



Full length article

Fetal phthalate exposure and asthma outcomes from infancy to adolescence: Individual participant data *meta*-analysis in the EU Child Cohort Network

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ABSTRACT

Objective: Early-life exposure to phthalates, widely used in consumer products, may induce developmental lung adaptations and predispose to respiratory morbidity throughout childhood. We assessed the associations of fetal phthalate exposure with wheezing, asthma, and lung function from birth to adolescence.

Methods: We performed 1-stage individual participant data *meta*-analyses with data from six European birth cohorts (3,745 mother–child pairs) to assess associations of pregnancy-averaged maternal urinary concentrations of 7 phthalate metabolites and 3 phthalate groups (high- and low-molecular-weight phthalate metabolites and sum of di-2-ethylhexyl phthalate metabolites) with wheezing in infancy (0–1 years) and at preschool age (1–5 years), and asthma and lung function at school age (5–12 years).

Results: Higher maternal pregnancy urine phthalate concentrations were not associated with wheezing in infancy or preschool age. Higher maternal pregnancy urine mono-benzyl phthalate concentrations were associated with an increased risk of asthma at school age (odds ratio (95% confidence interval): 1.13 (1.01–1.26) per natural log interquartile range unit increase in concentration), but not with wheezing or lung function and attenuated into

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non-significance after multiple testing correction. Higher maternal pregnancy concentrations of mono-2-ethyl-5-hydroxyhexyl phthalate, mono-*iso*-butyl phthalate, mono-*n*-butyl phthalate and low-molecular-weight phthalate metabolites were associated with higher FEV₁, FEV₁/FVC and FEF₇₅ z-scores after multiple testing correction. **Conclusion:** Fetal exposure to higher phthalate concentrations is associated with lung function adaptations, while overall no consistent associations were observed with childhood wheezing or asthma. Future studies are needed to assess the causality of the observed associations, to identify the underlying mechanisms, and to assess potential respiratory consequences in adult life.

1. Introduction

Phthalates are endocrine-disrupting chemicals and have recently become of interest due to their extensive use in food packaging and personal care products (Serrano et al., 2014; Braun et al., 2013). They have estrogenic and anti-androgenic capacities, are associated with higher oxidative stress markers, and have shown to bind to nuclear transcription factors that stimulate lipid accumulation and regulate inflammation (Philips et al., 2017). Through these mechanisms, the fetal period might be a specific sensitive period for their adverse effects. Phthalate metabolites can pass the placenta and affect the rapidly developing fetus (Mose et al., 2007; Nahar et al., 2015). Specifically, fetal exposure to phthalate metabolites may affect fetal lung development and predispose individuals to the development of impaired lung function and risk of asthma (Berger et al., 2019, 2020; Buckley et al., 2018; Casas and Gascon, 2020; Gascon et al., 2015; Jøhnk et al., 2020; Vernet et al., 2017; Wu et al., 2020; Karramass et al., n.d.). A recent meta-analysis using aggregate effect estimates of published studies suggested associations of higher maternal urine concentrations of mono-benzyl, mono-2-ethyl-5-hydroxyhexyl and mono-2-ethyl 5-carboxypentyl phthalate metabolites in the third trimester with higher asthma risk among 14,000 children between birth and the age of 11 years (Wu et al., 2020). The specific focus on the third trimester may have led to missing earlier sensitive windows, as previous studies have also identified the first trimester as critical for certain developmental outcomes (Almeida-Toledano et al., 2024). However, compared to that meta-analysis a more recent large cohort study among 1020 children at the age of 13 years yielded conflicting results and reported no associations of fetal phthalate metabolites exposure in any trimester with asthma risk, but only an association of fetal exposure to higher mono-*iso*-butyl phthalate concentrations in the second trimester with higher FEV₁/FVC (Karramass et al., n.d.). Overall, current studies present conflicting results. From an etiologic and prevention perspective, insight into the potential effects of fetal phthalate exposure on childhood respiratory health outcomes is urgently needed.

Therefore, we performed an individual participant data meta-analysis with data from six European birth cohorts within the EU Child Cohort Network including 3,745 mother–child pairs to assess the associations of maternal urinary phthalate concentrations in two trimesters during pregnancy with wheezing during infancy and preschool age, and asthma and lung function at school age.

2. Methods

2.1. Design

We included 3745 mother–child pairs from six European population-based birth cohorts collaborating in the EU Child Cohort Network, established by the LifeCycle Project and further advanced through EUCAN Connect and ATHLETE (Advancing Tools for Human Early Lifecourse Exposome Research and Translation) Projects (Jaddoe et al., 2020; Vrijheid et al., 2021). Cohorts included the Etude des Déterminants pré et post natus du développement et de la santé de l'Enfant (EDEN) (Heude et al., 2016), France, Generation R, the Netherlands (Kooijman et al., 2016), Generation R Next, the Netherlands, (Boxem et al., 2024) Infancia y Medio Ambiente (INMA),

Spain (Guxens et al., 2012), the Perturbateurs endocriniens: Etude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (PELAGIE) (Warembourg et al., 2024), France, and Rhea, Greece (Chatzi et al., 2017). The populations in the cohorts used in this study were recruited between 2001 and 2008, apart from Generation R Next in which the participants were recruited between 2017 and 2021. Information on the profile and design of each study is provided in [Supplementary Methods 1](#). Cohorts were eligible for this study if they had information about maternal urinary concentrations of phthalate metabolites measured in pregnancy, and information on respiratory outcomes (current wheezing, current asthma, and lung function) in children or adolescents aged 0–12 years. The flowchart of the current study population is given in [Supplementary Fig. 1](#). Availability of data on maternal urinary concentrations of phthalate metabolites and on child respiratory outcomes per included cohort is shown in [Fig. 1](#). All cohorts received approval from their local institutional review boards, and all study participants gave written informed consent to participate in the respective cohorts and secondary data analyses. Data were harmonized across these cohorts. The harmonized data were kept within each institution and analyzed through the R-based federated data analysis platform DataSHIELD (Avraam et al., 2024; Gaye et al., 2014; Marcon et al., 2021; Wilson et al., 2017). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Vandenbroucke et al., 2007).

2.2. Urine phthalate concentrations in women during pregnancy

Phthalate concentrations (ng/mL) were quantified in spot urine samples obtained from each woman at a single time point (EDEN, PELAGIE, RHEA), two time points (Generation R Next, INMA) or three time points (Generation R) during pregnancy. The availability of data on maternal urinary concentrations is shown in [Fig. 1](#). Details on collection, transportation, and analysis methodology in general and per cohort are provided in [Supplementary Methods 2](#). We only included phthalate metabolites that were available in all cohorts. Of these phthalate metabolites the percentage of samples with a value above LOD was at least 80%, except for mono-benzyl phthalate in Generation R Next (64% in first and third trimester). Of the included phthalate metabolites, concentrations below the LOD were imputed by the LOD divided by the square root of 2 (Hornung and Reed, 1990). Seven phthalate metabolites were assessed individually: mono-benzyl phthalate (mBzP); mono-2-ethyl 5-carboxypentyl phthalate (mECP); mono-2-ethyl-5-hydroxyhexyl phthalate (mEHPP); mono-2-ethyl-5-oxohexyl phthalate (mEOHP); mono-ethyl phthalate (mEP); mono-*iso*-butyl phthalate (mIBP), mono-*n*-butyl phthalate (mnBP) as well as in groups of low-molecular-weight phthalate metabolites (LMWP), high-molecular-weight phthalate metabolites (HMWP), and parent compound di-2-ethylhexyl phthalate (DEHP) (specific metabolites that are included in each group are described in [Supplementary Methods 2](#)). To create these groups and to make effect estimates comparable between the phthalate metabolites, concentrations were converted from ng/mL to nmol/L using molecular weights. The measured maternal urine phthalate concentrations and LODs per cohort are provided in [Supplementary Tables 1 and 2](#). To account for differences in phthalate concentrations between cohorts, concentrations were standardized by dividing each value by the interquartile range (IQR) of that specific phthalate within each cohort.

To adjust for right-skewness of the concentrations, all standardized maternal urine phthalate concentrations were log-transformed. All estimates are therefore expressed per natural log-transformed IQR unit of the concentration. To account for urinary dilution, we adjusted for creatinine by including pregnancy-averaged creatinine in the models (O'Brien et al., 2016; Philippat and Calafat, 2021). Maternal urinary phthalate concentrations available in multiple trimesters during pregnancy were analyzed per trimester and were averaged to obtain a single pregnancy-averaged concentration. This approach reduced the risk of exposure misclassification due to temporal variability and enabled comparisons between cohorts, despite differences in the number and timing of measurements.

2.3. Wheezing, asthma, and lung function in childhood

Information on wheezing was collected from birth to 5 years, as asthma diagnosis at early ages is challenging, and was used to assess wheezing in infancy (between birth and age 1 year) and at preschool age (between age 1 and 5 years). Current asthma was defined according to the Mechanism of the Development of Allergy (MeDALL) definition as having two of the following criteria: ever doctor diagnosis of asthma, wheezing in the past 12 months or use of asthma medication in the past 12 months (Pinart et al., 2014). Records of participants with missing data on 2 of the 3 criteria were coded as missing. We constructed current asthma at school age (between age 5 and 12 years, median age 7 years). Questions on wheezing and current asthma were adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) questionnaire, commonly used for respiratory epidemiological research (Asher et al., 1995). Lung function at school age was available between age 3 and 11 years (median age 8 years) in EDEN, Generation R, INMA, and Rhea and was measured using spirometry according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (Graham et al., 2019). Lung function parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), the Tiffeneau-index (FEV₁/FVC ratio), and forced expiratory flow after exhaling 75% of FVC (FEF₇₅) and were converted to age-, sex-, height-, and ethnicity-adjusted z-scores based on the Global Lung Function Initiative (GLI) reference equations (Cooper et al., 2017). Based on these lung function z-scores, obstructive and restrictive lung

function phenotypes were additionally derived. In cases with repeated data available within the age periods on wheezing, asthma and lung function we selected the assessment that was closest to the median age of the study population. Details of the lung function measurements are described in [Supplementary Methods 3](#).

2.4. Covariates

A set of covariates was selected a priori, based on literature search, and is presented in a Directed Acyclic Graph (DAG) [Supplementary Fig. 2](#), and included maternal and child socio-demographic, environmental and health factors. The selected maternal variables included age at delivery (years), ethnicity (Western, non-Western), education level (low, medium/high), pre-pregnancy body mass index (kg/m²), parity (0, 1, >2 previous born children), tobacco smoking during pregnancy (no, yes), folic acid use during pregnancy (no, yes), history of asthma (no, yes), history of eczema (no, yes). Paternal covariates included education level (low, medium, high) and history of asthma (no, yes). Information on covariates was primarily obtained from questionnaires. Other methods to obtain information on covariates in early life included the use of midwife or child healthcare center reports, registry data, or interviews. A detailed definition of each covariate is described in [Supplementary Methods 4](#).

2.5. Statistical analysis

First, we described the participant characteristics per cohort and for all cohorts combined. We calculated Pearson correlation coefficients of the correlation of maternal pregnancy urine averaged concentrations of all phthalate metabolites and phthalate groups with all respiratory outcomes. Second, we conducted a 1-stage fixed-effect individual participant data meta-analysis using multivariable logistic and linear regression analyses to assess the associations of maternal pregnancy-averaged urine phthalate concentrations with risk of wheezing in infancy and at preschool age, and risk of asthma and altered lung function at school age. For these analyses, individual participant data from all cohorts were combined in a 1-stage analysis and were modelled simultaneously considering the clustering of participants within studies by using a fixed coefficient at cohort level. Models were first adjusted for

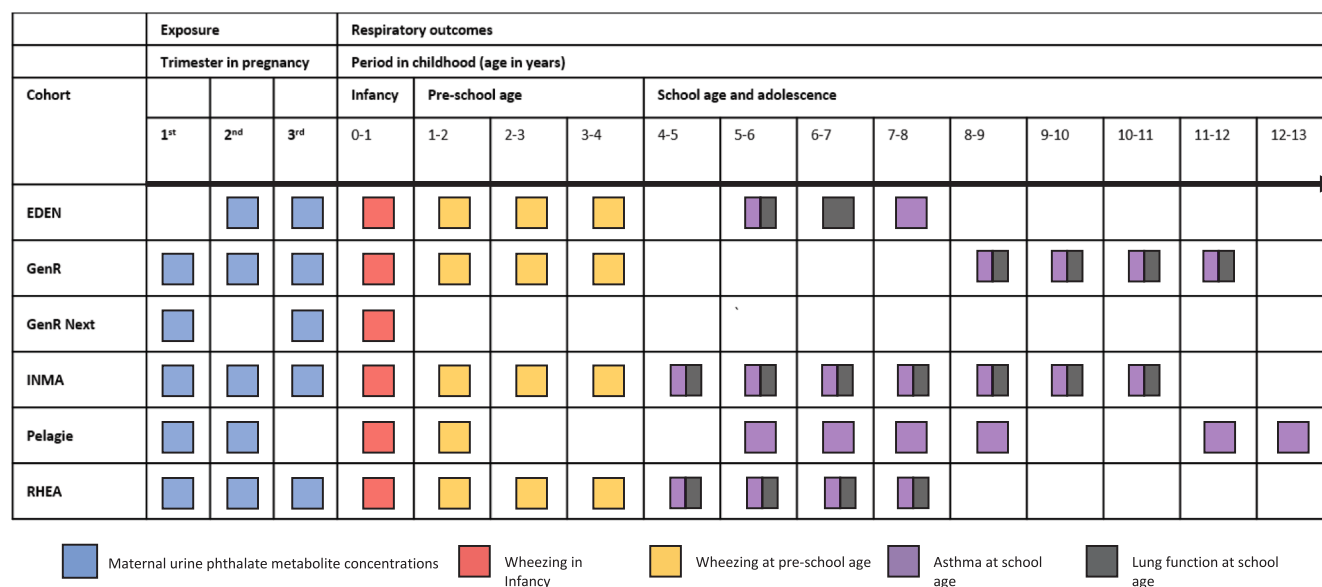


Fig. 1. Cohorts and Timeline with Availability of Maternal Urinary Phthalate Concentrations and Child Respiratory Outcomes per Included Cohort. Coloured squares represent the time points at which data on maternal urine phthalate metabolite concentrations and respiratory outcomes were collected in each cohort. These squares indicate the availability of measurements within the cohort, but not the number of measurements per participant, as some participants contributed data at only one visit while others had measurements at multiple time points.

cohort effects and subsequently for confounders without high collinearity (Variance Inflation Factor > 5), including maternal age at delivery, education, pre-pregnancy BMI, parity, tobacco smoking during pregnancy, parental education and asthma history, and child age and sex. We did not adjust or stratify for ethnicity as all cohorts except Generation R and Generation R Next predominantly had one ethnicity group. Since the effect of exposures on childhood outcomes might be modified by a possible protective effect of folic acid use during pregnancy against phthalate metabolites (Gules et al., 2019; Dolinoy et al., 2007; Pauwels et al., 2017), and child sex due to hormonal interaction of

phthalate metabolites (Vafeiadi et al., 2018; Jahreis et al., 2018; Doherty et al., 2017), we tested for statistical interaction of the maternal folic acid supplementation and child's sex, considering a p-value threshold of 0.10. In addition, we tested for effect modification by school-age asthma status specifically for the associations between maternal urine pregnancy-averaged phthalate concentrations and lung function. Interaction p-values for folic acid supplementation and school-age asthma status were not statistically significant. Stratified analyses were therefore not performed, as the number of non-users of folic acid supplementation and the number of participants with school age asthma

Table 1

Maternal, Paternal and Child characteristics of covariates in original datasets of participating cohorts.

Maternal characteristics	EDEN, France n = 691	Generation R, The Netherlands n = 1205	Generation R Next, The Netherlands n = 712	INMA, Spain n = 480	PELAGIE, France n = 415	Rhea, Greece n = 242
Age at birth, mean (SD)	30.0 (4.7)	31.5 (4.6)	32.3 (3.8)	31.8 (4.0)	30.8 (3.9)	30.74 (4.44)
Missing, n (%)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)
Ethnicity, n (%)						
Western	611 (99.4)	735 (61.4)	566 (82.6)	470 (98.1)	408 (98.0)	240 (99.9)
Non-Western	4 (0.7)	463 (38.7)	119 (17.4)	9 (1.9)	7 (2.0)	1 (0.01)
Missing	76 (11)	7 (0.6)	27 (3.8)	1 (0.2)	0 (0)	1 (0.01)
Education level, n (%)						
Lower/Middle	269 (44.3)	534 (45.7)	129 (18.6)	307 (55.6)	123 (29.6)	141 (58.3)
High	394 (59.4)	634 (54.3)	565 (81.4)	170 (36.3)	292 (70.4)	101 (41.7)
Missing	28 (4.1)	37 (3.1)	18 (2.5)	66 (13.7)	0 (0.0)	0 (0)
Pre-pregnancy BMI, mean (SD)	23.1 (4.4)	23.6 (4.2)	23.82 (4.1)	23.6 (4.5)	22.0 (3.3)	24.46 (4.47)
Missing, n (%)	9 (1.3)	105 (8.7)	14 (2.0)	0 (0.0)	4 (1.0)	1 (0.41)
Parity, n (%)						
0	312 (45.2)	748 (62.4)	470 (67.4)	273 (57.1)	163 (39.4)	37 (15.3)
1	255 (37.0)	331 (27.6)	180 (25.8)	179 (37.5)	163 (39.4)	104 (43)
>2	123 (17.8)	120 (10.0)	47 (6.7)	26 (5.4)	88 (21.3)	101 (41.7)
Missing	1 (0.1)	6 (0.5)	15 (2.1)	2 (0.4)	1 (0.2)	0 (0)
Tobacco smoking in pregnancy, n (%)						
No	528 (76.5)	835 (76.2)	655 (92.4)	338 (71.0)	310 (75.1)	165 (70.5)
Yes	162 (23.5)	261 (23.8)	54 (7.6)	138 (29.0)	103 (24.9)	69 (29.5)
Missing	1 (0.1)	109 (9.1)	3 (0.4)	4 (0.8)	2 (0.5)	8 (3.3)
Folic acid use during pregnancy, n (%)						
No	218 (79.9)	166 (17.1)	3 (0.6)	74 (15.4)	329 (81.6)	60 (28.6)
Yes	55 (20.2)	804 (82.9)	492 (99.4)	406 (84.6)	74 (18.4)	150 (71.4)
Missing	418 (60.5)	235 (19.5)	217 (30.5)	0 (0.0)	12 (2.9)	32 (13.2)
History of asthma, n (%)						
No	613 (88.8)	985 (92.6)	540 (89.9)	436 (91.0)	NA	222 (96.5)
Yes	77 (11.2)	79 (7.4)	61 (10.2)	43 (9.0)	NA	8 (3.5)
Missing	1 (0.1)	141 (11.7)	111 (15.6)	1 (0.2)	NA	12 (5)
History of eczema, n (%)						
No	593 (85.9)	1003 (93.8)	NA	419 (87.5)	NA	200 (85.8)
Yes	97 (14.1)	66 (6.2)	NA	60 (12.5)	NA	33 (14.2)
Missing	1 (0.1)	136 (11.3)	NA	1 (0.2)	NA	9 (3.7)
Paternal characteristics						
Education level, n (%)						
Lower	186 (10.0)	35 (4.1)	42 (6.2)	165 (34.7)	82 (22.3)	77 (32)
Middle	856 (46.0)	308 (35.8)	139 (20.7)	198 (41.7)	66 (17.9)	105 (43.6)
High	818 (44.0)	517 (60.1)	492 (73.1)	112 (23.6)	220 (59.8)	59 (24.5)
Missing	142 (7.1)	345 (28.6)	39 (5.5)	55 (1.0)	47 (11.3)	1 (0.4)
History of asthma, n (%)						
No	622 (90.1)	816 (98.3)	593 (91.8)	447 (93.3)	329 (85.9)	229 (98.3)
Yes	68 (9.9)	14 (1.7)	53 (8.2)	32 (6.7)	54 (14.1)	4 (1.7)
Missing	1 (0.1)	375 (31.1)	66 (9.3)	1 (0.2)	32 (7.7)	9 (3.7)
Child characteristics						
Sex, n (%)						
Male	603 (87.3)	612 (50.8)	378 (53.1)	251 (52.3)	239 (57.6)	139 (57.4)
Female	88 (12.7)	593 (49.2)	334 (46.9)	229 (47.7)	176 (42.4)	103 (42.6)
Gestational age at birth (weeks), mean (SD)	39.7 (1.6)	40.7 (1.4)	39.6 (1.7)	39.9 (1.4)	39.6 (1.4)	38.6 (1.4)
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.41)
Birth weight, grams mean (SD)	3345 (484)	3457 (491)	3404 (524)	3256 (397)	3452 (467)	3198 (410)
Missing, n (%)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.4)

Abbreviations: NA, not available; SD, standard deviation; BMI, body mass index.

Values represent mean (standard deviations) or absolute numbers (valid percentages). Percentages may not total 100 due to rounding. There were participants with missing values for child's sex. Data are shown of participants who were included only when at least one of the exposures and one of the outcomes was available.

was too small in most cohorts. To account for multiple testing, we applied the Benjamini-Hochberg procedure to control the false discovery rate (FDR) and set the significance level at an FDR of 0.05. Details on the multiple testing correction applied in this study are described in [Supplementary Methods 5](#). The percentages of missing values for the covariates ranged from 0 (INMA) to 60.5% (EDEN) for folic acid use during pregnancy in the samples with information on at least one exposure and one outcome ([Table 1](#)). Missing values in the dataset for analysis of maternal urine phthalate concentrations, respiratory outcomes and covariates were imputed for each cohort separately using Multiple Imputation by Chained Equations (MICE) from the MICE package in R ([Buuren and Groothuis-Oudshoorn, 2011](#)). Ten imputed datasets per cohort were created using ten iterations, and no important differences in prevalence of covariates were found between the original and the pooled imputed datasets for each cohort. We only present results of the analyses based on the pooled imputed dataset using Rubin's rules. We performed the following sensitivity analyses: first, we conducted a 2-stage random effects *meta-analysis* of the association of pregnancy-averaged maternal urine phthalate concentrations with child respiratory outcomes across all cohorts to assess both individual cohort effects and the overall effect, while assessing between-cohort heterogeneity. Second, we conducted a 1-stage *meta-analysis* of the association of maternal urine phthalate concentrations of each trimester separately with child respiratory outcomes. Imputation and all statistical analyses were conducted using R statistical software (version 4.3.2) with appropriate packages specifically designed for the federated analysis platform DataSHIELD. Information on this federated platform is described elsewhere ([Gaye et al., 2014](#)).

3. Results

3.1. Subject characteristics

[Table 1](#) presents the characteristics of the study population across cohorts. Almost all mothers were of Western ethnicity in all cohorts, except for Generation R and Generation R *Next*, which included nearly 40% and 17% non-Western participants, respectively. The prevalence of smoking during pregnancy ranged from 7.6% in Generation R *Next* to 29.5% in Rhea. Folic acid use during pregnancy ranged from 18.4% of mothers in PELAGIE to 99.4% in Generation R *Next*.

[Table 2](#) presents the characteristics of the respiratory outcomes. The prevalence of wheezing in infancy ranged from 6.6% (Rhea) to 29.1% (Generation R). At preschool age, wheezing prevalence ranged from 6% (Rhea) to 29.8% (INMA). The prevalence of current asthma at school age was lowest in Generation R (6.8%) and highest in EDEN (10.1%).

[Supplementary Table 2](#) presents characteristics of maternal urine phthalate concentrations. The metabolite mEP had the highest median concentrations, ranging from 10.21 µg/L in Generation R *Next* (in the second trimester of pregnancy) to 320.63 µg/L in INMA (in the third trimester of pregnancy). The lowest concentrations were found in diisobutyl phthalate (DiNP) metabolites, ranging from 0.71 µg/L for mono-4-methyl-7-hydroxyoctyl phthalate (oh-mINP) in EDEN to 3.37 µg/L in INMA.

Table 2
Characteristics of Wheezing, Asthma and Lung Function in Participating Cohorts.

Respiratory outcome	EDEN, France n = 691	Generation R, The Netherlands n = 1205	Generation R <i>Next</i> , The Netherlands n = 712	INMA, Spain n = 480	PELAGIE, France n = 415	Rhea, Greece n = 242
<i>Wheezing in infancy, n (%)</i>						
No	501 (73.4)	466 (70.9)	516 (72.5)	31 (83.8)	234 (90)	222 (93.3)
Yes	182 (26.7)	191 (29.1)	196 (27.5)	6 (16.2)	26 (10)	16 (6.7)
Missing	8 (1.2)	548 (45.5)	0 (0)	443 (92.3)	155 (37.4)	4 (1.7)
<i>Wheezing at preschool age, n (%)</i>						
No	570 (86.0)	938 (84.7)	NA	337 (70.2)	228 (88.4)	215 (94.7)
Yes	93 (14.0)	169 (15.3)	NA	143 (29.8)	30 (11.6)	12 (5.3)
Missing	28 (4.1)	98 (8.1)	NA	0 (0)	157 (37.8)	15 (6.2)
<i>Asthma at school age, n (%)</i>						
No	536 (89.9)	921 (93.2)	NA	420 (86.6)	370 (92.5)	163 (92.6)
Yes	60 (10.1)	67 (6.8)	NA	38 (8.3)	30 (7.5)	13 (7.4)
Missing	95 (13.8)	217 (18)	NA	22 (4.6)	15 (3.6)	66 (27.3)
<i>Lung function Z-score, mean (SD)</i>						
FEV ₁	−0.73 (0.98)	0.12 (1.00)	NA	0.1 (1.08)	NA	0.15 (1.02)
FVC	−1.07 (0.96)	0.16 (0.94)	NA	0.31 (1.06)	NA	0.26 (1.04)
FEV ₁ /FVC	0.89 (1.02)	−0.10 (0.98)	NA	−0.29 (0.97)	NA	−0.23 (0.89)
FEF ₇₅	0.20 (0.90)	0.00 (0.92)	NA	−0.06 (1.05)	NA	−0.09 (0.96)
Missing, n (%)	271 (39.2)	140 (11.6)	NA	66 (15.9)	NA	76 (31.4)
<i>Obstructive phenotype, n (%)</i>						
No	412 (98)	1036 (98)	NA	384 (93)	NA	155 (93.4)
Yes	8 (2)	29 (2)	NA	30 (7)	NA	11 (6.6)
Missing	271 (39.2)	140 (11.6)	NA	66 (15.9)	NA	76 (31.4)
<i>Restrictive phenotype, n (%)</i>						
No	309 (74)	1043 (98)	NA	405 (98)	NA	159 (95.8)
Yes	111 (26)	22 (2)	NA	9 (2)	NA	7 (4.2)
Missing	271 (39.2)	140 (11.6)	NA	66 (15.9)	NA	76 (31.4)

Abbreviations: NA, not available; SD, standard deviation; FEV₁, forced expiratory volume expired in 1 s; FVC, forced vital capacity; FEF₇₅, forced expiratory flow when 75% of FVC is expired. Infancy, preschool age, and school age are defined as age 0–1 years, age 1–5 years and 5–12 years, respectively. Values represent mean (standard deviations) or absolute numbers (valid percentages). Percentages may not total 100 due to rounding. Participants included only when at least one of the outcomes was available.

3.2. Maternal pregnancy urine phthalate concentrations and childhood wheezing and asthma

Fig. 2 and Supplementary Table 3 show that maternal urine pregnancy-averaged phthalate concentrations were not associated with wheezing in infancy or at preschool age. Higher maternal urine pregnancy-averaged mBzP concentrations were associated with a higher risk of asthma at school age (odds ratio (OR) (95% confidence interval (CI)): 1.13 (1.01–1.26) per natural log IQR unit increase in concentration). The association attenuated into non-significance after correction for multiple testing. The 2-stage *meta*-analyses are shown in Supplementary Table 4 and demonstrated that the direction of this association was consistent and was mainly driven by the EDEN and Generation R cohorts (Supplementary Table 4.3). Moreover, sex-stratified analyses show no sex specific modifying effect after correcting for multiple testing (Supplementary Table 5). Trimester specific analyses showed no associations of maternal pregnancy urine phthalate concentrations in each trimester with wheezing in infancy, wheezing at preschool or asthma at school age after correcting for multiple testing (Supplementary Table 6).

3.3. Maternal pregnancy urine phthalate concentrations and childhood lung function

Fig. 3 and Supplementary Table 7 show that maternal urine pregnancy-averaged mnBP and LMWP concentrations were associated with a higher FEV₁ Z-score (Z-score difference (95% CI): 0.06 (0.02–0.10) and 0.03 (0.01–0.05) per natural log IQR unit increase in concentration, respectively). Moreover, higher maternal urine pregnancy-averaged mEHHP, mIBP, mnBP and LMWP concentrations were associated with a higher FEV₁/FVC Z-score (Z-score difference (95% CI): 0.04 (0.01–0.08), 0.06 (0.02–0.10), 0.07 (0.03–0.11), 0.03 (0.01–0.05) per natural log IQR unit increase in concentration, respectively). The 2-stage *meta*-analyses are shown in Supplementary Table 8 and demonstrated consistent overall effect estimates that were mainly driven by the Generation R and INMA cohorts (Supplementary Tables 8.1 and 8.3). Higher maternal urine pregnancy-averaged mEP, mnBP, mIBP and LMWP concentrations were associated with a higher FEF₇₅ Z-score (Z-score difference per natural log IQR unit increase in concentration (95% CI): 0.03 (0.00–0.05), 0.06 (0.02–0.09), 0.08 (0.04–0.12), 0.04 (0.02–0.06), respectively). The 2-stage *meta*-analysis showed that the direction of this association was consistent in all cohorts and was mainly driven by the Generation R cohort (Supplementary

Table 8.4). Moreover, sex-stratified analyses show no sex specific modifying effect after correcting for multiple testing (Supplementary Table 9). The association of higher maternal urine pregnancy-averaged mEP concentrations with FEF₇₅ Z-score attenuated and lost significance after correction for multiple testing. Trimester specific associations showed that third trimester maternal urine pregnancy LMWP concentrations were associated with a higher FEF₇₅ Z-score (Z-score difference per natural log IQR unit increase in concentration (95% CI): 0.02 (0.01–0.04)) after correcting for multiple testing (Supplementary Table 10).

4. Discussion

In this individual participant data *meta*-analysis among 3,745 mother–child pairs from six European birth cohorts, we assessed the association of fetal phthalate exposure with wheezing, asthma, and lung function from birth to adolescence. Our results demonstrate that higher maternal urine pregnancy-averaged phthalate concentrations were not associated with wheezing in infancy or at preschool age. Higher maternal urine pregnancy-averaged concentrations of mBzP tended to be associated with an increased risk of asthma at school age. Higher maternal urine concentrations of mnBP and LMWP averaged during pregnancy were associated with higher FEV₁ Z-scores. Higher maternal urine concentrations of mnBP, mEHHP, mIBP and LMWP were associated with higher FEV₁/FVC Z-scores. Moreover, higher maternal urine concentrations of mnBP, mIBP and LMWP in the third trimester were associated with higher FEF₇₅ Z-scores after multiple testing correction. These results suggest that fetal exposure to higher phthalate concentrations may be associated with a school-age asthma risk and lung function adaptations.

4.1. Comparison with previous literature

Numerous individual cohort studies have examined the association of prenatal phthalate exposure with wheezing, asthma and lung function, but findings have been inconsistent across study cohorts, exposure windows during pregnancy and phthalate metabolites (Adgent et al., 2020; Buckley et al., 2018; Jøhnk et al., 2020; Jurewicz and Hanke, 2011; Preece et al., 2022; Whyatt et al., 2014; Wu et al., 2020; Karramass et al., n.d.; Ku et al., 2015). Several studies observed that higher maternal concentrations of specific phthalate metabolites were associated with an increased risk of wheezing in infancy or early childhood (Jurewicz and Hanke, 2011; Adgent et al., 2020; Ku et al., 2015; Preece

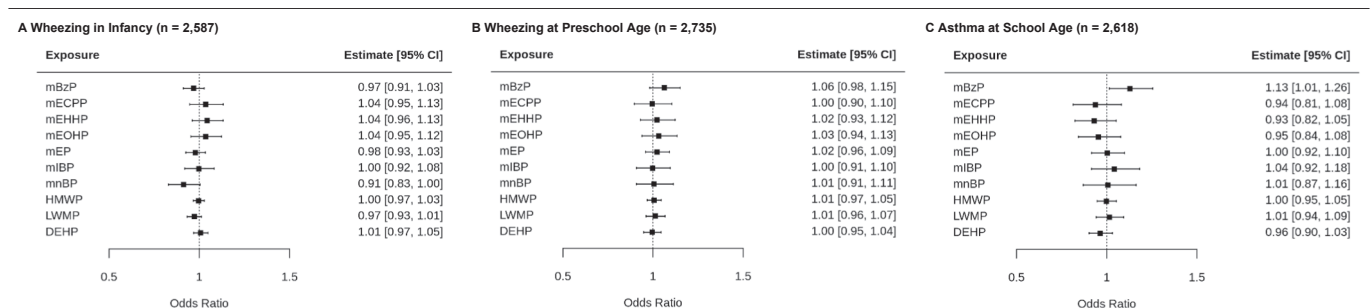


Fig. 2. 1-Stage Meta-Analysis on the Associations of Average Maternal Urine Phthalate Concentrations with Wheezing and Asthma. Abbreviations: mBzP: mono-benzyl phthalate; mECPP: mono-2-ethyl 5-carboxypentyl phthalate; mEHPP: mono-2-ethyl-5-hydroxyhexyl phthalate; mEOHP: mono-2-ethyl-5-oxohexyl phthalate; mEP: mono-ethyl phthalate; mIBP: mono-iso-butyl phthalate; mnBP, mono-n-butyl phthalate; HMWP: High molecular weight phthalates; LMWP: low-molecular-weight phthalates; DEHP: di-2-ethylhexyl phthalates. Values represent odds ratios (95% confidence interval) in the associations between a natural log IQR unit increase of pregnancy-averaged maternal urine phthalate concentrations with wheezing in infancy (A), wheezing in preschool age (B) and current asthma at school age (C). Models are adjusted pregnancy-averaged creatinine, maternal age at birth, maternal education, prepregnancy body mass index, parity, maternal tobacco smoking during pregnancy, maternal history of asthma, maternal history of eczema, paternal education, and paternal history of asthma. Included cohorts are EDEN, Generation R, Generation R Next (only for wheezing at infancy), INMA, PELAGIE and Rhea. The INMA cohort was not included in the logistic regression model including wheezing at infancy due to limited event counts and quasi-complete separation, which limited model convergence. Corresponding data are presented in Supplementary Table 3.1.

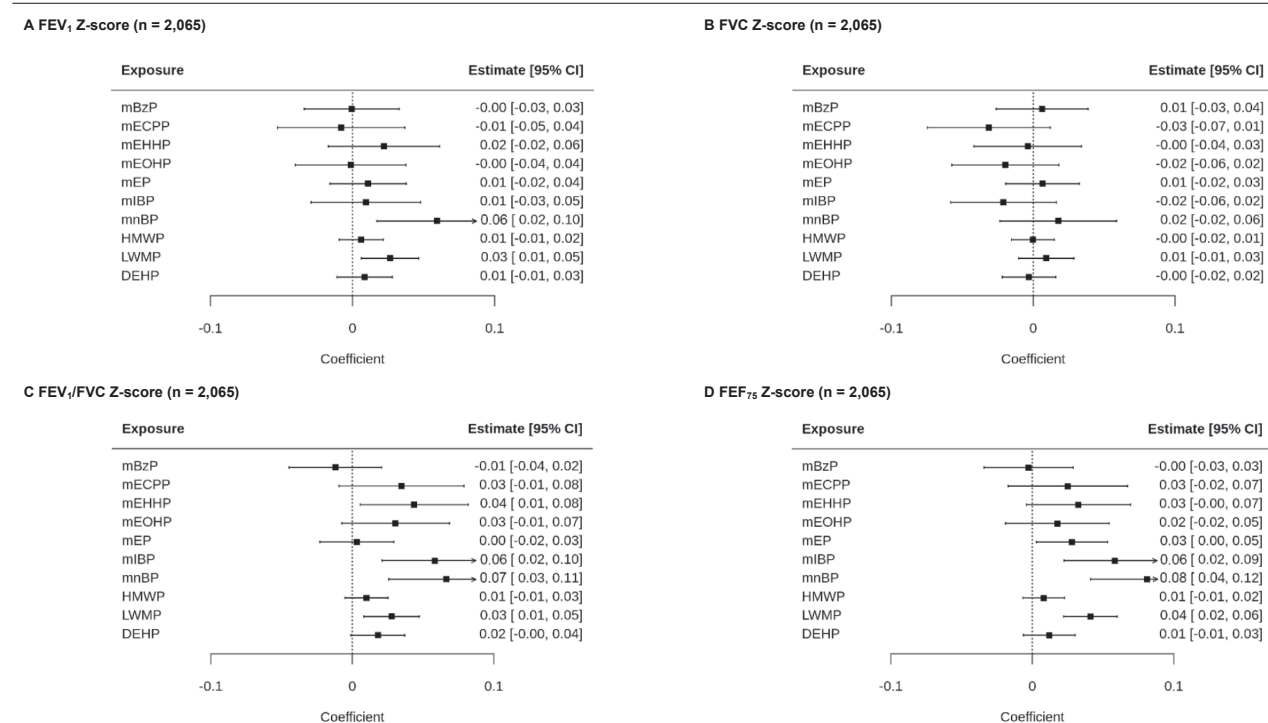


Fig. 3. 1-Stage Meta-Analysis on the Associations of Average Maternal Urine Phthalate Concentrations with Lung Function Measures. Abbreviations, mBzP, mono-benzyl phthalate; mECP, mono-2-ethyl 5-carboxypentyl phthalate; mEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; mEOHP, mono-2-ethyl-5-oxohexyl phthalate; mEP, mono-ethyl phthalate; mIBP, mono-iso-butyl phthalate; mNB, mono-n-butyl phthalate; HMWP, high molecular weight phthalates; LMWP, low-molecular-weight phthalates; DEHP, di-2-ethylhexyl phthalates. Values represent z-score (95% confidence interval) in the associations between a natural log IQR unit increase of pregnancy-averaged maternal urine phthalate concentrations with FEV₁ z-score (a), FVC z-score (b), FEV₁/FVC z-score (c) and FEF₇₅ z-score (d). Lung function z-scores are sex, height and age adjusted according to the Global Lung Index reference. Models are adjusted pregnancy-averaged creatinine, maternal age at birth, maternal education, prepregnancy body mass index, parity, maternal tobacco smoking during pregnancy, maternal history of asthma, maternal history of eczema, paternal education, and paternal history of asthma. Included cohorts are eden, generation r, inma and rhea. Corresponding data are presented in supplementary table 3.2.

et al., 2022), while other studies reported no association, or even protective associations (Jøhnk et al., 2020; Buckley et al., 2018). In our study, which represents the largest sample size of individual participant data so far, we did not observe associations of maternal urine pregnancy-averaged phthalate concentrations or trimester-specific maternal phthalate concentrations and wheezing in infancy or at preschool age. The absence of an association with wheezing may be due to the heterogeneous nature of this outcome. Wheezing is common in infancy and early childhood, often triggered by viral infections rather than underlying asthma, whose heterogeneity may explain the wide range of prevalences observed across cohorts (Global Initiative for Asthma, 2025). Parental reporting of wheezing may also have contributed to misclassification, which could have led to underestimated associations (Michel et al., 2006). Moreover, in the Generation R Next cohort we observed lower maternal urine phthalate concentrations compared to the earlier Generation R cohort and the other cohorts, however, associations of the 2-stage analysis in the Generation R Next cohort were not materially different than for the other cohorts. Furthermore, in contrast to the wheezing outcomes, asthma was defined based on a physician diagnosis, representing a more specific and reliable outcome.

A recent meta-analysis using aggregate effect estimates of published studies including over 14,000 children reported associations of higher prenatal concentrations of mBzP, mEHHP and mECP with a higher risk of childhood asthma (Wu et al., 2020). Another more recent analysis among 1,020 children participating in the Generation R study reported no associations of maternal urine pregnancy phthalate concentrations of either mBzP, mEHHP and mECP with asthma risk at age 13 years (Karramass et al., n.d.). Maternal urinary phthalate concentrations in our study were generally comparable to those reported in previous

European studies that assessed school age asthma. In our study, higher maternal urine pregnancy-averaged concentrations of mBzP were also associated with an increased risk of asthma at school age. However, we did not observe an association of maternal urine pregnancy-averaged concentrations of mEHHP with childhood asthma. This latter finding was consistent with findings from a smaller study among 300 children aged 5–11 years (Whyatt et al., 2014).

Several recent studies observed that higher maternal concentrations of specific phthalate metabolites were associated with higher lung function Z-scores in childhood and adolescence (Foong et al., 2023; Hu et al., 2024; Karramass et al., n.d.), while other studies reported no association (Vernet et al., 2017), or inverse associations (Berger et al., 2019; Bosch de Basea et al., n.d.). Our findings indicate that higher maternal urine pregnancy concentrations of LMWP were associated with higher FEV₁ z-scores. Additionally, our results show that higher maternal urine pregnancy concentrations of LMWP, mIBP and mEP were associated with higher FEV₁/FVC and FEF₇₅ z-scores. Overall, literature remains inconsistent regarding the direction and magnitude of associations, and findings vary depending on the timing of exposure and the phthalate metabolite studied.

4.2. Underlying mechanisms

Since previous literature shows inconsistent results, future studies should further elucidate the underlying biologic relation of prenatal phthalate exposure with respiratory outcomes in childhood. Experimental studies have shown that phthalate metabolites can act as adjuvants by stimulating Th₂-type immune responses, increasing Th₂ cytokine secretion and promoting IgE production (Bornehag and

Nanberg, 2010). These pathways are implicated in asthma development. In our study, only mBzP was associated with asthma, which is a metabolite of butyl benzyl phthalate (BBzP) that is commonly used in vinyl flooring (Jurewicz and Hanke, 2011). Although BBzP has shown no adjuvant properties in animal studies, other animal studies demonstrate fibrosis in mice, and an *in vivo* study on human bronchial epithelial cell lines has demonstrated that it induces bronchial smooth muscle proliferation and migration, promotes airway remodeling and increases expression of inflammatory mediators (Wang et al., 2022; Larsen et al., 2003). These mechanisms may help explain the observed association prenatal mBzP exposure and asthma at school age. However, the lack of data on allergic sensitization and airway inflammatory markers in our study limited sub-phenotyping of asthma into TH₂-high versus TH₂-low endotypes. This might be an important focus for future studies aiming to elucidate the specific biological role of mBzP in asthma pathogenesis (Tsai et al., 2012). Also, the mechanisms for the associations of fetal phthalate exposure with respiratory tract infections may at least partly overlap with those for the associations with asthma (Gascon et al., 2015). Data on respiratory tract infections were not available across all cohorts in our study. Future studies should study the associations of fetal phthalate exposure with respiratory tract infections.

The associations of maternal urine pregnancy phthalate concentrations with lung function outcomes may be explained by hormonal effects during critical periods of lung development (Seaborn et al., 2010). The third trimester includes the sacular and alveolar phases of lung development, during which estrogen plays a key role in alveologenesis (Seaborn et al., 2010). Previous research has shown that higher third trimester mEP concentrations and higher second trimester concentrations di-isobutyl phthalate, the parent metabolite of mIBP, tended to be associated with increased maternal estrogen levels. These hormonal changes may stimulate alveolar formation and lead to improved lung function in later childhood. In our study, pregnancy averaged mIBP and LMWP were associated with higher FEV₁, FEV₁/FVC and FEF₇₅ Z-scores, supporting the hypothesis of a hormone-mediated effect on alveolar development. While FEV₁ reflects large airway function, FEF₇₅ is considered to reflect small airway function, and therefore indicates that prenatal exposure to phthalate metabolites may affect both large and peripheral airway development (Qin et al., 2021). We did not observe sex-specific associations or effect modification by maternal folic acid supplementation or school-age asthma status, which may partly reflect limited statistical power. Moreover, in our study pregnancy averaged mnBP concentrations were associated with FEV₁, FEV₁/FVC and FEF₇₅ Z-scores of which the exact mechanism remains unclear, while it is known that mnBP may affect lung function adaptation through reactive oxygen species overproduction and impaired antioxidant responses involving NF-κB and Nrf2 pathways (Quoc et al., 2022).

Altogether, the observed differences between the increased asthma risk and improved lung function, may reflect distinct biological mechanisms. Asthma is primarily driven by immunological and inflammatory processes, whereas lung function may be more directly influenced by airway development.

4.3. Strengths and limitations

The major strength of this study is the analysis of individual participant data from different birth cohorts collecting information by following-up children and their mothers from early fetal life until adolescence, which ensures robust statistical power for small effects and the temporal sequence to be clearly established. The findings are the results from individual participant data *meta-analysis* with harmonized data of covariates and respiratory outcomes, enabling more precise estimates of associations and reducing heterogeneity across cohorts while increasing comparability across cohorts. Also, well-known phthalate metabolite concentrations were available in two to three trimesters, which represents a more nuanced assessment of the exposure during pregnancy and provided additional information on trimester specific

effects on wheezing- and asthma risk, and lung function. However, some methodological considerations should be mentioned. First, the short biological half-life of phthalate metabolites and the single measurement per trimester might have led to exposure misclassification. To minimize the impact of this potential misclassification, we used the average phthalate concentrations across pregnancy. Second, maternal urine samples from different cohorts were analyzed in different laboratories, which may have led to measurement bias. To address this, we normalized the concentrations by dividing them by the phthalate- and lab specific IQR within each cohort. Third, residual confounding may have been present in our study as some confounders may have limited variability, such as ethnicity, and unknown risk factors or confounders may exist, and measurement error or misclassification of risk factors may have occurred despite our extensive efforts to identify and include all relevant risk factors and applying strict data harmonization protocols. In particular, the observed associations of higher maternal urinary concentrations of mIBP and mnBP with higher FEV₁, FEV₁/FVC, and FEF₇₅ z-scores, could be driven by confounding. However, the currently known determinants of mnBP and mIBP exposure, such as use of personal care products, food packaging, house dust exposure, and flooring type, are unlikely to directly enhance lung function, suggesting that additional and unidentified biological mechanisms may be involved. Future studies integrating genetic, metabolic, and endocrine analyses are needed to determine the mechanisms underlying the associations of fetal phthalate exposure with lung development and function. Fourth, we applied multiple imputation to mitigate bias due to missing data, but data may have been missing not at random, which could have introduced bias into our imputation. However, relying on complete case analysis would not necessarily have eliminated this bias either, and may have led to reduced statistical power and biased estimates (Van Ginkel et al., 2020). Fifth, the data on wheezing, asthma and lung function were available at different ages across cohorts (Fig. 1). We created age periods (infancy, preschool age and school age) in which the outcome was present, but we were unable to identify the effects on a particular age. Sixth, while the ATS/ERS criteria allowed for standardization of lung function measurements, estimates involving lung function should be interpreted carefully, as the measurement error across different cohorts may be larger than the true small effects found in this study. We used FEF₇₅ because FEF₂₅₋₇₅ was not available across most participating cohorts. We acknowledge that FEF₂₅₋₇₅ is considered a more stable marker of mid-expiratory flow, as it reflects airflow over a volume range and is less sensitive to single-point variability than FEF₇₅ (Quanjer et al., 2014). Future studies, particularly in the context of asthma, should include FEF₂₅₋₇₅. Furthermore, the numbers for the associations with obstructive and restrictive lung function phenotypes as outcomes were too small, resulting in insufficient statistical power for association analyses focused on these phenotypes. Seventh, while the study population of the included cohorts, except INMA and RHEA, are primarily from higher educational backgrounds in high-income countries, which may limit the generalizability of the findings to populations with lower educational attainment and to low-and middle-income countries, this individual participant *meta-analysis* on phthalate exposure and respiratory outcomes included the largest number of participants from different geographical regions of Europe to date. Lastly, although this study included the largest sample to date examining associations between maternal urinary phthalate concentrations and respiratory outcomes, the observed effect estimates were small. This suggests that even larger study populations may be needed to detect associations more reliably. In future research, mixture analyses with other endocrine-disrupting chemicals may help to better identify the associations by capturing potential larger joint effects and by limiting the number of analyses.

4.4. Conclusion

In this European multi-cohort individual participant analysis, our results suggest that fetal exposure to higher phthalate metabolite

concentrations may be associated with an increased risk of school-age asthma and is associated with lung function adaptations. Future studies are needed to assess the causality of the observed associations, to identify the underlying mechanisms, and to assess potential respiratory consequences in adult life.

Author contributions

TK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. DA and SB contributed to the data analysis and were responsible for checking the analysis. AKS and CT were responsible for the phthalate analysis done at NIPH. All authors contributed to the interpretation of the data, drafted the article, revised it critically for important intellectual content, and gave final approval of the version to be published. LT, and VJ contributed to the conception and design, and acquisition of data.

CRediT authorship contribution statement

Tarik Karramass: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Liesbeth Duijts:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Demetris Avraam:** Writing – review & editing, Formal analysis. **Sophia Blaauwendraad:** Methodology, Formal analysis. **Paula Carrasco:** Writing – review & editing, Data curation. **Nuria Güil-Oumrait:** Writing – review & editing, Data curation. **Amaia Irizar:** Writing – review & editing, Data curation. **Manik Kadawathagedara:** Writing – review & editing, Data curation. **Marianna Karachaliou:** Writing – review & editing, Data curation. **Maria-Jose Lopez-Espinosa:** Writing – review & editing, Data curation. **Antonios Myridakis:** Writing – review & editing, Data curation. **Elke Rouxel:** Writing – review & editing, Data curation, Conceptualization. **Amrit Kaur Sakhi:** Writing – review & editing, Data curation. **Cathrine Thomsen:** Writing – review & editing, Data curation. **Chloe Vainqueur:** Writing – review & editing, Data curation. **Martine Vrijheid:** Writing – review & editing, Data curation. **Charline Warembourg:** Writing – review & editing, Data curation. **Marieke Welten:** Data curation. **Carlos Zabaleta:** Writing – review & editing, Data curation. **Leonardo Trasande:** Writing – review & editing, Methodology, Funding acquisition, Data curation, Conceptualization. **Vincent Jaddoe:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2026.110069>.

Data availability

Data will be made available on request.

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