.[32]

The optimal number of classes was identified using the following statistical criteria: Bayesian Information Criterion, Akaike Information Criterion, entropy (≥0.80), all classes contained ≥5% of the study sample, and the average posterior probability of class membership ≥0.80. We also considered interpretability using subject-matter knowledge.[33] We assigned participants to the class that corresponded to their highest posterior inclusion probability. We visualized the mean trajectories for each class by graphically displaying the predicted weight or BMI standard deviation score and 95% confidence interval (CI). We note that we were unable to find a solution for BMI standard deviation score trajectories that satisfied our criteria. Therefore, we present these results supplementally. For our statistical models, we used the weight and BMI classes with the largest proportion of participants as the referent.

Covariates

We collected data on maternal characteristics during pregnancy using questionnaires, which included age at enrollment, prepregnancy weight, ethnicity, parity, marital status, folic acid intake, household income, smoking and alcohol use, and highest completed education. Prepregnancy weight and height measured during the first trimester were used to calculate prepregnancy BMI. Education was considered as low (<3 years of high school), intermediate (≥3 years of secondary education), or high (university degree or higher vocational training). The questionnaire collected information about maternal ethnicity according to the categorization used by the Central Bureau of Statistics in the Netherlands.[34] This information was summarized as Dutch, other-Western (Indonesian, American Western, Asian Western, and European), and non-Western (Cape Verdean, Moroccan, Dutch Antilles, Surinamese, Turkish, African, American non-Western, Asian non-Western, and Oceanian).[21]

Dietary intake information was collected using a modified version of a validated semi-quantitative food frequency questionnaire (FFQ) administered at study enrollment.[35] The FFQ assessed information about nutritional intake during the previous 3 months, corresponding to approximately the first trimester of pregnancy. From the FFQ, we considered fruit and vegetable intake as potential determinants of exposure and fetal-to-childhood growth.[36,37] Average daily caloric intake was calculated using the Dutch food composition table of 2006.

Multiple Imputations

We imputed missing covariate and exposure data using multiple imputations by chained equations, generating 10 imputed datasets using 20 iterations per dataset (eAppendix 2; http://links.lww.com/EDE/C164).[38,39]

Statistical Analyses

We tabulated the n (%) or median (25th, 75th percentile) of demographic and growth characteristics in the overall cohort and according to weight and BMI trajectory class membership. We calculated the GM and the 5th, 25th, 50th, 75th, and 95th percentile concentration of each exposure biomarker in the overall cohort. We determined Pearson correlation coefficients of log-transformed biomarkers.

Single-pollutant Analysis

Given the novelty of our approach, we first investigated associations with individual exposure biomarkers for (1) comparability with previous analyses in this and other cohorts,[17,22] and (2) because metabolites belonging to the same chemical class or parent chemical may have different toxicities.[40] We estimated unadjusted and adjusted odds ratios (OR) and 95% CI of weight or BMI cluster membership relative to referent cluster membership associated with an interquartile range (IQR)-increase in each ln-transformed exposure biomarker using multinomial logistic regression. Model covariates were chosen a priori based on previous literature in the Generation R Study population examining nonpersistent chemical

exposures[36,37] and their associations with fetal growth.[22,30,41] We adjusted our models for maternal age, prepregnancy BMI, maternal education, household income, parity, marital status, smoking, alcohol consumption, folate intake, vegetable intake, fruit intake, and total caloric intake. Because trajectory group membership varied by child sex and because we estimated sex-specific effects, we also included child sex in our models.

We carried out several sensitivity analyses. First, we reconstructed our models excluding either folate intake or vegetable and fruit intake due to their rate of missingness (20–23%). We also explored sex-specific effects by re-constructing our models with an interaction term between each biomarker and child sex and tested for significance ($P < 0.10$) using a multivariate Wald test. To estimate sex-specific associations, we stratified our analysis by child sex.

Multi-pollutant Analysis

We used logistic quantile g-computation models to estimate the OR (95% CI) for the joint association between a simultaneous 1-quartile increase in exposure biomarkers and weight or BMI cluster membership relative to a referent cluster.[38] We estimated joint associations for the overall mixture of exposure biomarkers and individual chemical classes adjusted for the same covariates used in our single-pollutant models. For models of individual chemical classes, we co-adjusted for the remaining exposure biomarkers.

RESULTS

Participant Characteristics

Among the 777 maternal-child dyads in this analysis, mothers had a median age of 30.9 years at enrollment and a prepregnancy BMI of 22.4 kg/m^2 (Table 1). They were mostly Dutch (57%), with high education (55%), a household income >2000 € per month (71%), and were married or living with a partner (90%). Mothers were mostly nulliparous (63%). Fourteen percent reported continued smoking and 43% reported continued alcohol consumption during pregnancy.

Children in this analysis had an average of 12 weight (range:4–15) measurements between 18 weeks gestation and 13 years of age and 9 BMI (range:1–12) measurements between 2 months and 13 years of age (eTable 1; http://links.lww.com/EDE/C164).

Biomarkers of Chemical Exposure

We detected all dialkyl phosphates, phthalate metabolites, and bisphenol A (BPA) in at least 99% of participants (Table 2). We detected bisphenol F (61%) and bisphenol S (86%) less frequently. Most exposure biomarkers were positively correlated with one another, with the strongest correlations among biomarkers within the same chemical class (eFigure 1; http://links.lww.com/EDE/C164).

TABLE 1. Distribution of Demographics and Lifestyle Characteristics in Generation R Participants Included in This Analysis (n = 777)

Variable	Median (25th, 75th Percentile) or n (%)
Maternal age at enrollment, median (25th, 7th percentile)	30.9 (27.8, 33.9)
Maternal ethnicity, n (%)	
Dutch	445 (57)
Other Western	97 (13)
Non-Western	235 (30)
Maternal education, n (%)	
Low	113 (15)
Intermediate	228 (30)
High	411 (55)
Missing (n)	25
Household income, n (%)	
<1200 € per month	86 (13)
1200–2000 € per month	112 (17)
>2000 € per month	477 (71)
Missing (n)	102
Pre-pregnancy BMI, kg/m^2, median (25th, 75th percentile)	22.4 (20.7, 25.1)
Missing (n)	97
Parity, n (%)	
0	483 (63)
1	204 (26)
2+	86 (11)
Missing (n)	4
Marital status, n (%)	
Married/living with partner	670 (90)
No partner	78 (10)
Missing (n)	29
Smoking, n (%)	
No smoking during pregnancy	550 (77)
Until pregnancy recognized	62 (9)
Continued during pregnancy	102 (14)
Missing (n)	63
Alcohol consumption, n (%)	
No alcohol during pregnancy	271 (38)
Until pregnancy recognized	130 (18)
Continued during pregnancy	305 (43)
Missing (n)	71
Folate intake, n (%)	
None	97 (16)
Started in first 10 weeks of pregnancy	211 (34)
Started preconception	314 (51)
Missing (n)	155
Vegetable intake, kcal, median (25th, 75th percentile)	140.8 (107.9, 182.7)
Missing (n)	174
Fruit intake, kcal, median (25th, 75th percentile)	191.4 (121.9, 231.3)
Missing (n)	174
Total caloric intake, kcal, median (25th, 75th percentile)	2095.8 (1733.8, 2449.4)
Missing (n)	174
Fetal sex assigned at birth, n (%)	
Male	392 (51)
Female	385 (50)

Percentages missing: maternal education (3%), paternal education (27%), household income (13%), body mass index (13%), parity (1%), marital status (4%), smoking (8%), alcohol consumption (9%), folate intake (20%), vegetable intake (23%), fruit intake (23%), total caloric intake (23%).

BMI indicates body mass index.

TABLE 2. Distribution of Average Exposure Biomarker Concentrations (ng/mL) in the Generation R Participants Included in this Analysis (n = 777)

Biomarker	LOD	N (%) > LOD[a]	GM	Percentiles				
				5th	25th	50th	75th	95th
OP pesticides								
DEP	0.50	776 (100)	4.33	1.60	2.89	4.38	6.44	12.0
DETP	0.12	770 (99)	1.05	0.23	0.61	1.12	1.92	4.04
DMDTP	0.09	767 (99)	0.48	0.14	0.28	0.47	0.77	1.95
DMP	0.26	777 (100)	14.8	6.76	10.7	14.9	20.8	34.0
DMTP	0.40	777 (100)	12.4	3.27	8.18	13.3	20.3	35.7
Phthalates								
MEP	0.06	777 (100)	150	24.1	62.5	154	348	922
MMP	0.06	777 (100)	5.78	2.19	3.74	5.30	7.84	21.7
MiBP	0.09	777 (100)	20.2	6.32	12.2	18.8	31.4	87.1
MBP	0.14	777 (100)	15.7	5.04	9.99	15.4	24.3	49.9
MECPP	0.29	777 (100)	19.0	7.03	12.6	18.5	27.9	58.1
MCMHP	0.04	777 (100)	7.60	3.00	5.31	7.25	10.7	21.7
MEHHP	0.08	777 (100)	11.2	3.53	7.36	11.3	17.7	35.7
MEOHP	0.04	777 (100)	9.99	3.14	6.32	9.92	15.7	31.4
MCPP	0.008	777 (100)	1.7	0.67	1.11	1.69	2.48	4.73
MBzP	0.015	777 (100)	3.69	0.39	2.07	4.25	7.95	19.6
PA	1.11	777 (100)	110	40.4	68.6	108	166	331
Bisphenols								
BPA	0.15	773 (99)	1.45	0.43	0.85	1.42	2.42	5.44
BPF	0.18	475 (61)	0.28	0.10	0.17	0.27	0.45	0.98
BPS	0.05	666 (86)	0.14	0.04	0.07	0.13	0.24	0.61

Biomarker concentrations displayed have been corrected for urine dilution using a covariate-adjusted standardization approach with urine creatinine.

[a]N (%) of participants with at least one biomarker measurement above the LOD.

BPA indicates bisphenol A; BPF, bisphenol F; BPS, bisphenol S; DEP, diethylphosphate; DETP, diethylthiophosphate; DMDTP, dimethyldithiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; GM, geometric mean; LOD, limit of detection; MBP, mono-n-butyl phthalate; MBzP, monobenzyl phthalate; MCMHP, mono[(2-carboxymethyl) hexyl] phthalate, MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; MMP, monomethyl phthalate; OP, organophosphate; PA, phthalic acid.

Growth Trajectories

We selected a 4-class solution for fetal-to-childhood weight trajectories (Figure 1; eTable 2; http://links.lww.com/EDE/C164). We observed a trajectory with increasing weight from the prenatal period into infancy and average weight during childhood (Class 1, n = 317) and another with average weight during the prenatal period and low weight during childhood (Class 2, n = 200). In addition, we observed a trajectory with weight that declined from the prenatal period through infancy and average weight throughout childhood (Class 3, n = 189). Last, we observed a class with a lower weight during the prenatal period and a higher weight during childhood (Class 4, n = 71). We designated Class 1 as the referent. Demographic and lifestyle characteristics according to class membership are in eTable 3; http://links.lww.com/EDE/C164.

We selected a 3-class solution for infant-to-childhood BMI trajectories (eFigure 2; http://links.lww.com/EDE/C164 and eTable 4; http://links.lww.com/EDE/C164). One class had approximately average BMI throughout childhood (Class 1, n = 400), and another had increasing BMI (Class 2, n = 212) or decreasing BMI (Class 3, n = 165). Demographics and lifestyle characteristics by class membership are shown in eTable 5; http://links.lww.com/EDE/C164. We designated Class 1 as the referent. Cross-tabulation of weight and BMI trajectory membership is shown in eTable 6; http://links.lww.com/EDE/C164.

Single-pollutant Associations with Growth Trajectories

After adjusting for potential confounders, diethylphosphate (OR = 0.78; 95% CI = 0.61, 1.0), dimethyldithiophosphate (OR = 0.79; 95% CI = 0.62, 1.0) and dimethylphosphate (OR = 0.75; 95% CI = 0.60, 0.94) were associated with lower odds of membership in Class 2, characterized by average prenatal and smaller childhood weight, relative to the referent Class 1 (Figure 2; eTable 7; http://links.lww.com/EDE/C164). We observed positive associations between phthalic acid (OR = 1.4; 95% CI = 1.1, 1.9) and BPA (OR = 1.5; 95% CI = 1.0, 2.2) and the odds of membership in Class 4, characterized by smaller prenatal and larger childhood weight, relative to Class 1.

We observed consistent associations in unadjusted models (eTable 8; http://links.lww.com/EDE/C164) and models excluding fruit and vegetable intake (eTable 9; http://links.lww.com/EDE/C164) or folate intake (eTable 10; http://links.lww.com/EDE/C164). We observed little evidence of sex-specific effects, except for monoisobutyl phthalate ($p_{interaction}$ = 0.06), though 95% CIs for sex-specific estimates overlapped substantially in stratified models (eTable 11; http://links.lww.com/EDE/C164). Associations for membership in the Class 4 class tended to be stronger for males than females. For example, the association between PA was positive among males (OR = 2.5; 95% CI = 1.6, 3.8) and null among females (OR = 0.98; 95% CI = 0.62, 1.5) in stratified models.

For BMI trajectories, we observed a positive association between phthalic acid and membership in Class 2 (OR = 1.3; 95% CI = 1.1, 1.6), which comprised children with increasing BMI, and several negative associations between phthalate metabolites, including phthalic acid, and Class 3, which comprised children with decreasing BMI, relative to Class 1 (eTable 12; http://links.lww.com/EDE/C164).

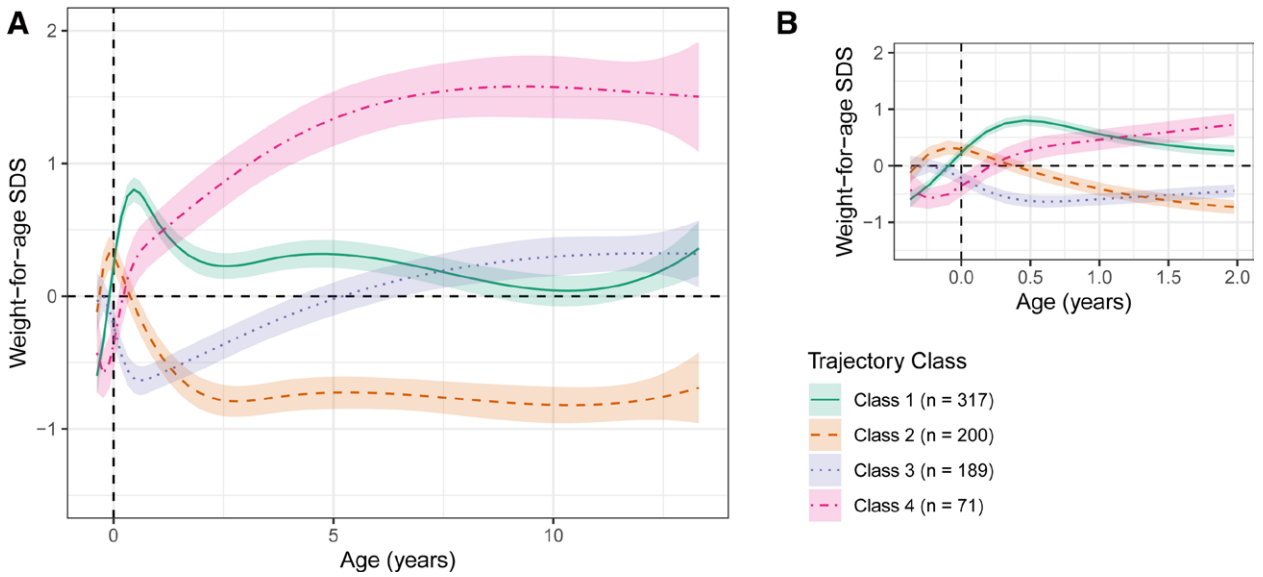

FIGURE 1. Trajectories of weight development in Generation R participants. (A) Predicted mean weight standard deviation score (SDS) from 18 weeks gestation to age 13 for each trajectory class identified in the Generation R participants included in this analysis (n = 777). (B) Close-up view of predicted mean weight SDS trajectories between 18 weeks gestation and age 2. Models include a cubic b-spline for age with 3 knots. Black dashed line indicates average growth (SDS = 0).

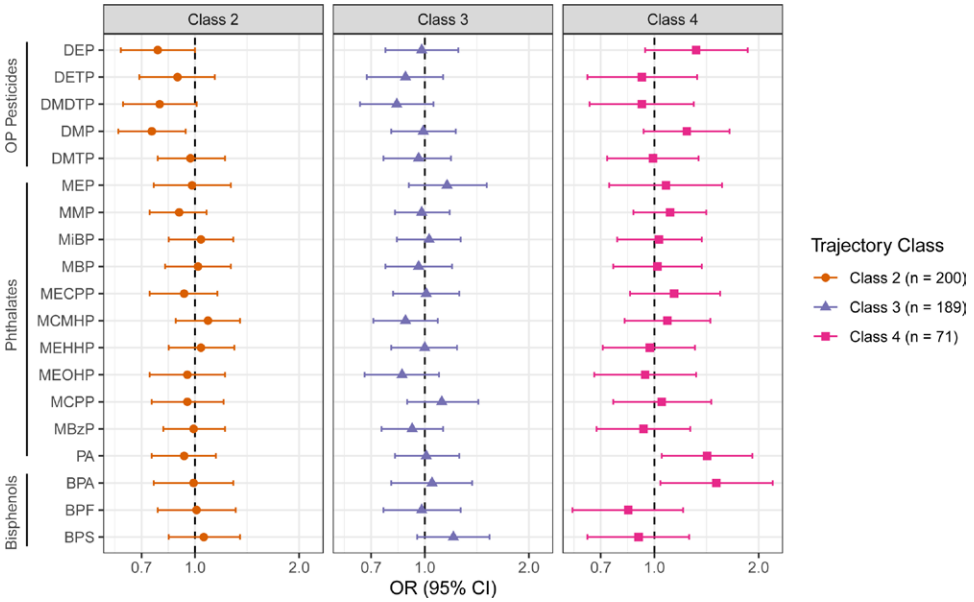

FIGURE 2. Adjusted odds ratio (OR) (95% confidence interval [CI]) of weight trajectory class membership associated with an interquartile range width increase in each exposure biomarker for Generation R participants included in this analysis (n = 777). Multinomial logistic regression models adjusted for maternal age, pre-pregnancy BMI, maternal education, household income, parity, marital status, smoking, alcohol consumption, folate intake, vegetable intake, fruit intake, total caloric intake, and fetal sex. Class 1 (n = 317) is the referent.

Multi-pollutant Associations with Growth Trajectories

We found null associations for the overall mixture and weight trajectories (Figure 3; eTable 13; http://links.lww.com/EDE/C164). When we examined multi-pollutant associations by chemical class, we observed an inverse association between a simultaneous 1-quartile increase in all dialkyl phosphates and Class 2 membership (OR = 0.77; 95% CI = 0.60, 0.98), characterized by average prenatal and low childhood weight, relative to Class 1. We found no associations between the mixtures and BMI trajectory classes (eTable 14; http://links.lww.com/EDE/C164).

DISCUSSION

In participants from the Generation R study, we investigated associations between prenatal exposure to organophosphate pesticides, phthalates, and bisphenols with weight trajectories from the prenatal period to 13 years of age and BMI trajectories from 2 months to 13 years of age. Notably, among the weight trajectories we identified, we observed one characterized by smaller weight during the prenatal period and larger childhood weight, which is similar to patterns of "catch-up" growth that have previously been associated with adverse cardiometabolic outcomes.[4–6] We further observed that prenatal exposure to phthalic acid and BPA was associated with membership in this trajectory compared to a referent characterized by a larger weight from the prenatal period to infancy and average childhood weight. In addition, we observed that prenatal exposure to dialkyl phosphate was associated with lower odds of a trajectory characterized by average weight during the prenatal period and smaller childhood weight compared to the same referent.

The associations we identified between growth trajectories and phthalate exposure were limited to phthalic acid, a nonspecific metabolite produced as a common final metabolite of all phthalates.[42] In the absence of associations with specific phthalate metabolites, this could reflect (1) joint effects of multiple phthalates represented by phthalic acid, although our quantile g-computation results do not support this interpretation, or (2) effects of unmeasured phthalates not included on standard biomarker panels. Previous studies in the Generation R cohort have provided evidence consistent with our findings. For example, an analysis examining prenatal phthalate exposure and fetal growth reported associations between phthalic acid and smaller size during gestation and at delivery.[41] A separate study of prenatal phthalate exposure and adiposity at age 10 found that phthalic acid was also associated with higher BMI and pericardial fat index.[43] While these previous studies provide evidence that phthalates alter in utero and childhood growth, they do not elucidate whether this is a pattern of growth experienced by single individuals or whether separate groups are affected at different life stages. By using growth mixture models, we identified subgroups of individuals in the population with shared trajectories of growth, including one characterized by smaller prenatal and larger childhood weight. Notably, this trajectory was associated with exposure to several biomarkers of exposure, including phthalic acid. Taken together, these findings further provide support for the

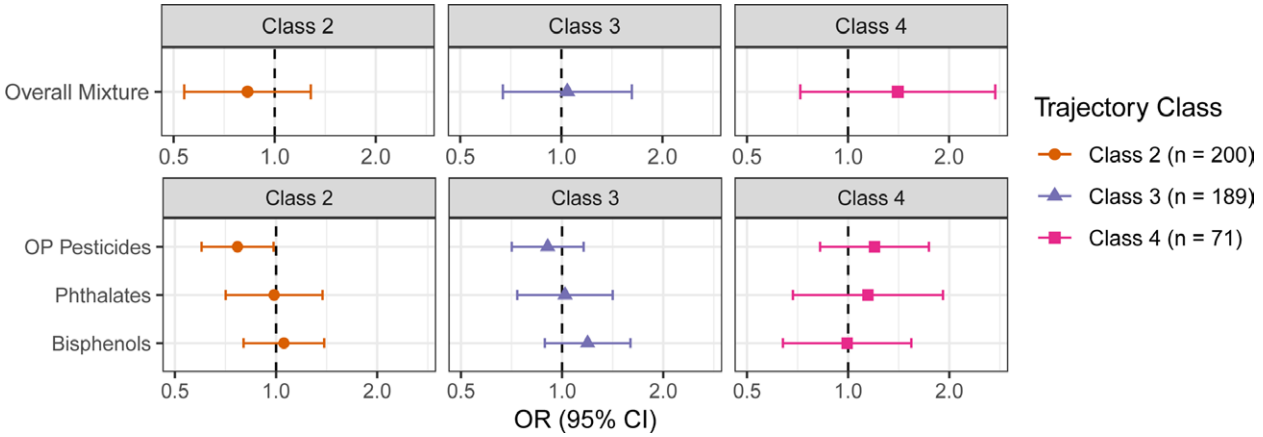

FIGURE 3. Adjusted odds ratio (OR) (95% confidence interval [CI]) of weight trajectory class membership associated with a simultaneous 1-quartile increase in the overall mixture and by chemical class for Generation R participants included in his analysis (n = 777). Multinomial logistic regression models adjusted for maternal age, prepregnancy BMI, maternal education, household income, parity, marital status, smoking, alcohol consumption, folate intake, vegetable intake, fruit intake, total caloric intake, and fetal sex. Estimates for chemical classes are co-adjusted for all others. Class 1 (n = 317) is the referent. Chemical classes defined as organophosphate (OP) pesticides (including diethylphosphate [DEP], diethylthiophosphate [DETP], dimethyldithiophosphate [DMDTP], dimethylphosphate [DMP], and dimethylthiophosphate [DMTP]), phthalates (including monoethyl phthalate [MEP], monomethyl phthalate [MMP], monoisobutyl phthalate [MiBP], mono-n-butyl phthalate [MBP], mono(2-ethyl-5-carboxypentyl) phthalate [MECPP], mono[(2-carboxymethyl) hexyl] phthalate [MCMHP], mono(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP], mono(2-ethyl-5-oxohexyl) phthalate [MEOHP], mono(3-carboxypropyl) phthalate [MCPP], monobenzyl phthalate [MBzP], and phthalic acid [PA]), and bisphenols (including bisphenol A [BPA], bisphenol F [BPF], and bisphenol S [BPS]).

hypothesis that phthalate exposure is associated with reduced prenatal growth and increased growth during childhood.

Previously, an analysis using data from The Infant Development and the Environment Study (n = 780) examined fetal-to-childhood growth trajectories and prenatal phthalate exposure. While the analysis identified similar latent trajectories of weight development in The Infant Development and the Environment Study participants, as we report in the present analysis, associations between these trajectories and phthalate exposure were null.[44] Other studies have also applied growth mixture models to derive trajectories of childhood growth and adiposity, though no others included prenatal measures. For example, analyses from the Center for the Health Assessment of Mothers and Children of Salinas (n = 335) and the Programming Research in Obesity, Growth Environment, and Social Stress (n = 514) cohort both reported associations between metabolites of di(2-ethylhexyl) phthalate and trajectories of high childhood adiposity.[45,46] In agreement with these findings, a recent systematic review of prenatal phthalate exposure and child adiposity highlighted other prospective studies that similarly reported associations with higher child weight or BMI.[13] In addition, there is some toxicologic evidence to support a link between prenatal phthalate exposure and growth trajectories. Specifically, prenatal di(2-ethylhexyl) phthalate exposure in male rats resulted in a lower proportion of body fat at birth, followed by catch-up by postnatal day 21, and excess body fat during the postpubertal and adult stages.[47] However, the literature is far from consistent. For example, a recent analysis of birth-to-childhood BMI trajectories in the Infancia y Medio Ambiente (n = 1911) study reported null associations with phthalate exposure.[17]

We also observed an association between maternal BPA exposure and the weight trajectory, characterized by smaller prenatal and higher childhood weight. In contrast, previous Generation R studies have found null associations between BPA exposure and both fetal[30] and childhood[43] growth. Other studies on BPA exposure and fetal growth have also reported primarily null findings,[48–50] while studies examining childhood growth have reported inconsistent directions of effect.[16,51,52] Notably, two previous studies have examined prenatal BPA exposure and birth-to-childhood trajectories of BMI. A study of children in Mexico City (n = 249) and an analysis from the Infancia y Medio Ambiente cohort reported null associations with BMI trajectories, though weight trajectories were not considered.[14,17] Results from the corresponding animal literature are also mixed. However, several in vivo studies have shown that low dose in utero exposure to BPA results in higher weight and/or adiposity in offspring.[53–57]

Fewer studies have examined the association between organophosphate pesticides and either fetal or childhood growth, though they have been linked with other developmental outcomes.[18] In the current analysis, we found that dialkyl phosphates, individually and as a mixture, were negatively associated with a weight trajectory characterized by average prenatal and smaller childhood weight compared to a referent trajectory of larger weight from the prenatal

period into infancy and average weight during childhood. Previous studies in Generation R have observed smaller fetal size associated with dialkyl phosphates, though associations with birthweight[22,29] and childhood adiposity were null.[58] Notably, an occupational study in Denmark that examined children (n = 177) born to women working in greenhouses during pregnancy reported that children with high in utero pesticide exposure had lower birthweights and higher measures of adiposity during childhood.[59] While this study did not capture measures of exposure to specific pesticides, participants reported frequent use of organophosphate pesticides.[60] Similarly, in rats, gestational and lactational exposure to chlorpyrifos, an organophosphate pesticide that, in part, metabolizes to diethylphosphate and diethylthiophosphate, did not alter birthweights but did induce an increase in weight later in development.[61] Together, these studies provide some evidence that prenatal exposure to organophosphate pesticides may alter fetal-to-childhood growth trajectories, though more research is needed.

This study has several limitations. First, we used a subset of the Generation R study that had complete measures of dialkyl phosphate, phthalate metabolites, and bisphenols and data available at age six. The selected participants were more likely to be Dutch, had higher educational attainment, and had higher household incomes than the underlying cohort.[22] Therefore, there is the potential for selection bias to affect the internal validity of these results. However, previous studies have not found evidence of bias in sensitivity analyses accounting for differences between this sample and the overall Generation R Study.[40,62–64] Second, we used growth mixture models to identify trajectories of weight and BMI. While these trajectories are treated as fixed in our analysis, the group assignments contain uncertainty, which may bias exposure-outcome associations toward the null.[33,65] Third, while our study is novel in that it includes growth from the prenatal period to early adolescence, weights during these life stages are measured with different precision and standardized using different referent populations. The shape and, therefore, interpretation of our trajectories may be biased at the transitions between growth charts. For example, research on the transition between the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH 21st), newborn growth charts and the World Health Organization childhood growth charts demonstrated the potential for misleading trajectories of growth depending on the timing of delivery, even among term births.[66] This could lead to bias in our findings if the exposures under investigation in this study were also associated with the timing of delivery. However, there is limited evidence for such associations in this study population.[30,41] Fourth, we measured exposure biomarkers at three different timepoints during pregnancy. While this is more timepoints than previous studies on this topic,[17,44–46] attenuation bias may still be present due to the nonpersistent properties of these chemicals. In addition, while the large number of exposures available for analysis is a strength, it increases the risk of making a type 1 error due to multiple comparisons. Last, we considered the prenatal period as a critical window of susceptibility but were unable to investigate the role of exposures during different life stages. Previous studies have demonstrated the low correlation between nonpersistent exposure biomarkers measured at different life stages, suggesting that this would not be a source of bias in our study.[67,68]

Our study is strengthened by using a relatively large (n = 777) sample from a well-characterized prospective cohort. The Generation R study collected weight at up to 15 visits and BMI at up to 12 visits, which were used for an application of growth mixture models to derive weight and BMI trajectories. While several studies have examined chemical exposure and childhood growth trajectories using similar methodologies,[17,44–46] ours includes measures of fetal, infant, and child size, which is unique compared to other populations. We also had 19 different biomarkers of exposure corresponding to three chemical classes (e.g., organophosphate pesticides, phthalates, and bisphenols), which we considered individually and as mixtures. Last, though we could not account for all possible lifestyle and demographic factors that could act as confounders, we were able to adjust for dietary factors that may be related to both exposure and growth.[36,37]

CONCLUSIONS

In this analysis of chemical exposures and fetal-to-childhood growth trajectories in the Generation R Study, we identified associations between nonpersistent chemical exposures and growth characterized by small prenatal and large childhood weight. Given existing evidence that links similar growth trajectories to adverse outcomes during adulthood, these results support the hypothesis that prenatal chemical exposures have long-lasting impacts on health.

REFERENCES

1. Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. *JAMA Pediatr*. 2020;174:772–781.
2. de Mendonça E, de Lima Macêna M, Bueno NB, de Oliveira ACM, Mello CS. Premature birth, low birth weight, small for gestational age and chronic non-communicable diseases in adult life: a systematic review with meta-analysis. *Early Hum Dev*. 2020;149:105154.
3. Hundscheid TM, Villamor-Martinez E, Villamor E. Association between endotype of prematurity and mortality: a systematic review, meta-analysis, and meta-regression. *Neonatology*. 2023;120:407–416.
4. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med*. 2005;353:1802–1809.
5. Castanys-Muñoz E, Kennedy K, Castañeda-Gutiérrez E, et al. Systematic review indicates postnatal growth in term infants born small-for-gestational-age being associated with later neurocognitive and metabolic outcomes. *Acta Paediatr*. 2017;106:1230–1238.
6. Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. *BMJ*. 2001;322:949–953.
7. Zheng T, Zhang J, Sommer K, et al. Effects of environmental exposures on fetal and childhood growth trajectories. *Ann Glob Health*. 2016;82:41–99.

8. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. *Environ Health Perspect*. 2011;119:878–885.
9. Martin L, Zhang Y, First O, et al. Lifestyle interventions to reduce endocrine-disrupting phthalate and phenol exposures among reproductive age men and women: a review and future steps. *Environ Int*. 2022;170:107576.
10. Lu C, Barr DB, Pearson MA, Waller LA. Dietary intake and its contribution to longitudinal organophosphorus pesticide exposure in urban/suburban children. *Environ Health Perspect*. 2008;116:537–542.
11. Kamai EM, McElrath TF, Ferguson KK. Fetal growth in environmental epidemiology: mechanisms, limitations, and a review of associations with biomarkers of non-persistent chemical exposures during pregnancy. *Environ Health*. 2019;18:43.
12. Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nat Rev Endocrinol*. 2017;13:161–173.
13. Gao H, Wang Y-f, Wang Z-w, Wang Y, Tao F-b. Prenatal phthalate exposure associated with age-specific alterations in markers of adiposity in offspring: a systematic review. *Ecotoxicol Environ Saf*. 2022;232:113247.
14. Yang TC, Peterson KE, Meeker JD, et al. Exposure to bisphenol A and phthalates metabolites in the third trimester of pregnancy and BMI trajectories. *Pediatr Obes*. 2018;13:550–557.
15. Vafeiadi M, Roumeliotaki T, Myridakis A, et al. Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood. *Environ Res*. 2016;146:379–387.
16. Braun JM, Lanphear BP, Calafat AM, et al. Early-life bisphenol a exposure and child body mass index: a prospective cohort study. *Environ Health Perspect*. 2014;122:1239–1245.
17. Montazeri P, Güil-Oumrait N, Marquez S, et al. Prenatal exposure to multiple endocrine-disrupting chemicals and childhood BMI trajectories in the INMA cohort study. *Environ Health Perspect*. 2023;131:107006.
18. Muñoz-Quezada MT, Lucero BA, Barr DB, et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: a systematic review. *Neurotoxicology*. 2013;39:158–168.
19. Svensson K, Tanner E, Gennings C, et al. Prenatal exposures to mixtures of endocrine disrupting chemicals and children's weight trajectory up to age 5.5 in the SELMA study. *Sci Rep*. 2021;11:11036.
20. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol*. 2016;31:1243–1264.
21. Hofman A, Jaddoe VW, Mackenbach JP, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. *Paediatr Perinat Epidemiol*. 2004;18:61–72.
22. van den Dries MA, Keil AP, Tiemeier H, et al. Prenatal exposure to non-persistent chemical mixtures and fetal growth: a population-based study. *Environ Health Perspect*. 2021;129:117008.
23. van den Dries MA, Ferguson KK, Keil AP, et al. Prenatal exposure to non-persistent chemical mixtures and offspring IQ and emotional and behavioral problems. *Environ Sci Technol*. 2021;55:16502–16514.
24. Kruithof CJ, Kooijman MN, van Duijn CM, et al. The generation R Study: biobank update 2015. *Eur J Epidemiol*. 2014;29:911–927.
25. Verburg BO, Steegers EA, De Ridder M, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol*. 2008;31:388–396.
26. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol*. 1985;151:333–337.
27. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand*. 1991;80:756–762.
28. Gaillard R, Steegers EA, de Jongste JC, Hofman A, Jaddoe VW. Tracking of fetal growth characteristics during different trimesters and the risks of adverse birth outcomes. *Int J Epidemiol*. 2014;43:1140–1153.
29. Ferguson KK, van den Dries MA, Gaillard R, et al. Organophosphate pesticide exposure in pregnancy in association with ultrasound and delivery measures of fetal growth. *Environ Health Perspect*. 2019;127:87005.
30. Sol CM, van Zwol-Janssens C, Philips EM, et al. Maternal bisphenol urine concentrations, fetal growth and adverse birth outcomes: a population-based prospective cohort. *Environ Health*. 2021;20:60.
31. Verburg BO, Mulder PG, Hofman A, Jaddoe VWV, Witteman JCM, Steegers EAP. Intra- and interobserver reproducibility study of early fetal growth parameters. *Prenat Diagn*. 2008;28:323–331.
32. Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. *J Stat Softw*. 2017;78:1–56.
33. Van De Schoot R, Sijbrandij M, Winter SD, Depaoli S, Vermunt JK. The GRoLTS-checklist: guidelines for reporting on latent trajectory studies. *Struct Equ Modeling*. 2017;24:451–467.
34. Alders M. Classification of the population with a foreign background in the Netherlands. Statistic Netherlands, paper for the conference. "The measure and mismeasure of populations. The statistical use of ethnic and racial categories in multicultural societies", Paris, 2001;18.
35. Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, et al. Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. *Eur J Clin Nutr*. 1998;52:588–596.
36. Philips EM, Jaddoe VWV, Asimakopoulos AG, et al. Bisphenol and phthalate concentrations and its determinants among pregnant women in a population-based cohort in the Netherlands, 2004–5. *Environ Res*. 2018;161:562–572.
37. van den Dries MA, Pronk A, Guxens M, et al. Determinants of organophosphate pesticide exposure in pregnant women: a population-based cohort study in the Netherlands. *Int J Hyg Environ Health*. 2018;221:489–501.
38. Keil A. qgcomp: Quantile G-Computation. 2022.
39. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw*. 2011;45:1–67.
40. Dries MA, Guxens M, Spaan S, et al. Phthalate and bisphenol exposure during pregnancy and offspring nonverbal IQ. *Environ Health Perspect*. 2020;128:077009.
41. Santos S, Sol CM, van Zwol-Janssens C, et al. Maternal phthalate urine concentrations, fetal growth and adverse birth outcomes. A population-based prospective cohort study. *Environ Int*. 2021;151:106443.
42. Bang DY, Lee IK, Lee BM. Toxicological characterization of phthalic acid. *Toxicol Res*. 2011;27:191–203.
43. Sol CM, Santos S, Duijts L, et al. Fetal exposure to phthalates and bisphenols and childhood general and organ fat. A population-based prospective cohort study. *Int J Obes (Lond)*. 2020;44:2225–2235.
44. Ferguson KK, Bommarito PA, Arogbokun O, et al. Prenatal phthalate exposure and child weight and adiposity from in utero to 6 years of age. *Environ Health Perspect*. 2022;130:47006.
45. Heggeseth BC, Holland N, Eskenazi B, Kogut K, Harley KG. Heterogeneity in childhood body mass trajectories in relation to prenatal phthalate exposure. *Environ Res*. 2019;175:22–33.
46. Kupsco A, Wu H, Calafat AM, et al. Prenatal maternal phthalate exposures and trajectories of childhood adiposity from four to twelve years. *Environ Res*. 2022;204:112111.
47. Strakovsky RS, Lezmi S, Shkoda I, Flaws JA, Helferich WG, Pan Y-X. In utero growth restriction and catch-up adipogenesis after developmental di (2-ethylhexyl) phthalate exposure cause glucose intolerance in adult male rats following a high-fat dietary challenge. *J Nutr Biochem*. 2015;26:1208–1220.
48. Guo J, Liu K, Yang J, Su Y. Prenatal exposure to bisphenol A and neonatal health outcomes: a systematic review. *Environ Pollut*. 2023;335:122295.
49. Casas M, Valvi D, Ballesteros-Gomez A, et al. Exposure to Bisphenol A and phthalates during pregnancy and ultrasound measures of fetal growth in the INMA-Sabadell Cohort. *Environ Health Perspect*. 2016;124:521–528.
50. Cowell W, Jacobson MH, Long SE, et al. Maternal urinary bisphenols and phthalates in relation to estimated fetal weight across mid to late pregnancy. *Environ Int*. 2023;174:107922.
51. Harley KG, Schall RA, Chevrier J, et al. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. *Environ Health Perspect*. 2013;121:514–520.
52. Valvi D, Casas M, Mendez MA, et al. Prenatal bisphenol A urine concentrations and early rapid growth and overweight risk in the offspring. *Epidemiology*. 2013;24:791–799.
53. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, Vom Saal FS. Exposure to bisphenol A advances puberty. *Nature*. 1999;401:763–764.
54. Wei J, Lin Y, Li Y, et al. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology*. 2011;152:3049–3061.
55. Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. *Endocrinology*. 2004;145:592–603.

56. Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect*. 2001;109:675–680.
57. Patisaul HB, Bateman HL. Neonatal exposure to endocrine active compounds or an ERβ agonist increases adult anxiety and aggression in gonadally intact male rats. *Horm Behav*. 2008;53:580–588.
58. Blaauwendraad SM, Stevens DR, van den Dries MA, et al. Fetal organophosphate exposure and childhood adiposity measures in the general population. *Environ Health Perspect*. 2023;131:087014.
59. Wohlfahrt-Veje C, Main KM, Schmidt IM, et al. Lower birth weight and increased body fat at school age in children prenatally exposed to modern pesticides: a prospective study. *Environ Health*. 2011;10:79.
60. Naksen W, Prapamontol T, Mangklabruks A, et al. Associations of maternal organophosphate pesticide exposure and PON1 activity with birth outcomes in SAWASDEE birth cohort, Thailand. *Environ Res*. 2015;142:288–296.
61. Lassiter TL, Brimijoin S. Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos. *Neurotoxicol Teratol*. 2008;30:125–130.
62. Jusko TA, van den Dries MA, Pronk A, et al. Organophosphate pesticide metabolite concentrations in urine during pregnancy and offspring nonverbal IQ at age 6 years. *Environ Health Perspect*. 2019;127:17007.
63. van den Dries MA, Lamballais S, El Marroun H, et al. Prenatal exposure to organophosphate pesticides and brain morphology and white matter microstructure in preadolescents. *Environ Res*. 2020;191:110047.
64. Mulder TA, van den Dries MA, Korevaar TIM, Ferguson KK, Peeters RP, Tiemeier H. Organophosphate pesticides exposure in pregnant women and maternal and cord blood thyroid hormone concentrations. *Environ Int*. 2019;132:105124.
65. Kamata A, Kara Y, Patarapichayatham C, Lan P. Evaluation of analysis approaches for latent class analysis with auxiliary linear growth model. *Front Psychol*. 2018;9:130.
66. Perumal N, Ohuma EO, Prentice AM, et al. Implications for quantifying early life growth trajectories of term-born infants using INTERGROWTH-21st newborn size standards at birth in conjunction with World Health Organization child growth standards in the postnatal period. *Paediatr Perinat Epidemiol*. 2022;36:839–850.
67. Quirós-Alcalá L, Alkon AD, Boyce WT, et al. Maternal prenatal and child organophosphate pesticide exposures and children's autonomic function. *Neurotoxicology*. 2011;32:646–655.
68. Shoaff J, Papandonatos GD, Calafat AM, et al. Early-life phthalate exposure and adiposity at 8 years of age. *Environ Health Perspect*. 2017;125:097008.