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Prenatal exposure to phthalates and child growth trajectories in the first 24 months of life

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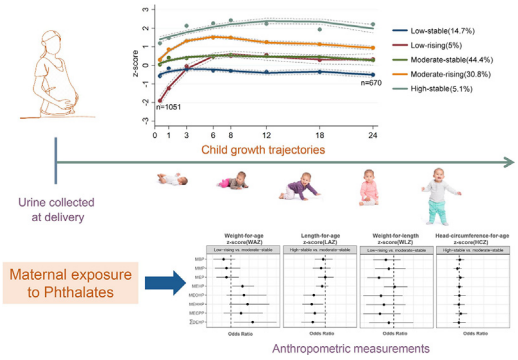
HIGHLIGHTS

- GBTM is a method for estimating latent trajectories using trajectory groups.
- The GBTM approach is effective in revealing heterogeneity in growth trajectories.
- Phthalate exposure was associated with postnatal child growth trajectories.
- Prenatal phthalate exposure affects child growth differently by gender.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Phthalates are a class of environmental chemicals with endocrine-disrupting properties. Prenatal phthalate exposure has been associated with adverse developmental outcomes in childhood. However, data assessing the effects of prenatal phthalate exposure on postnatal infant growth trajectories are sparse.
Objectives: To evaluate the associations of prenatal phthalate exposure with child growth trajectories from birth to 24 months old.
Methods: Within a Chinese birth cohort study, 1051 mother-offspring pairs were included. Seven phthalate metabolites were quantified in maternal urine collected between weeks 33 and 39 of gestation. The trajectories for weight-for-age z-score (WAZ), length-for-age z-score (LAZ), weight-for-length z-score (WLZ) and head-circumference-for-age z-score (HCZ) were determined by group-based trajectory modeling (GBTM). Multinomial logistic regression and the weighted quantile sum approach (WQS) were used to investigate the association between individual and phthalate mixture exposure and the growth trajectories of four anthropometric metrics.
Results: Five trajectory groups were identified for each anthropometric measure using GBTM. Higher prenatal exposure to several phthalate metabolites (MEHP, MEHHP, MEOHP, MECCP, summed DEHP metabolites, as well as MBP) was associated with child growth trajectories, especially for WAZ and LAZ in the first 24 months of life. The associations

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were further confirmed by a mixture analysis of phthalate metabolites and a sex-specific effect was observed in the WAZ and LAZ trajectories.
Conclusion: Prenatal phthalate exposure had heterogeneous associations with postnatal growth trajectories. More studies are warranted to confirm and elucidate the meaning of our findings.

1. Introduction

Phthalates are widely used as plasticizers in various consumer products, such as cosmetics, personal care products, food packaging, children's toys, and medical devices (Téllez-Rojo et al., 2013). About several million tons of phthalates are consumed annually worldwide, and China is one of the biggest consumer markets (Wang et al., 2018). High-molecular-weight phthalates, such as di(2-ethylhexyl) phthalate (DEHP), are frequently used in polyvinyl chloride (PVC) products, including construction materials, and consumer goods (clothing, food packaging and toys). Low-molecular-weight phthalates, such as diethyl phthalate (DEP) and dibutyl phthalate (DBP), are primarily used in non-PVC applications, including personal-care products, paints and enteric-coated capsules (Valvi et al., 2015). The public is widely exposed to phthalates via inhalation, ingestion, skin contact, and medical procedures (Gao et al., 2022b). Notably, most women of reproductive age (15–44 years old) in the US have urinary concentrations of phthalates that are above the levels of detection (88–100 %) (Pacyga et al., 2019). As one of the endocrine-disrupting chemicals, phthalates can pass through the fetal placental barrier during pregnancy, thus posing a threat to the fetus' development in the early stages of life (Tang et al., 2020).

Several systematic reviews and meta-analyses have investigated how prenatal phthalate exposure affects birth size, preterm birth, and obesity in postnatal childhood (Gao et al., 2022c; Radke et al., 2019; Zhong et al., 2021); however, the association of phthalate exposure with growth early in life is still controversial. Prenatal phthalate exposure may exhibit contradictory and complex connections with childhood growth at various developmental stages (Shoaff et al., 2016; Suzuki et al., 2010; Zhu et al., 2018). Whereas, it is suggested that the growth process in the first two years of life should receive more consideration than other periods of life, as this is the time with the greatest change in weight gain rate (Gao et al., 2022d). Furthermore, most previous studies that have investigated the relationship between phthalate exposure and growth outcomes virtually exclusively employed static anthropometric techniques (generalized least squares, linear mixed effects model or estimating equation model), leaving out crucial details on dynamic growth processes (Buckley et al., 2016b; Gyllenhammar et al., 2018; Maresca et al., 2016). Given that infant development during the early stages of life is diverse, including variations in weight gain, height growth, and other aspects, it is necessary to account for these differences by using sophisticated analytical methods to model multiple growth trajectories, instead of relying on a single average growth pattern (Herle et al., 2020). Importantly, childhood growth trajectories are more predictive of subsequent health than any cross-sectional assessment (Song et al., 2018).

Numerous methods have been put forth to detect different growth trajectories in early childhood (Gao et al., 2022c; Tu et al., 2013). To distinguish between several trajectory groups within the same population, group-based trajectory modeling (GBTM) offers a flexible method for achieving this goal (Nagin and Tremblay, 2001). Recently, the GBTM approach has become more popular in biomedical research, such as studies of childhood BMI (Zhang et al., 2022). Nevertheless, few studies have used GBTM to evaluate the relationship between prenatal phthalate exposure and postnatal development trajectories (Gao et al., 2022a).

Given the existing evidence on the association between prenatal exposure to phthalates and adverse health outcomes during early childhood, we hypothesized that prenatal exposure to phthalates would be associated with alterations in the growth trajectories of Chinese infants during the first 24 months of life. To test this hypothesis, we used GBTM to profile growth trajectories and examined the relationship between phthalate exposure and specific trajectory groups.

2. Methods

2.1. Study population

This study was implemented within the birth cohort study conducted at Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital) from November 2012 and October 2019, for which detailed information can be found elsewhere (Liu et al., 2020). The inclusion criteria for recruiting participants are as follows: a) resident of Wuhan city, b) a singleton pregnancy <16 weeks of gestation at recruitment and c) prenatal care and delivery are planned at the study hospital. Between 2014 and 2016, a total of 1069 pregnant women were enrolled at their first prenatal visit and were followed. The enrollment rate was approximately 10 %. Details of the difference between enrolled and non-enrolled participants were listed in Table S1. The current study excluded 18 participants who had pre-existing diabetes or chronic hypertension (n = 15), lacked information on phthalates exposure (n = 1), or had birth defects in their newborns (n = 2). The final analysis included 1051 mother-offspring pairs. Among them, about 97 % were followed up at 1 month, 70–80 % at 3, 6, 8 and 12 months, and 60–65 % at 18 and 24 months. The comparison between the group lost to follow-up and those who continued in the study were listed in Table S2. The study protocol was approved by the Ethics Committee of Wuhan Women and Children Medical and Healthcare Center and Tongji Medical College, Huazhong University of Science and Technology. All mothers submitted signed informed consent after fully comprehending the research protocol.

2.2. Phthalate metabolite measurements

Maternal urine samples for phthalate metabolite measurements were collected between weeks 33 and 39 of gestation, and eight commonly detected phthalate metabolite [mono-butyl phthalate (MBP), mono-benzyl phthalate (MBzP), mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)] were measured by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Additionally, the sum of the molar concentrations of MEHP, MEOHP, MEHHP, and MECPP was used to calculate the total concentration of DEHP, expressed as ΣDEHP (Yu et al., 2021). The methods for phthalate measurement have been previously detailed (Li et al., 2021). The blank samples and quality control (QC) samples were analyzed together with every batch of test samples. The within-batch coefficient of variation (CV) and the between-batch CV were both <9.9 % and 13.7 %, respectively. Additional information about the analytical methods can be found in the Supplemental materials (Table S3). The limits of detection (LODs) were 0.5 μg/L for MMP, MBP, MEP and MEHP, 0.1 μg/L for MBzP, and 0.2 μg/L for MEOHP, MEHHP, and MECPP. Levels of urine phthalate metabolites below the LOD were replaced by the LOD divided by the square root of 2 (Hornung, 1990). To focus on the phthalate metabolites that are most relevant to our population, MBzP was not included in the analysis due to its low detection rate of 53.98 %, while all other metabolites had detection rates above 80 %. To adjust for urine dilution, urinary phthalate concentrations were corrected by urinary specific gravity (SG) according to the following formula: $P_{SG} = P[(1.012–1)/SG_i\text{-}1]$, where P_{SG}

represents the SG-corrected phthalates concentration, P denotes the original phthalates concentration, the value 1.012 is the median SG in this study population, and SG_i denotes the SG of the individual urine samples (Teass et al., 1998). For statistical analysis, the SG-corrected phthalate concentrations were used.

2.3. Anthropometric measurements

Weight and length at eight-time points were assessed by trained and standardized interviewers when the children were born, 1, 3, 6, 8, 12, 18 and 24 months old. Head circumferences were measured at all visits except at birth. Length and head circumference were measured using calibrated stadiometers or measuring tapes, to the nearest 0.1 cm, and undressed weight was measured using calibrated balance scales, to the nearest 0.1 kg. Using these measurements, we calculated the age-and sex-specified z-scores of weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), and head-circumference-for-age (HCZ) for children under 24 months old according to the 2006 World Health Organization growth reference standards(WHO, 2006). In particular, weight-for-length was used in this study instead of body mass index (BMI) because it was considered a more appropriate measurement for children under 2 years old (Gao et al., 2022d).

2.4. Covariates

A directed acyclic graph (DAG) was utilized to represent our priori causal hypotheses regarding the relationships between the phthalate metabolites and infant growth trajectories and to guide the variable selection approach. Based on the DAG theory and the available data, the analyses were adjusted for the following variables: maternal age at delivery, gestational age, educational level, pre-pregnancy BMI, gestational weight gain, parity, as well as active or passive smoking during pregnancy, delivery method, and infant sex (Santos et al., 2021; Stevens et al., 2022). Maternal age at delivery (continuous, years), pre-pregnancy BMI self-reported (continuous, kilograms per square meter), educational level (high school or less, associate, bachelor and graduate), as well as active or passive smoking during pregnancy (yes/no) were obtained by a structured questionnaire at recruitment. Maternal weight gain (in continuous kilograms) during pregnancy was calculated by subtracting pre-pregnancy weight (self-reported) from weight at the time of delivery admission. Data on parity (nulliparous/multiparous), delivery method, and infant sex (boys and girls) were obtained from hospital records. The DAG results highlighted maternal age, maternal education, and pre-pregnancy BMI as minimally sufficient adjustment sets (Fig. S1), which were adjusted in the main analysis. To account for any residual confounding, sensitivity models were further adjusted for gestational weight gain, active or passive smoking during pregnancy, delivery method, and infant sex.

2.5. Statistical analysis

A primary research aim was to determine the growth trajectories of WAZ, LAZ, WLZ, and HCZ from up to eight-time points between birth and 24 months of age. The development of these parameters from birth to two years old was evaluated using GBTM. GBTM is a special form of finite mixture modeling where it is assumed that the population consists of some meaningful subgroups that show statistically similar trajectories (Nagin et al., 2018). Moreover, GBTM could accommodate missing data by fitting the model using maximum likelihood estimation. More details regarding the statistical basis of GBTM can be found elsewhere (Bommarito et al., 2023).

Model selection strategies for GBTM were performed based on recommendations from early studies (Song, 2019). The optional group model (including the shape and the interpretability of the trajectories) was established based on the model fit using the Bayesian Information Criterion (BIC) and some rules as follows: (a) an average group posterior probability (AvePP) value for all groups should be >0.7; (b) the odds of correct classification based on the posterior probability of group membership exceed 5; (c) a preference for a practical, efficient model that accurately predicted the data; (d) a sufficient sample size in each group; and (e) confidence intervals that are reasonably narrow (Nagin and Odgers, 2010).

A descriptive analysis was performed to summarize the distribution of maternal characteristics. We also used Spearman correlation coefficients to calculate pairwise correlations between certain gravity-adjusted metabolites. Meanwhile, phthalate concentrations were log2-transformed to stabilize variances and facilitate interpretation of the study results on a multiplicative scale. Multinomial logistic regression was performed to assess the relationship between prenatal phthalate exposure and trajectory groups after controlling for possible confounding factors. Odds ratio (OR) with a 95 % confidence interval (CI) results were presented. The estimated effect was interpreted as the odds of being in a trajectory group for a doubling in prenatal phthalate concentrations compared to the reference group. We further explored the potential effect modification of fetal sex by including an interaction term (sex × phthalate) in the regression model. We considered modifications to be statistically significant if the *p*-value for the likelihood ratio test of the interaction term was <0.10.

The weighted quantile sum (WQS) regression model was implemented to evaluate the joint effect exposure to seven phthalate metabolites on each trajectory(Carrico et al., 2015). We developed a WQS index by first classifying the concentrations of various chemicals into ordinal variables (quartiles) based on their distribution in the study population. We then assigned a weight contribution to each chemical based on its relative importance in the overall index. Estimated weights were determined using 500 bootstrapped samples, with weights limited to a sum of 1(Yu et al., 2021). To build the WQS regression model, we determined the direction of the association between the chemical exposure and growth outcome for each individual analysis (positive or negative). We then used these directions to guide the direction of the chemical assessment in the WQS regression model. The GBTM analyses were conducted using a plug-in (PROC TRAJ) in Stata 15.1. The WQS regression was carried out using the gWQS R package. All other statistical analyses were performed using R 4.1.0. Two-side *p* values of <0.05 were considered statistically significant. The false discovery rate (FDR) (Benjamini and Hochberg, 1995) method was used to correct significance values in all multiple comparisons. Specifically, we applied an FDR correction with a threshold of $\alpha = 0.10$ to balance the risk of type I errors (false positives) and type II errors (false negatives) and to maintain a reasonable level of statistical power.

3. Results

3.1. Characteristics of the study population

Characteristics of the 1051 pregnant women included were shown in Table 1. The mean age of the women was 28.76 years old. The pre-pregnancy BMI and gestational weight gain were 20.85 ± 2.79 (ranging from 14.98 to 35.26) kg/m^2 and 16.57 ± 5.30 (ranging from 2.00 to 35.00) kg, respectively. The majority (78.3 %) of pregnant women in this study population were nulliparous. About 24 % of participants were exposed to active or passive smoking during pregnancy. Infant anthropometric indexes were shown in Table 2. Weights (mean with SD, kg) of infants at eight-time points were 3.31(0.43), 4.77(0.60), 6.84(0.82), 8.47(0.94), 9.23 (0.99), 10.23(1.07), 11.52(1.10) and 12.64(1.39), respectively. As for body length, the average values (SD) were 50.13(1.62), 55.20(2.07), 62.18 (2.21), 68.19(2.39), 71.63(2.44), 76.68(2.84), 82.95(2.80), 88.61(3.30) cm, respectively. The average values (SD) of head circumferences (except at birth) were 37.35(1.29), 40.35(1.42), 43.00(1.40), 44.42(1.38), 45.92 (1.35), 47.18(1.35), 48.20(1.32) cm, respectively. The details of WAZ, LAZ, WLZ, and HCZ were also displayed in Table 2.

3.2. Anthropometric measure trajectories

In this study, five trajectory groups were identified by the GBTM for WAZ, LAZ, WLZ, and HCZ. The detailed initial and follow-up values for five

Table 1
Basic demographics of the study participants (n = 1051).

Characteristics	n	Mean ± SD or percent (%)
Maternal age (year)	1051	28.76 ± 3.71
<25	108	10.3
25–29	442	42.1
30–34	392	37.3
≥35	109	10.4
Gestational age (week)	1051	39.19 ± 1.30
Maternal education		
High school or less	425	40.4
Associate or bachelor	347	33.0
Graduate	279	26.6
Pre-pregnancy BMI (kg/m^3)	1051	20.85 ± 2.79
<18.5	204	19.4
18.5–24.9	694	66.0
≥25	153	14.6
Gestational weight gain (kg)	1051	16.57 ± 5.30
<12	179	17.1
12–14.9	223	21.2
15–17.9	223	21.2
≥18	426	40.5
Parity		
Nulliparous	823	78.3
Multiparous	228	21.7
Delivery method		
Vaginal delivery	158	15.0
Cesarean delivery	893	85.0
Active or passive smoking during pregnancy		
No	799	76.0
Yes	252	24.0
Infant sex		
Boys	574	54.6
Girls	477	45.4

Note: BMI, body mass index; SD, standard deviation.

trajectories of each anthropometric measure were described in Table S4. The BIC for GBTM according to the number of trajectories and shapes and the average posterior probability for GBTM were presented in Table S5-8. Fig. 1 shows the specific trajectory groups for each anthropometric index. The beginning values (low, moderate, high) and trends of the trajectory groups (falling, stable, rising) were used to assign labels to each group. The moderate-stable trajectory of each anthropometric measure included a considerable fraction of the study population and a mean z-score close to zero in the first 24 months of life, which served as the reference group.

3.3. Maternal urinary levels of phthalate metabolites

Maternal urine levels of eight phthalate metabolites in the third trimester were presented in Table 3. The analysis included seven phthalate metabolites that were detected in >80 % of urine samples. Concentrations (median with 25th percentile -75th percentile, ng/mL) for MBP, MMP, MEP, MEHP, MEHHP, MEOHP, MECPP, and ΣDEHP were 114.60 (45.18–239.79), 11.13(5.45–21.24), 8.80(4.09–18.14), 2.12(0.73–5.33), 8.76(5.06–15.29), 7.75(4.48–13.27), 9.86(5.92–16.68), and 33.86 (20.79–55.22), respectively. Besides, the phthalate metabolite pairwise correlation values ranged from 0.10 to 0.73 (Fig. S2).

3.4. Association between individual phthalate exposure and growth trajectories

Fig. 2 (numerical values are provided in Table S9) illustrates the relationship of prenatal individual phthalate exposure with child growth trajectories for each anthropometric measure. With regard to WAZ, higher MBP, MEOHP and MEHHP were significantly associated with greater odds of the moderate-rising trajectory when compared with the moderate-stable trajectory; MEHP and ΣDEHP were positively associated with the low-rising trajectory; MBP was negatively associated with the high-stable trajectory (FDR corrected $p < 0.1$). For LAZ, MEOHP, MEHHP, and ΣDEHP were associated with lower OR for the high-stable group; MBP, MEHP, MECPP and ΣDEHP were associated with lower OR for the moderate-rising group (FDR corrected $p < 0.1$); For WLZ, negative associations were found between MEP and the low-rising group as well as MBP and the low-stable group, respectively (FDR corrected $p < 0.1$). For HCZ, there was no evidence of a relationship between phthalate metabolites and any groups.

The numbers of participants in each trajectory by infant sex are shown in Table S10. In a sex-specific analysis (Fig. 3; numerical values are provided in Table S11-12), phthalate metabolites were associated with lower ORs for the low-rising WAZ trajectories and higher ORs for the moderate-rising WLZ trajectories among girls but not boys. Infant sex modified the relationships between phthalate metabolites (MBP and MEP) and the low-rising group. A doubling increase in prenatal MBP was associated with a nearly null OR (1.06, 0.83–1.34) and a lower OR (0.75, 0.60–0.95) for the low-rising WAZ trajectories in boys and girls, respectively (FDR corrected $p < 0.1$, p interaction = 0.05). MEP was associated with a higher OR (1.10, 0.89–1.36) and a lower OR (0.74, 0.57–0.96) for the low-rising WAZ trajectories in boys and girls, respectively (FDR corrected $p < 0.1$, p interaction = 0.03).

For the moderate-rising WLZ trajectory, the gender differences were most noticeable. For instance, MEOHP (OR 0.88, 95%CI 0.69–1.10), MECPP (OR 0.84, 95%CI 0.68–1.05) and ΣDEHP (OR 0.86, 95%CI 0.67–1.10) were associated with decreased OR in boys, whereas MEOHP (OR 1.18, 95%CI 0.91–1.53), MECPP (OR 1.29, 95%CI 1.01–1.66) and ΣDEHP (OR 1.23, 95%CI 0.95–1.59) were associated with higher OR in girls (FDR corrected $p < 0.1$), and p for interaction were 0.07, 0.01, and 0.04, respectively.

Table 2
Anthropometric measures in children at birth, 1 month, 3 months, 6 months, 8 months, 12 months 18 months and 24 months.

	Mean (SD)							
	At birth	1 month	3 months	6 months	8 months	12 months	18 months	24 months
Weight								
N	1051	1007	852	833	768	893	702	662
Original value (kg)	3.31(0.43)	4.77(0.60)	6.84(0.82)	8.47(0.94)	9.23(0.99)	10.23(1.07)	11.52(1.10)	12.64(1.39)
z-score	−0.01(0.91)	0.44(0.86)	0.65(0.90)	0.76(0.90)	0.79(0.88)	0.70(0.83)	0.60(0.76)	0.45(0.85)
Length/height								
N	1051	1003	852	834	767	871	702	662
Original value (cm)	50.13(1.62)	55.20(2.07)	62.18(2.21)	68.19(2.39)	71.63(2.44)	76.68(2.84)	82.95(2.80)	88.61(3.03)
z-score	0.31(0.86)	0.26(0.98)	0.40(0.93)	0.49(0.99)	0.64(0.98)	0.55(1.08)	0.35(0.94)	0.56(0.90)
Weight-for-length								
N	1051	1003	852	833	767	871	702	670
z score	−0.31(0.90)	0.33(1.08)	0.56(0.99)	0.74(0.97)	0.69(0.91)	0.61(0.89)	0.59(0.80)	0.16(0.90)
Head-circumference								
N	/	897	785	773	747	704	667	616
Original value (cm)	/	37.35(1.29)	40.35(1.42)	43.00(1.40)	44.42(1.38)	45.92(1.35)	47.18(1.35)	48.20(1.32)
z-score	/	0.15(1.02)	−0.03(1.05)	0.04(1.05)	0.22(1.03)	0.22(0.97)	0.20(0.97)	0.29(0.92)

Note: SD, standard deviation; the z-score was calculated based on child growth standards from World Health Organization.

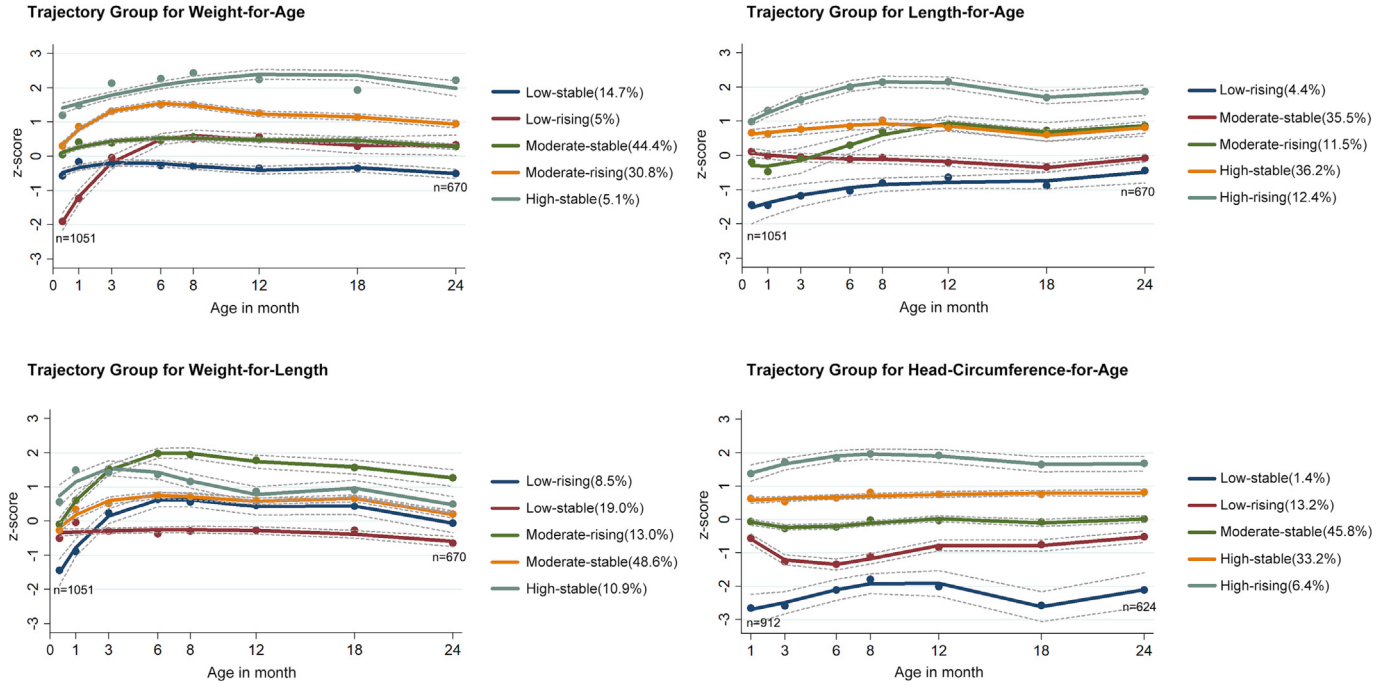

Fig. 1. The group-based trajectories for weight-for-age z-score (WAZ), length-for-age z-score (LAZ), weight-for-length z-score (WLZ), and head-circumference-for age z-score (HCZ).WAZ, LAZ and WLZ were available at birth and at 1, 3, 6, 8, 12, 18 and 24 months; HCZ was available at 1, 3, 6, 8, 12, 18 and 24 months. The group are labeled based on the initial value and following trend. Dash lines around the solid lines represent confidence for the calculated trajectory.

Although there were some variations in the sensitivity analyses (as shown in Table S13) when considering factors such as parity, gestational weight gain, infant sex, delivery method as well as active or passive smoking during pregnancy, the differences observed were mainly in the strength and statistical significance of the associations between the phthalate metabolites and infant growth trajectories. However, the overall direction of the associations remained consistent with those observed in our primary study.

3.5. Association between mixed phthalate exposure and growth trajectories

The WQS method involves interpreting the weights of the associated components if the coefficient is significantly different from 0. In particular, the highest weight values can be identified as the relevant contributors to the association. When using WQS analysis, the phthalate metabolite mixture was related to higher odds for the low-rising WAZ trajectory (OR 1.53, 95%CI 1.01–2.46) and the moderate-rising WAZ trajectory (OR 1.23, 95%CI 1.00–1.55), where MEHP and MEP had the highest weights (0.74 and 0.39) respectively. In terms of LAZ, the phthalate metabolite mixture was associated with lower odds (OR 0.76, 95%CI 0.46–1.01) for the moderate-rising group in the adjusted model, with MEOHP having the highest weight (0.28) (Table S14, S15 and S18). No relationship was observed between the total phthalate metabolite mixture and the WLZ and HCZ trajectories (Table S16–17).

Table 3
Distribution of specific-gravity corrected urinary phthalate metabolites concentrations (μg/L) among pregnant women (n = 1051).

Phthalates	LOD(ng/ml)	% > LOD	Concentrations				
			5th	25th	50th	75th	95th
MBP	0.5	99.99	11.49	45.18	114.60	239.79	679.25
MBzP	0.1	53.98	0.02	0.04	0.08	0.16	0.68
MMP	0.5	97.48	1.36	5.45	11.13	21.24	54.76
MEP	0.5	97.57	1.16	4.09	8.80	18.14	107.77
MEHP	0.5	80.17	0.16	0.73	2.12	5.33	22.77
MEHHP	0.2	99.99	2.13	5.06	8.76	15.29	33.63
MEOHP	0.2	99.82	1.98	4.48	7.75	13.27	30.33
MECPP	0.2	99.63	2.41	5.92	9.86	16.68	37.21
ΣDEHP	/	/	9.89	20.79	33.86	55.22	117.74

Note: LOD, limit of detection.

4. Discussion

In this prospective study, we observed that higher prenatal exposure to several phthalate metabolites was associated with child growth trajectories, especially for WAZ and LAZ in the first 24 months of life. Among them, maternal levels of DEHP metabolites, including MEHP, MEHHP, MEOHP, MECCP, summed DEHP metabolites, as well as MBP, showed more statistically significant relationships. Phthalate metabolite mixture analysis further confirmed the above findings. The association of phthalate exposure with the WAZ and LAZ trajectories might be modified by infant sex.

Our findings support previous evidence of a two-way relationship between prenatal phthalate exposure and infant growth at birth and early childhood, consisting of lesser birth weight and length, higher adiposity at 3–4 years of age (Ferguson et al., 2022), higher height at 2–11 years, higher head circumference at 11–20 years of age (Berman et al., 2021), and a more rapid BMI growth in the first 6 months of life (Valvi et al., 2015). Numerous previous studies have examined growth in mid-childhood and beyond; however, several discrepancies have also been found (Ribeiro et al., 2019; Shoaff et al., 2017). The inconsistent results could be attributed to variations among the studies included in the analysis. These variations encompass differences in study design, population demographics, and the factors that were adjusted for in each study. The research design comprises various cross-sections, cohorts, and case-control groups, while the population demographics consist of diverse factors such as age, race, and more. Furthermore, there could be differences in the levels of phthalate metabolites concentration and the factors adjusted for in each study. In particular, our research focused on the first two years of life. Compared with the latter stages of life, prenatal phthalate exposure in infancy and early childhood may be more strongly associated with growth variance, which could potentially contribute to the difference between the findings in this study and those in other studies. To compensate for intrauterine restraint, neonates with growth restriction are more vulnerable to fast postnatal weight gain in the first two years of life (Ong et al., 2000), potentially leading to metabolic diseases later in life. Therefore, the possible influence

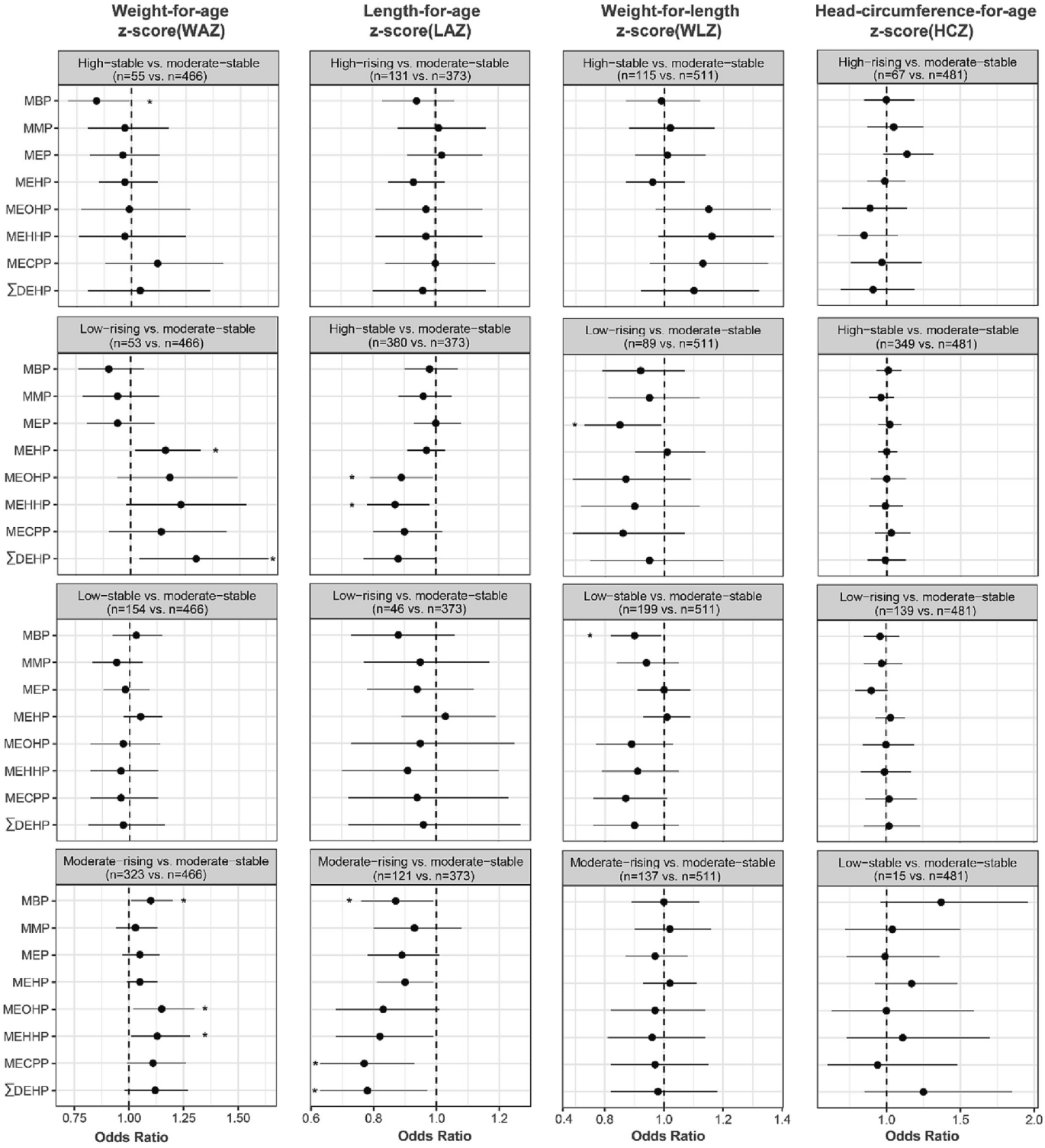

Fig. 2. Odds ratio (OR) and 95 % confidence interval (CI) for trajectory groups in each anthropometrical measure according to per doubling increase in prenatal phthalate metabolites concentrations (μg/L) in multinomial logistic regression models. All models were adjusted for maternal age, education and pre-pregnancy BMI. Lines with asterisk mean FDR-corrected $p < 0.1$. BMI: body mass index; FDR: false discovery rate.

of prenatal phthalate exposure on early postnatal development might be an important public health issue.

The majority of previous research almost always employed static growth metrics (weight, height, and BMI), and only a small number of longitudinal studies have used high dimensional data models to analyze postnatal growth over time (Ferguson et al., 2022; Heggeseth et al., 2019). Due to their cross-sectional nature, traditional approaches could not capture the dynamic characteristics of development. Growth trajectory modeling, on the other hand, can offer a more thorough description of dynamic growth processes, enabling more precise identification of modifiable risk factors and health outcome prediction. To our knowledge, only limited studies have investigated the association of prenatal phthalate exposure with child growth trajectories. In a prospective pregnancy cohort study that included 780 mother-child pairs, the effects of maternal exposure to

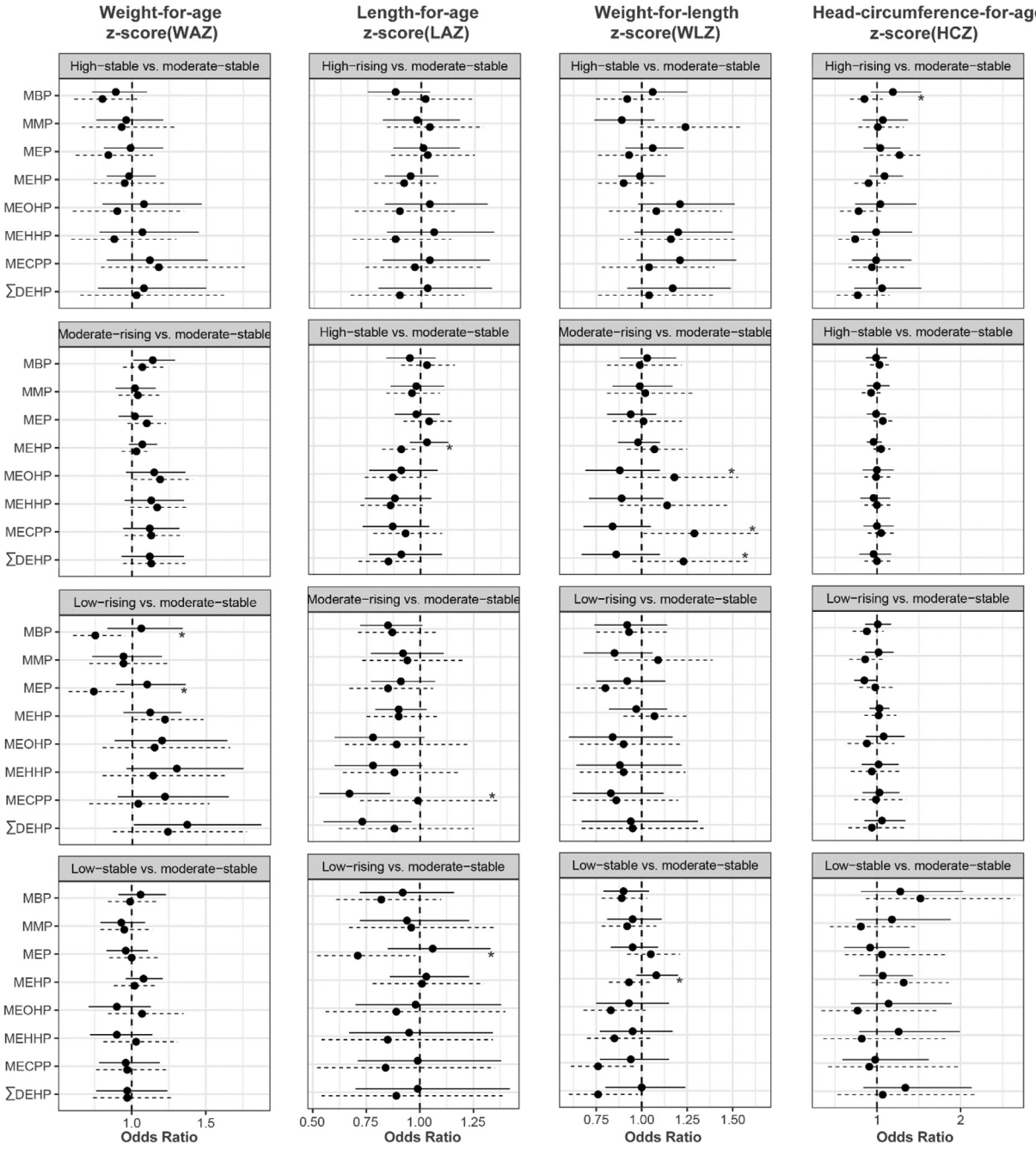

Fig. 3. Stratified analysis by infant sex using multinomial logistic regression models. The solid line represents boys, and the dashed line represents girls. Lines with asterisk mean a $p < 0.1$ for the comparison between boys and girls. All models were adjusted for maternal age, education and pre-pregnancy BMI. BMI: body mass index.

phthalates (in urine collected during early and late gestation) on weight and adiposity from birth to childhood (birth and 1, 3, 4, and 6 years of age) were assessed using linear mixed-effect models. The results showed that phthalate exposure was associated with lower birth weight but not with postnatal weight. Regarding adiposity, phthalate exposure was associated with low adiposity at birth and high adiposity at 3–4 years of age (Ferguson et al., 2022). Another study followed 514 mother-child pairs from pregnancy through twelve years, researchers measured the concentrations of nine phthalate biomarkers in maternal urine samples. Child BMI z-score, fat mass index, and waist-to-height ratio were measured at three study visits between four and twelve years of age, and adiposity trajectories were identified using multivariate latent class growth modeling. The study's findings indicated that the prenatal levels of urinary DEHP, diisononyl phthalate, and monocarboxylic-isononyl phthalate (MCNP) metabolites were associated with the patterns of adiposity in children over time, whereas there was no association observed with the total phthalate mixture (Kupsco et al., 2022). Their results suggested that concentrations of phthalate metabolites in prenatal urine were related to childhood obesity trajectories, and no gender-specific or mixed associations were observed. However, our study investigated both individual and mixed phthalate exposure as well as four birth outcomes, offering more comprehensive evidence for the impact of early prenatal phthalate exposure on infant development.

Prenatal phthalate exposure was associated with low-rising WAZ trajectories when we use the standardized anthropometric measures in our study. These results supported the hypothesis that phthalate exposure during pregnancy may result in early-life catch-up growth gain (Neier et al., 2019). There is convincing evidence confirming the notion that “accelerated” growth or growing too fast at critical periods in early life has a

negative impact on the long-term risk of obesity and cardiovascular disease (Singhal, 2017). Recently, based on the Shanghai birth cohort, Gao et al. reported excessive catch-up weight growth, in which the late z-score of the low-rising WAZ trajectory was higher than that of the average trajectory (Gao et al., 2022d). This suggested that children who had a slower rise in WAZ during infancy had a greater increase in WAZ later in childhood, leading to excessive catch-up weight growth. This finding highlights the importance of identifying different adiposity trajectories and their associations with early life exposures, such as prenatal phthalate exposure, in understanding long-term weight and adiposity outcomes. While in the current study, we only found catching up and not exceeding the average trajectory, which could be attributed to differences in population structure and exposure timing. Gao et al. study was conducted in a Shanghai birth cohort, which may have different population characteristics and environmental exposures than our population. It should be noted that the exposure timing in the Gao et al. study was during the first trimester, whereas in our study, it was during the third trimester. Considering the possible adverse consequences of the catch-up growth pattern, our findings suggest that more attention should be paid to the long-term health effects of prenatal phthalate exposure.

Apart from WAZ, we discovered that high phthalate concentrations were also related to a decreased likelihood of being in the high-stable or moderate-rising LAZ trajectory, which suggests a complicated and diverse relationship between phthalate exposure and postnatal development. Although no obvious association of mixed phthalate exposure with WLZ and HCZ trajectories was found, our results also indicated that increased individual MEP was related to a low-rising WLZ trajectory, which was consistent with the previous study (Ferguson et al., 2022). Therefore, our findings further indicated that GBTM is especially effective in revealing heterogeneity in growth trajectories.

Furthermore, we discovered potential sex differences in the effects of phthalate exposure. In this study, girls appeared to be more sensitive to phthalate exposure, with lower ORs for the associations between phthalate metabolites and WAZ and LAZ low-rising trajectories than boys. These results were consistent with a pooled analysis of 707 children from three prospective cohort studies in the US, which found that metabolites of diethyl phthalate and DEHP were associated with lower BMI in girls aged 4 to 7 years, but not in boys, suggesting that prenatal exposures may have sexually dimorphic effects on physical development (Buckley et al., 2016a). Several studies have investigated the sex-specific effects in prenatal or childhood growth associated with phthalate metabolites, but the results were mixed. Some of them showed an association between phthalate metabolites and child growth mainly in males. An analysis of NHANES data (2007–2010) found that mono-n-butyl phthalate (MnBP), MEP and mono-isobutyl phthalate (MiBP) were significantly associated with higher odds for obesity only in male children and adolescents (Buser et al., 2014). A study of 1102 pregnant women from the Taiwan Maternal and Infant Cohort Study (TMICS) revealed that high maternal MnBP exposure during the third trimester was associated with low birth weight or small-for-gestational-age outcomes in male infants (Chang et al., 2022). Another small-sample prospective study including 88 pregnant women found that maternal high exposure to MEP in the second trimester was associated with lower birth weight (−661 g, 95 % CI -1251 to −70.7) and length (−3.11 cm, 95 % CI -5.76 to −0.46) in male offspring when compared to those with low exposure (Uldbjerg et al., 2022). In contrast, the Ma'anshan birth cohort study, which included 990 mother-daughter pairs, reported significant associations between MEP and DEHP metabolites (MEHHP and MEOHP) and high BMI trajectories in girls during early childhood (Gao et al., 2022a). Furthermore, a study of 514 mother-child pairs from the Mexico City PROGRESS cohort, followed from pregnancy through twelve years, found no sex-specific or mixture associations between phthalate metabolites and childhood adiposity trajectory (Kupsco et al., 2022). Sex hormones may play a role in the impact of phthalates on body fat distribution and amount, which could explain the observed sex differences in the health effects of phthalates (Gao et al., 2022c). In addition, recent studies have demonstrated that phthalate exposure can affect thyroid function (Morgenstern et al., 2017), cardiometabolic characteristics (Vafeiadi et al., 2018), and neurodevelopment (Hyland et al., 2019), with significant sex differences in these effects. Therefore, further research is necessary to gain a better understanding of the effects of infant sex modification.

The mechanistic pathway between phthalate exposure and growth trajectory remains unclear, but several lines of evidence suggest a plausible relationship. One of the well-studied mechanisms is that phthalates could directly activate the peroxisome proliferator-activated receptor gamma (PPARγ) subunit. Abnormal activation of the PPAR signaling pathway during early development may increase susceptibility to weight gain (Hao et al., 2013; Hao et al., 2012). Other potential mechanisms include disruption of the thyroid axis and hypothalamic-pituitary-adrenal (HPA) axis function, as well as placental epigenetic changes, which may contribute to adverse infant developmental outcomes (Grindler et al., 2018; Zhu et al., 2018). Phthalates could also impact weight gain through their effects on preterm birth, which is also influenced by the HPA axis (Ferguson et al., 2019; Supornsilchai et al., 2007).

The strength of our study lies in its prospective design and the utilization of a large birth cohort with longitudinal follow-up. Moreover, we employed GBTM, which is a novel application in environmental epidemiology, to characterize postnatal growth trajectories using repeated measurements at eight-time points. In addition, to validate the single phthalate analysis and reduce the likelihood of chance findings, we assessed both the effects of individual metabolites and the joint phthalate mixtures. Both the individual and mixed analysis demonstrated consistent results, highlighting the robustness of our findings.

Some limitations of the current study need to be acknowledged. First, we did not have information on paternal phthalate exposure, which could potentially be transferred to the placenta. Second, self-reported pre-pregnancy weight may lead to misclassification resulting in incorrect estimates of measures. However, some studies have found that the bias resulting from self-reported weight tends to be relatively small and may not significantly affect the associations under investigation (Ng, 2019). Third, the low participation rate of approximately 10 % and observed differences between enrolled and non-enrolled populations may limit the generalizability of our findings. Moreover, the possibility of differential loss to follow-up cannot be ruled out entirely, and this may introduce selection bias into our results. However, we have taken steps to adjust for potential confounders in our statistical analyses to mitigate the impact of possible selection bias. Fourth, anthropometric indicators were not repeatedly measured, which may introduce measurement error. However, we used reliable measurement methods to minimize this potential impact. Fifth, misclassification may occur with trajectory analysis methods, potentially biasing the results by obscuring the true trajectory patterns and associations. However, the exact impact of misclassification is difficult to quantify and may depend on its magnitude and direction. It is important to note that misclassification is not a failure of the analysis method, but rather a reflection of the complexity and variability of human behavior and development. Sixth, we used growth trajectories as the outcome of our study, but their clinical significance is unclear. Further research is needed to better understand how growth trajectories affect future disease and clinical implications. Seventh, the urine samples were collected relatively late in pregnancy, potentially limiting the insights into the effects of phthalate exposure on child growth trajectories (Ferguson et al., 2014; Swan et al., 2015). Earlier measurements and more frequent sampling of phthalate metabolites in urine could improve exposure estimates during pregnancy. Eighth, the WQS method used to evaluate phthalate mixture effects has limitations, such as assuming directional homogeneity, linear and additive effects for individual exposure, which may introduce uncertainty about the combined effects of phthalates. Finally, co-pollutant confounding and other mixture effects may be relevant, which may bias our results.

5. Conclusions

In summary, we observed that higher phthalate levels were associated with increased odds for a low-rising WAZ trajectory and decreased odds for a moderate-rising LAZ trajectory using trajectory analysis of repeated

measurements of anthropometric indices throughout the first two years of life. There might be sex-specific associations between phthalate exposure and offspring growth. Multitrajectory modeling via GBTM sheds light on the complicated impacts of phthalate exposure on growth at various stages of development. Given the importance of growth trajectory on health outcomes, additional research is needed to confirm the current findings.

CRediT authorship contribution statement

MY and ZC performed the statistical analyses, interpreted the data, and drafted the manuscript. ZC, HM, and FX contributed to the data acquisition and review for important intellectual content. LH and LY revised the manuscript. HX and AZ conceived and designed this study, and final version approval. All authors have read and approved the final manuscript.

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Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.165518.

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