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Fetal exposure to phthalates and body mass index from infancy to adolescence. The Generation R study

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ABSTRACT

Prenatal exposure to phthalates might influence the development of childhood obesity. Most previous studies used body mass index (BMI) at a specific age instead of BMI development, which might be a better indicator of later health. We aimed to assess the association of prenatal phthalate exposure with longitudinal BMI development from infancy to adolescence. Among 1,379 mother-child pairs from a population-based cohort study, phthalate concentrations were measured in maternal spot urine samples, collected during first, second and third trimester. We estimated age- and sex-adjusted BMI standard deviation scores (SDS) at 6 months and 1, 2, 3, 4, 6, 10 and 13 years. We examined the associations of maternal phthalate urine concentrations during pregnancy with repeated measures of BMI using linear mixed effects models. An interquartile range higher natural log-transformed maternal first trimester high-molecular weight phthalate and di-2-ethylhexylphthalate (DEHP) urine concentrations were associated with a −0.10 (95% confidence interval (CI) −0.15 to −0.04), and −0.09 (95% CI -0.15 to −0.04) lower age- and sex-adjusted BMI at 6 months. An interquartile range higher natural log-transformed maternal first trimester phthalic acid and low-molecular weight phthalate urine concentrations were associated with a 0.11 (95% CI 0.03 to 0.18) and 0.13 (95% CI 0.04 to 0.21) higher age- and sex-adjusted BMI at 13 years old. No significant associations were observed for maternal second and third trimester phthalate urine concentrations with BMI. Thus, higher maternal phthalate metabolites urine concentrations appear to be related to lower BMI at early ages but with higher BMI at later ages.

1. Introduction

Phthalates are non-persistent endocrine disrupting chemicals that are used as plasticizers and solvents in many consumer items, such as cosmetics and food packaging materials (Koniecki et al., 2011; Schecter et al., 2013). The effects of phthalates might start prenatally, as phthalates can cross the placenta (Mose et al., 2007). The 'Developmental Origins of Health and Disease (DOHaD)' hypothesis suggests that being exposed to certain environmental factors during vulnerable periods, such as the fetal period, may have adverse and lifelong effects on development and health throughout life (Barker, 2007). In particular, it has been suggested that exposure to phthalates during fetal life might influence growth and body mass index (BMI) by affecting the lipid and carbohydrate metabolism, inducing oxidative stress or causing epigenetic changes (Campioli et al., 2014; Feige et al., 2007; Manikkam et al., 2013; Taxvig et al., 2012).

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Several previous studies have examined the association of maternal urine concentrations of phthalate metabolites with childhood obesity (Agay-Shay et al., 2015; Berger et al., 2021; Botton et al., 2016; Bowman et al., 2019; Buckley et al., 2016; Etzel et al., 2022; Ferguson et al., 2022; Gao et al., 2022, 2023; Güil-Oumrait et al., 2022; Harley et al., 2017; Heggeseth et al., 2019; Kupsco et al., 2022; Lee et al., 2020; Li et al., 2021; Maresca et al., 2016; Montes et al., 2022; Nidens et al., 2021; Shoaff et al., 2017; Sol et al., 2020; Stevens et al., 2023; Svensson et al., 2021; Vafeiadi et al., 2018; Valvi et al., 2015; Vrijheid et al., 2020; Yang et al., 2017, 2018). Most of these studies assessed BMI at relatively young ages (below 10 years old) and in small populations, and reported positive (Berger et al., 2021; Botton et al., 2016; Harley et al., 2017; Li et al., 2021), null (Agay-Shay et al., 2015; Buckley et al., 2016; Etzel et al., 2022; Güil-Oumrait et al., 2022; Nidens et al., 2021; Sol et al., 2020; Vafeiadi et al., 2018; Vrijheid et al., 2020), or negative associations (Bowman et al., 2019; Shoaff et al., 2017; Stevens et al., 2023; Yang et al., 2017), with four studies reporting sex-specific associations (Lee et al., 2020; Maresca et al., 2016; Montes et al., 2022; Valvi et al., 2015). In addition to the health risks of having obesity at a certain stage in life, research has evolved to understand that adverse BMI development is a stronger predictor of subsequent health than BMI at a certain age (Barker et al., 2005). However, a smaller number of studies examined prenatal phthalate exposure in relation to BMI or adiposity outcomes measured longitudinally throughout childhood (Botton et al., 2016; Buckley et al., 2016; Ferguson et al., 2022; Gao et al., 2022, 2023; Harley et al., 2017; Heggeseth et al., 2019; Kupsco et al., 2022; Montes et al., 2022; Svensson et al., 2021; Valvi et al., 2015; Yang et al., 2018). Those studies showed inconsistent results with somewhat more positive associations, most only included one or two measures of maternal phthalate urine concentrations and had small sample sizes (Botton et al., 2016; Buckley et al., 2016; Ferguson et al., 2022; Gao et al., 2022; Harley et al., 2017; Heggeseth et al., 2019; Kupsco et al., 2022; Montes et al., 2022; Svensson et al., 2021; Valvi et al., 2015; Yang et al., 2018). Thus, assessing the effects of fetal exposure to phthalates on BMI measured longitudinally at multiple time points from infancy until adolescence, rather than one measurement taken at any individual age, is of utmost importance.

In this prospective population-based cohort study of 1,379 mother-child pairs, we examined the associations of maternal urine phthalate metabolite concentrations during first, second and third trimesters of pregnancy with repeated measures of BMI from infancy to adolescence.

2. Methods

2.1. Study design

The present study is part of a larger research line into the effects of endocrine disruptors on childhood health, embedded in the Generation R Study, which is a population-based prospective cohort study that started during early fetal life and was performed in Rotterdam, the Netherlands (Kooijman et al., 2016). The study was approved by the Medical Ethics Committee of Erasmus MC, University Medical Center in Rotterdam. Written informed consent was obtained from all participants. Phthalate urine concentrations were measured in 1,405 mothers, of singleton children, who had collected spot urine samples during the first, second or third trimester of pregnancy and who participated in postnatal studies. The socio-demographic and lifestyle characteristics of these women were comparable to the whole Generation R cohort (Philips et al., 2018). In this study, we only included mothers for whom phthalate urine concentrations were available in the three trimesters of pregnancy, leading to a final sample size of 1,379 mothers and their singleton children (the specific sample per outcome is given in Supplemental Fig. S1).

2.2. Maternal phthalate urine concentrations

Methods of collection, transportation, and analysis of phthalate urine concentrations within the Generation R Study have been described elsewhere (Philips et al., 2018). Between February 2004 and July 2005, we collected spot urine samples from each woman during the first (median [25th-75th percentiles] 12.9 [12.1–14.5] weeks of gestation), second (median [25th-75th percentiles] 20.4 [19.9–20.9] weeks of gestation) and third (median [25th-75th percentiles] 30.2 [29.9–30.8] weeks of gestation) trimester and measured phthalate metabolite concentrations. Phthalate metabolites were grouped by parent phthalate molecule and their molecular weight (expressed in weighted molar sums). We only used information on a specific phthalate metabolite if $<$ 80% of the concentrations were below the limit of detection (LOD). The concentrations below LOD were replaced by LOD/$\sqrt{2}$ and the phthalate urine concentrations were converted to μmol/g creatinine to account for urinary dilution (Hornung RW, 1990). Table 1 shows the descriptive statistics of the individual and grouped phthalates per trimester and the percentage of values below the LOD. We also calculated the intraclass correlation coefficients (ICC) between the natural log-transformed phthalates (in nmol/L) over pregnancy, which ranged from 0.10 to 0.40 (Table 1). We calculated the pregnancy-averaged phthalate urine concentrations for the individual and grouped phthalates that had $>$20% of the concentrations above the LOD in all three trimesters.

2.3. Childhood body mass index

Childhood length or height and weight were measured according to standardized procedures at the ages of 6 months, 1, 2, 3, and 4 years in community health centres. At ages 6, 10 and 13 years old, children visited our dedicated research facility, where height and weight were measured. We calculated BMI (in kg/m^2) at each time point and then calculated age- and sex-adjusted standard deviation scores (SDS) for all BMI measurements using Dutch reference growth charts (Fredriks et al., 2000). The number of children in which BMI was measured differed per time point. The median number of postnatal BMI measurements was 6 (25th-75th percentiles: 5–7; full range: 1–8). Additionally, at each time point, age and sex-specific BMI z-scores were derived and categorized as underweight or normal weight ($\leq$1 SD) and overweight/obesity ($>$1 SD), based on the WHO growth standard and reference values (de Onis et al., 2007; WHO, 2006).

2.4. Covariates

Information on the following covariates was collected from questionnaires during pregnancy: maternal age at enrollment, pre-pregnancy weight, educational level, ethnicity, folic acid supplement use, parity, smoking habits and alcohol consumption. Maternal height was measured at enrollment and used to calculate pre-pregnancy BMI (kg/m^2). Participating mothers filled in a validated semi-quantitative food frequency questionnaire at enrollment that covered the average diet during the first trimester of pregnancy and that information was used to estimate the maternal diet quality score (Klipstein-Grobusch et al., 1998; Tielemans, 2017).

2.5. Statistical analysis

Characteristics of the study sample regarding the exposures, outcomes and covariates were summarized. For all analyses, the maternal phthalate urine concentrations were adjusted for the creatinine concentration and natural log-transformed. This conversion was performed to reduce variability and to further account for right skewedness of the distribution. Subsequently, the exposures were standardized by the interquartile range (IQR) to ease the interpretation of the effect sizes. We created a correlation matrix between all first trimester natural log-transformed grouped and individual phthalates (in nmol/L) and

Table 1
Maternal urinary concentrations of phthalates during pregnancy.

	First trimester		Second trimester		Third trimester		ICC
	Median (25th-75th percentile)	Percentage below LOD (%)	Median (25th-75th percentile)	Percentage below LOD (%)	Median (25th-75th percentile)	Percentage below LOD (%)	
Phthalic acid (PA) (nmol/L)	343.3 (181.8–730.3)	0.3	931.0 (373.0–1737.9)	0.1	418.6 (204.7–806.6)	0.4	0.20
Low-molecular-weight phthalates (LMWP) (nmol/L)	1087.1 (430.7–2934.9)	–	591.6 (245.2–1512.1)	–	1040.9 (416.2–2637.5)	–	0.36
Monomethylphthalate (mMP) (nmol/L)	30.2 (15.2–54.9)	0.1	19.3 (10.1–35.0)	0.1	22.7 (11.1–44.3)	0.5	0.30
Monoethylphthalate (mEP) (nmol/L)	710.8 (211.8–2509.1)	0.1	380.9 (129.0–1170.8)	0	684.1 (230.5–2172.4)	0	0.40
Mono-isobutylphthalate (mIBP) (nmol/L)	96.4 (43.0–205.4)	0.1	40.8 (21.0–82.6)	0	81.9 (42.2–172.4)	0.3	0.27
Mono-n-butylphthalate (mBP) (nmol/L)	72.5 (30.5–140.2)	0.7	43.9 (25.0–86.9)	0	54.3 (27.9–112.9)	0.1	0.23
High-molecular-weight phthalates (HMWP) (nmol/L)	222.3 (112.7–407.3)	–	134.3 (74.7–250.9)	–	172.7 (95.2–298.3)	–	0.21
Monobenzylphthalate (mBzBP) (nmol/L)	22.5 (9.0–47.4)	8.3	21.0 (8.7–44.3)	1.6	12.3 (4.6–25.4)	3.5	0.25
Mono-hexylphthalate (mHxP) (nmol/L)	0.9 (0.3–2.0)	23.6	NA	>80	NA	>80	NA
Mono-2-heptylphthalate (mHpP) (nmol/L)	2.1 (0.8–5.7)	35.4	NA	>80	NA	>80	NA
Di-2-ethylhexylphthalate (DEHP) (nmol/L)	174.3 (89.3–325.8)	–	98.8 (53.1–188.1)	–	142.9 (77.7–253.5)	–	0.19
Mono-(2-ethyl-5-carboxy-pentyl) phthalate (mECPP) (nmol/L)	53.2 (26.7–103.0)	0.1	34.2 (18.7–67.3)	0.1	58.9 (31.0–110.5)	0	0.26
Mono-(2-ethyl-5-hydroxy-hexyl) phthalate (mEHHP) (nmol/L)	41.0 (19.9–79.1)	0.1	19.1 (10.3–37.5)	0.1	35.0 (17.9–678.0)	0.1	0.12
Mono-(2-ethyl-5oxohexyl) phthalate (mEOHP) (nmol/L)	26.7 (12.1–53.0)	0	25.8 (12.6–56.9)	0	25.0 (13.2–48.2)	0.1	0.10
Mono-[(2-carboxymethyl)- hexyl] phthalate (mCMHP) (nmol/L)	45.9 (24.6–86.6)	0.1	13.4 (7.3–24.0)	0.2	11.3 (6.0–21.1)	1.1	0.14
Di-n-octylphthalate (DNOP) (nmol/L)		–		–		–	
Mono(3-carboxypropyl)-phthalate (mCPP) (nmol/L)	5.8 (3.1–11.0)	0	3.5 (2.1–6.8)	0	7.1 (3.8–12.6)	0.1	0.23

The ICC was calculated using a single measurement, absolute agreement and two-way mixed effects model. ICC, intraclass correlation coefficients; LOD, limit of detection; NA, not applicable due to >80% of concentrations below limit of detection.

between all childhood age- and sex-adjusted BMI measurements using Pearson correlation analysis. As part of the model-building process, we assessed nonlinearity using generalized additive mixed models fitted with thin plate regression splines. These spline-based models were compared to those incorporating only simple linear terms, using the Akaike Information Criterion (AIC), residuals diagnostics and other diagnostic plots. We inspected the pattern of associations of the phthalate concentrations with childhood BMI using generalized additive models and non-linearity was not observed. Thus, no consistent evidence was found to support a nonlinear relationship between BMI and age. Consequently, linear mixed effect models were used to assess the associations of first, second or third trimester, or pregnancy-averaged phthalate concentrations with childhood age- and sex-adjusted BMI SDS measured repeatedly during childhood. A random intercept and slope were included in all models. Additionally, we included an interaction term between the trimester-specific or pregnancy-averaged phthalate urine concentrations and child's age to allow the exposure-outcome association to change during childhood. For associations that differed by timing of outcome measurement, we used plots to illustrate the associations and the age at BMI measurement was centered at 6 months, 6 years and 13 years to obtain the effect estimates at these specific time points. As a sensitivity analysis, we also assessed these associations for the individual maternal urine phthalate concentrations. We additionally performed linear regression analyses to assess the associations of first, second or third trimester, or pregnancy-averaged phthalate concentrations with childhood age- and sex-adjusted BMI SDS at all ages separately.

Potential confounders were defined as any lifestyle, sociodemographic or nutritional characteristics that were related to both prenatal exposure to phthalates and childhood BMI in previous studies (relationships were presented in a directed acyclic graph (DAG) in Supplemental Fig. S2). Potential confounders were included in the models if they fulfilled the graphical criteria for confounding (i.e., if they block an open backdoor path) and changed the effect estimates >10% for at least one of the outcomes (Santos et al., 2019). Since the effects of endocrine disrupting chemicals on childhood growth may be sex-specific, we tested for statistical interaction of the maternal phthalate urine concentrations with child's sex in these associations (Qian et al., 2020). We did not find statistically significant interactions in the linear mixed effect models. However, as a sensitivity analysis, we stratified the analysis based on sex. We performed two sensitivity analyses in the linear regression models. First, to examine the independent associations of maternal first, second and third trimester phthalate urine concentrations, we simultaneously included the exposures during all three trimesters in one linear regression model, after ruling out potential problems with multicollinearity. Second, to assess the effect of adjusting the exposure for creatinine, we performed the analysis with exposures in nmol/L with creatinine added as a covariate into the model. Each p-value was compared with a threshold which was defined as 0.05 divided by the effective number of independent tests, which was estimated based on the correlation between the exposures to correct for multiple hypothesis testing, leading to a p-value threshold of 0.007 (Li et al., 2012). To maintain statistical power and reduce bias due to missing information on covariates, we performed multiple imputation according to the Markov Chain Monte Carlo method. The percentage of missing values for covariates ranged from 0 to 25%. No missing outcome measurements were imputed. We created ten imputed datasets and identified no substantial differences between the original and imputed

datasets. All presented results are based on these pooled imputed datasets. Statistical analyses were performed using the Statistical Package of Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) and R software (version 4.1.2). The software package *mgcv* was used to perform the generalized additive mixed models and generalized additive models and package *nlme* was used to perform the linear mixed effects models.

3. Results

3.1. Subject characteristics

Tables 2 and 3 show the descriptive statistics for covariates and outcome measures, respectively. The mean age of the mothers was 30.5 years, 61.9% was European, 50.3% was higher educated, 80.6% used folic acid supplementation during pregnancy and the median pre-pregnancy BMI was 22.7 kg/m^2 (Table 2). Depending on the age of measurement, the median BMI varied between 15.7 and 18.8 kg/m^2 and the percentage of children being overweight or obese varied between 10.1 and 15.7% (Table 3). The Pearson correlations between the individual and grouped natural log-transformed phthalates (in nmol/L) from first trimester (heat map in Supplemental Fig. S3) and between the age- and sex-adjusted childhood BMI measurements (heat map in Supplemental Fig. S4) were moderate to strong.

3.2. Maternal phthalate urine concentrations and BMI from infancy to adolescence

After adjusting for potential confounders, no associations were found for maternal second trimester phthalic acid (PA) and second and third trimester HMWP, DEHP and DNOP (Table 4, basic models are presented in Supplemental Table S1). The associations of maternal first and third trimester PA, LMWP in all trimesters and first trimester HMWP, DEHP and DNOP with childhood BMI differed based on timing of BMI measurement (p-values for interaction with age at time of measurement <0.05, Table 4). These associations were plotted and showed a general trend towards lower age- and sex-adjusted BMI SDS at younger ages and higher age- and sex-adjusted BMI SDS at older ages (Fig. 1). An IQR higher natural log-transformed maternal first trimester PA, HMWP, DEHP and DNOP urine concentrations was associated with a −0.07 (95% confidence interval (95% CI) −0.12 to −0.01), −0.10 (95% CI -0.15 to −0.04), −0.09 (95% CI -0.15 to −0.04) and −0.07 (95% CI −0.13 to −0.02) lower age- and sex-adjusted BMI SDS at 6 months old, of which the associations of first trimester HMWP and DEHP remained significant after correction for multiple testing. An IQR higher natural log-transformed maternal first and third trimester PA and first trimester LMWP urine concentration was associated with a 0.11 (95% CI 0.03 to 0.18), 0.11 (95% CI 0.03 to 0.19) and 0.13 (95% CI 0.04 to 0.21) higher age- and sex-adjusted BMI SDS at 13 years old, although the association of third trimester PA did not remain significant after correction for multiple testing. The associations found for maternal LMWP urine concentrations were driven mostly by monoethylphthalate (mEP) and monomethylphthalate (mMP), while the associations for maternal HMWP urine concentrations were driven mostly by the DEHP metabolites (Supplemental Table S2 and Supplemental Table S3). The associations for the pregnancy-averaged maternal urine phthalate concentrations were comparable to the trimester-specific associations, although the effect estimates were somewhat weaker (Supplemental Table S4). When exploring the associations among boys and girls separately, after adjusting for potential confounders, these associations were comparable between boys and girls and between the sex-specific analysis and the analysis in the whole cohort (Supplemental Table S5 and Supplemental Table S6 for boys and Supplemental Table S7 and Supplemental Table S8 for girls).

Table 2
Characteristics of participating mothers.

Maternal characteristics	Participants N = 1,379
Age, mean (SD) (years)	30.5 (4.8)
Parity, n (%), nullipara	839 (61.2%)
Ethnicity, n (%), European	846 (61.9%)
Highest education finished, n (%), higher	663 (50.3%)
Smoking during pregnancy, n (%), yes	305 (24.5%)
First trimester smoking, n (%), yes	262 (21.6%)
Second trimester smoking, n (%), yes	135 (11.3%)
Third trimester smoking, n (%), yes	126 (10.7%)
Alcohol consumption during pregnancy, n (%), yes	711 (57.4%)
First trimester alcohol consumption, n (%), yes	603 (49.5%)
Second trimester alcohol consumption, n(%), yes	408 (34.4%)
Third trimester alcohol consumption, n (%), yes	429 (36.5%)
Folic acid use, n (%), yes	887 (80.6%)
Prepregnancy body mass index, median (IQR) (kg/m^2)	22.7 (4.5)
Maternal diet quality score, mean (SD)	7.8 (1.5)
Male child, n (%)	696 (50.5%)

Values represent mean (SD), median (IQR), or number of subjects (valid %).

Table 3
Characteristics of participating children.

Number of participants, n	Age at measurement, mean (SD) years)	BMI, median (IQR) (kg/m^2)	Overweight/ obesity, n (%)
1,131	0.5 (0.0)	17.1 (1.9)	206 (14.9)
1,128	1.0 (0.1)	17.3 (1.8)	197 (17.5)
947	2.1 (0.1)	16.5 (1.8)	189 (20.0)
835	3.1 (0.1)	15.9 (1.6)	132 (15.8)
767	3.8 (0.1)	15.7 (1.8)	126 (16.4)
1,379	5.9 (0.2)	15.8 (1.8)	243 (17.6)
1,124	9.7 (0.3)	16.8 (2.9)	247 (22.0)
980	13.5 (0.3)	18.8 (3.7)	229 (23.4)

Values represent mean (SD), median (IQR), or number of subjects (valid %). Cutoffs to assess overweight or obesity were based on the WHO cutoffs, including ≥+1 SDS for age- and sex-adjusted BMI as having overweight or obesity (de Onis et al., 2007; WHO, 2006).

3.3. Maternal phthalate urine concentrations and BMI at each age across infancy and adolescence

After adjustment for potential confounders, higher concentrations of multiple phthalates were associated with a lower age- and sex-adjusted BMI SDS at 1, 2 or 3 years (Supplemental Table S9, basic models are presented in Supplemental Table S10). The associations of first trimester HMWP and DEHP with age- and sex-adjusted BMI SDS at 1 and 2 years and second trimester DNOP with age- and sex-adjusted BMI SDS at 2 years remained significant after correction for multiple testing. Higher first and third trimester maternal urine PA concentrations were associated with higher age- and sex-adjusted BMI SDS at 13 years old, although these associations did not remain significant after correction for multiple testing. The associations of the pregnancy-averaged maternal HMWP, DEHP and DNOP urine concentrations were comparable to the trimester-specific associations. The mutually adjusted model and the model with creatinine as a covariate in the model showed similar results, although the associations were somewhat diminished for the model with creatinine as a covariate (Supplemental Table S11 and Supplemental Table S12). When assessing the associations of maternal urine phthalate concentrations with the odds of developing overweight or obesity, we observed that, after correction for multiple testing, higher maternal urine HMWP and DEHP concentration sin first trimester were associated with a lower odds of having overweight or obesity at 12 months (Supplemental Table S13).

Table 4
Associations of maternal urinary phthalate concentrations during pregnancy with childhood BMI outcomes from 6 months to 13 years old. Final adjusted linear mixed effects model including age-interaction.

	Effect estimate[a] (95% CI)	p-value for interaction with child age at BMI measurement	Effect estimate[a] (95% CI)	p-value for interaction with child age at BMI measurement	Effect estimate[a] (95% CI)	p-value for interaction with child age at BMI measurement
	First trimester		Second trimester		Third trimester	
PA	−0.07 (−0.13; −0.01)*	0.000*	−0.06 (−0.13; 0.01)	0.107	−0.05 (−0.12; 0.01)	0.001*
LMWP	−0.06 (−0.13; 0.00)	0.000*	−0.06 (−0.13; 0.01)	0.016*	−0.06 (−0.13; 0.01)	0.013*
HMWP	−0.10 (−0.16; −0.04)†	0.000*	−0.03 (−0.09; 0.03)	0.242	0.00 (−0.06; 0.06)	0.445
DEHP	−0.10 (−0.16; −0.04)†	0.001*	−0.03 (−0.08; 0.03)	0.495	0.00 (−0.06; 0.06)	0.414
DNOP	−0.08 (−0.13; −0.02)†	0.003*	−0.06 (−0.12; 0.01)	0.224	−0.01 (−0.07; 0.05)	0.975

P-values for the interaction between the exposure and child age at BMI measurement obtained from linear mixed effects models. Main effects reflect the difference in sex- and age-adjusted BMI measures in SDS for an interquartile range increase in each natural log-transformed phthalate metabolite in μmol/g creatinine.
Main effects for the associations of maternal urine phthalate concentrations and child sex- and age-adjusted BMI measurements obtained from linear mixed effects models. Main effects reflect the difference in sex- and age-adjusted BMI measures in SDS for an interquartile range increase in each natural log-transformed phthalate metabolite in μmol/g creatinine.
Models include maternal age, pre-pregnancy BMI, educational level, ethnicity, parity, diet score during pregnancy, diet score during pregnancy, folic acid supplement use, smoking habits and alcohol consumption during pregnancy per trimester and child age at BMI measurement. Models include an interaction term between the exposure concentration and age at BMI measurement, a random intercept for each participant, and a random slope for age at BMI measurement.
BMI, body mass index; CI, confidence interval; DEHP, di-2-ethylhexylphthalate; DNOP, di-n-octylphthalate; HMWP, high molecular weight phthalates; LMWP, low molecular weight phthalates; PA, phthalic acid.
* p-value <0.05; † significant after correction for multiple testing (p-value threshold of 0.007).
[a] If there was evidence for a significant interaction of the maternal phthalate urine concentrations with child age at BMI measurement, the effect estimate presented here represents the effect estimate at ficticious age 0 months and the associations were further explored using graphs.

4. Discussion

4.1. Main findings

We found an association of higher maternal urine HMWP and DEHP concentrations with lower age- and sex-adjusted BMI SDS at younger ages within this population-based prospective cohort study. On the other hand, higher maternal urine PA and LMWP concentrations were associated with higher age- and sex-adjusted BMI SDS at older ages. It seems that first trimester might be a vulnerable period for these associations.

4.2. Interpretation of main findings

Previous literature hypothesized that exposure to phthalates, which already occurs during the vulnerable fetal period, affects growth and adiposity (Mose et al., 2007; Philips et al., 2017). Previously, we reported, using data from the current cohort study, that prenatal maternal phthalate urine concentrations were associated with fetal growth restriction but were not associated with childhood BMI at 10 years old (Santos et al., 2021; Sol et al., 2020). However, exploring the associations with BMI longitudinally is more important, as adverse BMI development during childhood is a strong predictor of subsequent health outcomes (Barker et al., 2005).

Previous studies exploring the associations of maternal phthalate urine concentrations during pregnancy with childhood BMI showed inconsistent results, although the studies including repeated measurements of BMI showed, more often, positive associations (Agay-Shay et al., 2015; Berger et al., 2021; Botton et al., 2016; Bowman et al., 2019; Buckley et al., 2016; Ferguson et al., 2022; Gao et al., 2022; Güil-Oumrait et al., 2022; Harley et al., 2017; Heggeseth et al., 2019; Kupsco et al., 2022; Lee et al., 2020, 2022; Li et al., 2021; Maresca et al., 2016; Shoaff et al., 2017; Sol et al., 2020; Svensson et al., 2021; Vafeiadi et al., 2018; Valvi et al., 2015; Vrijheid et al., 2020; Yang et al., 2017, 2018). In three American studies among 345–536 mother-child pairs, higher second and third trimester maternal urine concentrations of multiple phthalates were associated with higher BMI Z-scores between 4 and 14 years (Harley et al., 2017; Heggeseth et al., 2019; Kupsco et al., 2022). Similarly, in a recent US study among 780 mothers and their children, higher averaged concentrations of first and third trimester maternal phthalate concentrations were associated with higher BMI Z-scores at 3–6 years old (Ferguson et al., 2022). Furthermore, in a recent Chinese study among 990 mother-daughter pairs, higher pregnancy-averaged phthalate concentrations were associated with an increased probability of having a high BMI trajectory until 6 years old (Gao et al., 2022). In contrast, a US study among 707 mothers and their children from three cohorts reported that, among girls, higher maternal urine concentrations of mEP and DEHP metabolites were associated with lower BMI Z-scores between 4 and 7 years old (Buckley et al., 2016). Among 657 participants from the Spanish INMA study, the average of first and third trimester maternal urine phthalate concentrations were not associated with BMI Z-scores until 7 years old (Valvi et al., 2015). Furthermore, three previous studies explored weight and height growth instead of BMI. In a French study among 520 mother-son pairs, higher second trimester maternal urine mEP concentrations were associated with higher weight growth velocity at two and four years old while in a Swedish study among 1118 mother-child pairs, first trimester maternal phthalate urine concentrations was not associated with weight until 5.5 years old (Botton et al., 2016; Svensson et al., 2021). In a German study among 130 mothers and their children, maternal urine phthalate concentrations were again not associated with weight gain in the first two years (Nidens et al., 2021).

Finally, some studies explored more specific measurements of adiposity. A US study found that higher maternal phthalate urine concentrations were negatively associated with different measures of adiposity at 5 months old, mostly among boys (Stevens et al., 2023). In a Chinese study among 2950 mother-child pairs, however, maternal urine phthalate concentrations during pregnancy were associated with adverse body composition until 6 years old (Gao et al., 2023). In a small Mexican study, there was also an association of higher maternal urine DEHP concentrations with higher adipose mass among boys between 8 and 10 years old (Montes et al., 2022). Finally, a small US study showed no association of maternal phthalate urine concentrations with measures of body composition at 12 years (Etzel et al., 2022).

In our study, we found an association of higher maternal HMWP and

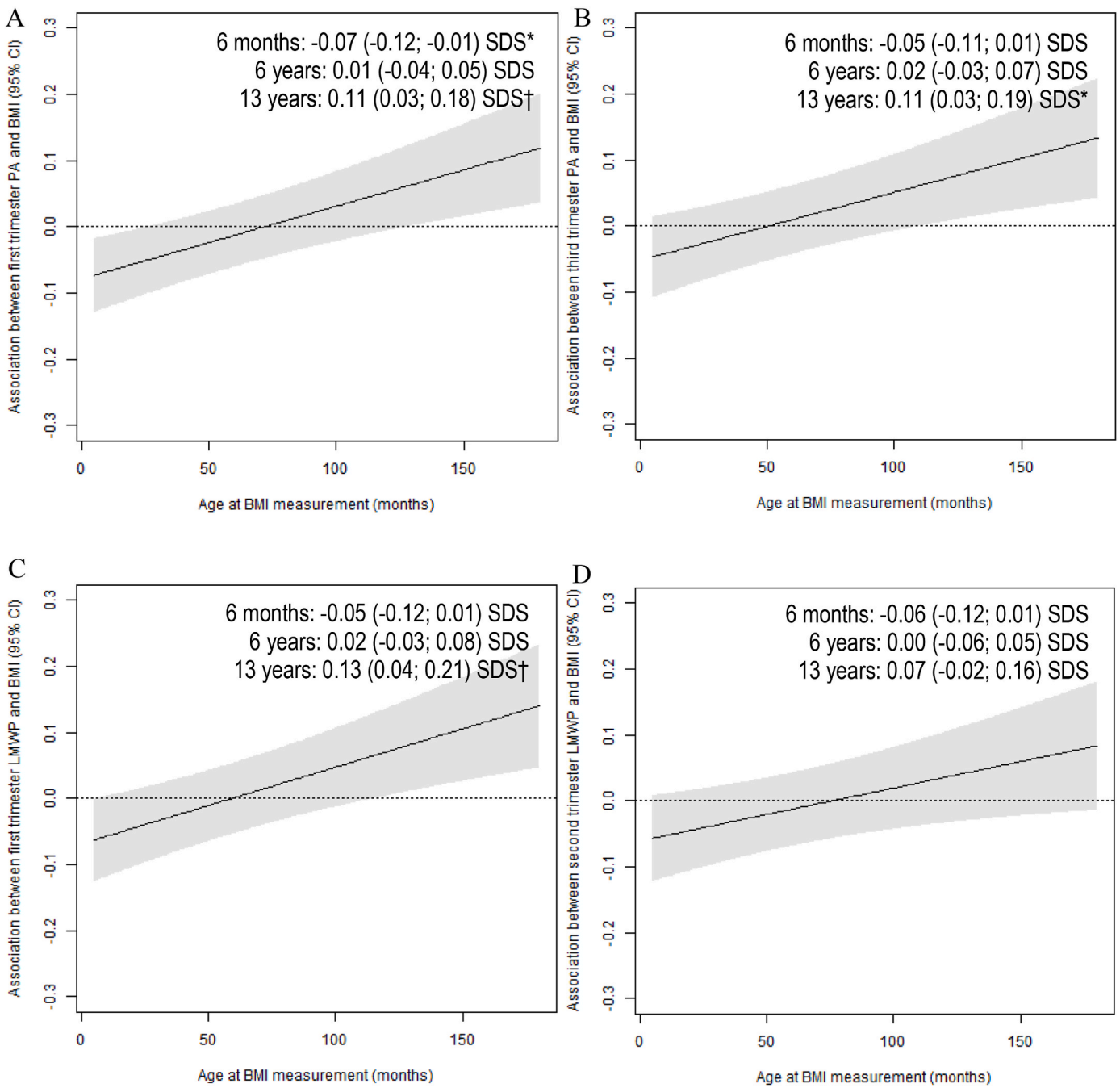

Fig. 1. Graphical representation of associations of maternal urinary phthalate concentrations during pregnancy with childhood BMI outcomes from 6 months to 13 years old. Final adjusted linear mixed effects model including age-interaction for associations that differed based on timing of BMI measurement.
Associations of maternal urine phthalate concentrations and child sex- and age-adjusted BMI measures in SDS for an interquartile range increase in each natural log-transformed phthalate metabolite in μmol/g creatinine.
Models include maternal age, pre-pregnancy BMI, educational level, ethnicity, parity, diet score during pregnancy, diet score during pregnancy, folic acid supplement use, smoking habits and alcohol consumption during pregnancy per trimester and child age at BMI measurement. Models include an interaction term between the exposure concentration and age at BMI measurement, a random intercept for each participant, and a random slope for age at BMI measurement.
* p-value < 0.05; † significant after correction for multiple testing (p-value threshold of 0.007). BMI, body mass index; CI, confidence interval; DEHP, di-2-ethylhexylphthalate; DNOP, di-n-octylphthalate; HMWP, high molecular weight phthalates; LMWP, low molecular weight phthalates; PA, phthalic acid.

DEHP urine concentrations with lower age- and sex-adjusted BMI SDS at younger ages. In contrast, higher maternal PA and LMWP urine concentrations were associated with higher age- and sex-adjusted BMI SDS at older ages. Multiple associations have been reported in the literature for maternal DEHP urine concentrations with childhood BMI or weight gain, although these are not consistent over multiple studies (Buckley et al., 2016; Gao et al., 2022; Harley et al., 2017; Heggeseth et al., 2019; Kupsco et al., 2022; Valvi et al., 2015; Yang et al., 2018). This inconsistency between studies might be explained by time-varying effects, i.e., the effect is not apparent across all age periods, which was also observed in our study. Maternal mEP urine concentrations were one of the drivers of the association of LMWP with higher BMI during childhood observed

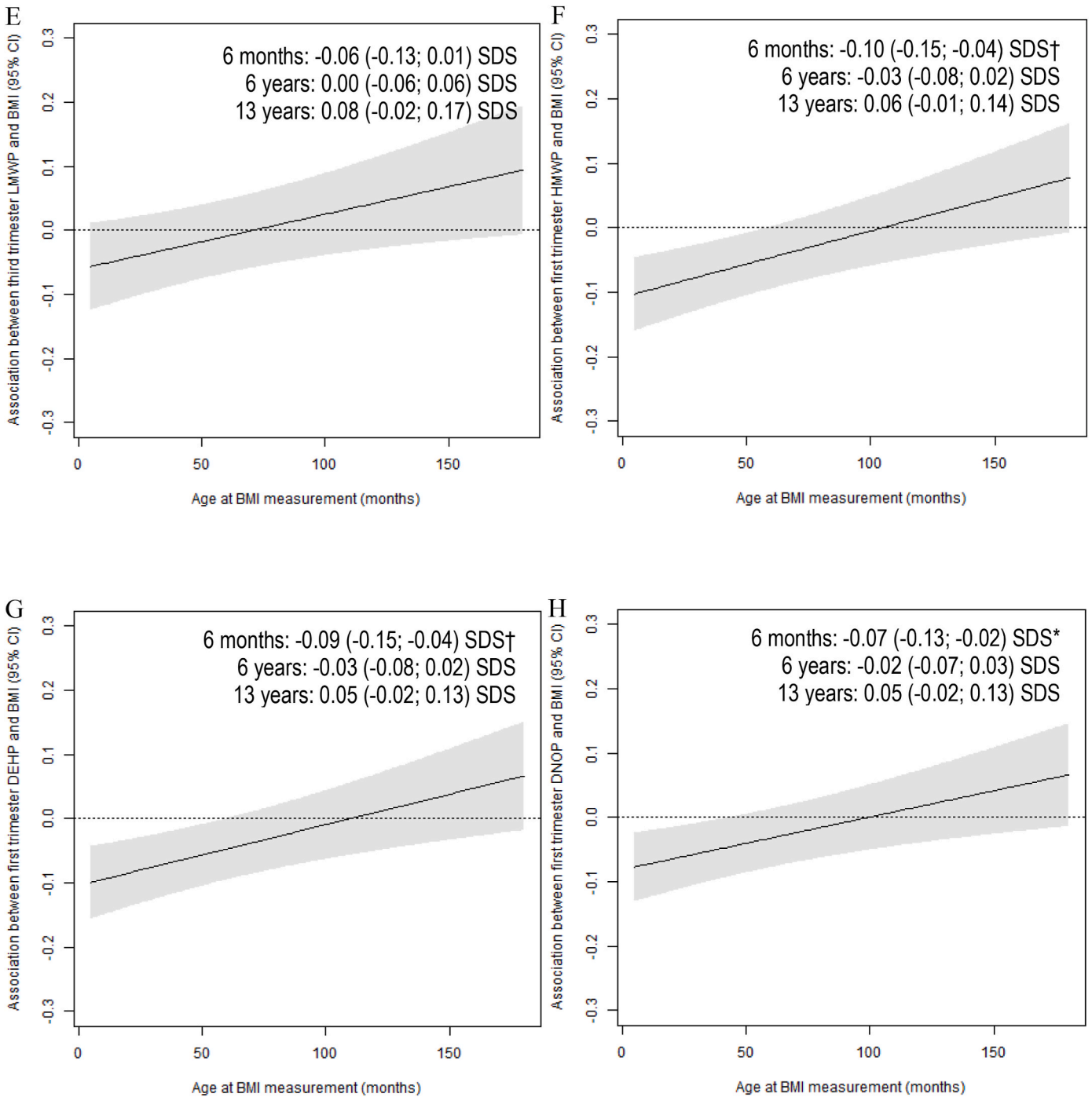

Fig. 1. (*continued*).

in our study. These results are consistent with multiple studies that have reported associations of mEP with higher BMI or weight growth velocity in either all participants or among boys specifically (Botton et al., 2016; Harley et al., 2017; Heggeseth et al., 2019). Studies that included birth weight in the longitudinal growth assessment have found an association of higher maternal urine phthalate concentrations with lower fetal growth and birth weight combined with changes in postnatal growth trajectories, which could indicate that there is some form of catch-up growth after exposure to phthalates during fetal life (Ferguson et al., 2022; Li et al., 2021; Svensson et al., 2021). Our results are consistent with this hypothesis, since we found that higher maternal urine phthalate concentrations were associated with lower BMI at early postnatal ages but with higher BMI at later ages. In two previous studies that included the same participants as this study, we found that higher maternal phthalate concentrations were associated with fetal growth restriction and we furthermore found that higher maternal first trimester phthalic acid concentrations were associated with higher pericardial fat index at 10 years of age, findings that are also consistent with this hypothesis (Santos, 2021; Sol, 2020). We did not find any sex-specific associations in this study, which is in line with most previous studies.

In our study, the largest effect estimates were found for first trimester maternal phthalate urine concentrations, suggesting this might be a vulnerable period for the effects of phthalates. This could be due to the fact that developmental disturbances during the first trimester can have major health implications by causing changes in the development of organ systems with long-lasting health effects. Most previous studies

included second or third trimester concentrations or averaged the concentrations over pregnancy and thus lack comparability with ours. Even though the effect estimates presented in this study are small, due to the widespread occurrence of phthalates in our environment and the difficulties of treating obesity and its adverse health consequences once it has developed, our findings are important from a public health perspective.

4.3. Potential underlying mechanisms

Many possible mechanisms have been suggested for the associations of maternal phthalate exposure during pregnancy with childhood adiposity. Phthalates are able to interact with the PPARgamma-receptor, which is of high importance in the regulation of adipogenesis (Barak et al., 1999; Feige et al., 2007; Rosen et al., 2002; Taxvig et al., 2012). Since disturbances in fetal growth could lead to an increased risk of obesity later in life and the PPARgamma-receptor is also involved in placental development, effects of phthalates on placental development might also play a role in its association with childhood BMI (Barak et al., 1999; Roseboom et al., 2006). As many phthalates are known to interfere with either the estrogen or androgen receptor, it is also possible that part of the association of prenatal exposure to phthalates occurs via influencing these receptors, although the specific effects could be dependent on the target tissues and could also vary for parent phthalates and their primary or secondary metabolites (Begum and Carpenter, 2022; Engel et al., 2017). Furthermore, phthalates are known to induce oxidative stress and inflammation, which is linked to the development of adiposity (Campioli et al., 2014). Finally, epigenetic changes induced by exposure to phthalates might influence obesity later in life (Manikkam et al., 2013; Martinez-Arguelles et al., 2014).

4.4. Methodological considerations

The main advantage of this study was that up to 8 BMI measurements were performed during infancy, childhood and adolescence, giving us the opportunity to assess BMI longitudinally. Our study is also one of the largest population-based cohort studies exploring the associations of phthalates with childhood health to date. Furthermore, we assessed exposure to phthalates at three different times during pregnancy, giving us the opportunity to assess both potential windows of vulnerability and the average exposure during pregnancy. Finally, due to the extensive data collection within the Generation R Study, we were able to adjust for many potential confounders including maternal diet. Of course, there are some limitations to our study. The main limitation of studies that explore the associations of exposure to phthalates, including ours, is that these exposure are highly variable due to their short half-lives (Wang et al., 2019). Nevertheless, it has been reported that for some phthalates such as mEP, the concentration in a spot urine sample could represent exposure up to three months (Hauser et al., 2004). In line with other studies conducted within Generation R on endocrine disruptors and childhood health, we have used a 20% detection rate as the minimum threshold to avoid excluding newer and, therefore, less prevalent chemicals from the analysis. However, as, in this study, the proportion of values below the detection is very low, the influence of the cutoff choice is minimal. Furthermore, we have used single substitution to impute values below the LOD. The use of single substitution could introduce bias if the percentage of values below the LOD is high. Again, as the detection rates in this study are generally high, we expect that this potential bias is of limited relevance in this study. In this study, we used BMI as a proxy for adiposity, while other measurements such as specific fat measurements might be more clearly associated with adiposity and its related health risks. Despite this, the assessment of BMI is both relatively easy to obtain in practice and a reasonable proxy of fat mass (Kakinami et al., 2014). Finally, although we tried to limit bias due to confounding by adjusting for multiple potential confounders in the analysis, residual confounding cannot be excluded.

5. Conclusions

In this study, we found an association of higher maternal first trimester HMWP and DEHP urine concentrations with lower age- and sex-adjusted BMI SDS at younger ages, while higher first trimester maternal phthalic acid and LMWP urine concentrations were associated with higher age- and sex-adjusted BMI SDS at older ages. These results are suggestive of an association of prenatal exposure to phthalates with growth restriction during pregnancy and early in life followed by catch-up growth and obesity later in life.

CRediT authorship contribution statement

Chalana M. Sol: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Geneviève Delgado:** Writing – original draft, Formal analysis. **Kurunthachalam Kannan:** Writing – review & editing, Methodology. **Vincent W.V. Jaddoe:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Leonardo Trasande:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Susana Santos:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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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.envres.2025.121253.

Data availability

Data will be made available on request.

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