Journal of Hazardous Materials 475 (2024) 134863

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Associations of prenatal exposure to phthalates and their mixture with lung function in Mexican children

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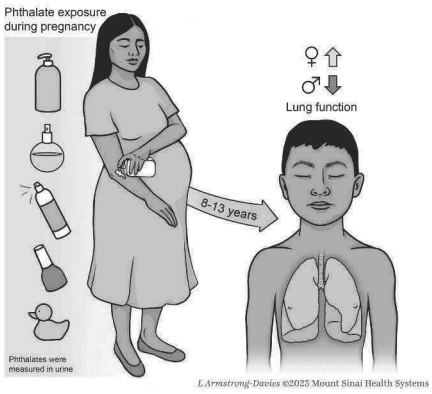
HIGHLIGHTS

- Prenatal phthalate mixture associated with childhood lung function in a sex-specific manner.
- 2nd trimester phthalate mixture linked to higher FEV_1 and FVC z-scores in females.
- 2nd trimester phthalate mixture associated with lower FEV_1 and FVC z-scores in males.
- Repeated holdout WQS and BKMR used to assess phthalate mixture effects on lung function.

GRAPHICAL ABSTRACT



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https://doi.org/10.1016/j.jhazmat.2024.134863
Received 20 April 2024; Received in revised form 28 May 2024; Accepted 7 June 2024
Available online 14 June 2024

ARTICLE INFO

Keywords:
Phthalates
Lung function
Child health
Mixture exposure

ABSTRACT

Early life phthalates exposure has been associated with adverse respiratory outcomes. However, evidence linking prenatal phthalates exposure and childhood lung function has been inconclusive. Additionally, few studies have examined phthalates exposure as a mixture and explored sexually dimorphic associations. We aimed to investigate sex-specific associations of prenatal phthalates mixtures with childhood lung function using the PROGRESS cohort in Mexico (N = 476). Prenatal phthalate concentrations were measured in maternal urine collected during the 2nd and 3rd trimesters. Children's lung function was evaluated at ages 8–13 years. Individual associations were assessed using multivariable linear regression, and mixture associations were modeled using repeated holdout WQS regression and hierarchical BKMR; data was stratified by sex to explore sex-specific associations. We identified significant interactions between 2nd trimester phthalates mixture and sex on FEV_1 and FVC z-scores. Higher 2nd trimester phthalate concentrations were associated with higher FEV_1 ($\beta = 0.054$, 95 % CI: 0.005, 0.104) and FVC z-scores ($\beta = 0.074$, 95 % CI: 0.024, 0.124) in females and with lower measures in males (FEV_1, $\beta = -0.017$, 95 %CI: −0.066, 0.026; FVC, $\beta = -0.014$, 95 %CI: −0.065, 0.030). This study indicates that prenatal exposure to phthalates is related to childhood lung function in a sex-specific manner.

1. Introduction

Phthalates are ubiquitous endocrine disruptors increasingly recognized as emergent risk factors impacting children's health [1,2]. These compounds are extensively used as plasticizers in the production of polyvinyl chloride (PVC) plastics and are also found in a range of consumer products including personal care items, shower curtains, solvents, toys, clothing, as well as cleaning and building materials [3–5]. Humans are exposed to phthalates through various routes, including diet, inhalation, breastmilk, and skin contact, leading to daily exposure to these synthetic chemicals [6–8]. Of particular concern is prenatal exposure to phthalates. The developing fetus has a limited capacity to metabolize chemical compounds compared to adults, making it more vulnerable to their effects [9,10]. In addition, the ubiquity of phthalates leads to multiple exposure pathways (e.g., personal care products, packaged foods, indoor air, medical devices) [11] for pregnant women, thereby facilitating the transplacental transfer of these chemicals to the developing fetus. Phthalate metabolites have been detected in cord blood, amniotic fluid, placental tissue, and neonatal meconium [12,13]. Exposure to phthalates during this critical developmental window has been reported to be associated with adverse health outcomes in childhood, notably affecting reproductive health [14], growth [15], cognitive development [16], and behavior [11,17]. Recent evidence also suggests associations of prenatal and postnatal exposure to phthalates with childhood respiratory health [1,18–22].

Lung development, which undergoes crucial structural changes during fetal life [1], plays a pivotal role in determining peak adult lung function and its subsequent decline [23,24]. Lung growth during childhood and adolescence not only correlates with lung function but also predicts respiratory diseases in later life, early onset of multiple morbidities, and premature mortality [25–28]. Prenatal environmental exposures have been implicated in respiratory diseases, potentially affecting lung development and growth both in childhood and adulthood [29,30]. Disruptions by environmental exposures can lead to long-term alterations in both the structure and function of the respiratory system. Therefore, understanding and identifying modifiable early-life risk factors is crucial for inform the timing of public health interventions for maximum impact.

Although the underlying mechanisms by which phthalates could impact respiratory health have not been fully elucidated, prior studies suggest several plausible pathways. These include endocrine disruption [31], particularly of sex hormones crucial for lung development, proinflammatory immune responses [19,32] promoting allergic and asthmatic phenotypes, increased airway inflammation [33] and hypersensitivity [34], and oxidative stress during the critical window of fetal lung maturation [35,36]. An increasing number of epidemiological studies have reported relationships of prenatal phthalate exposure with higher risk of childhood asthma [18,37–40], but its association with childhood lung function has not been completely elucidated. Studies assessing prenatal phthalate exposure in association with lung function have yielded inconsistent results [1,9,22,32,39,41–43] and only a few recent studies [9,19,42] examining mixtures of phthalates provide more accurate insights into the effects of real-world exposures to multiple phthalates simultaneously. Furthermore, while both susceptibility to phthalate exposure and lung development are sexually dimorphic, only a few of these studies examined sex-specific effects, none in the context of mixtures exposure. In the CHAMACOS study, higher maternal mono-ethyl phthalate (MEP) concentrations were associated with lower $FEF_{25–75\ \%}$ (forced expiratory flow over the middle half of the vital capacity) only in females [42]. The INMA cohort in Spain reported that stratified associations for prenatal phthalate exposure and lung function z-scores were stronger in males than in females but there was no evidence of a statistical interaction [9]. To address this gap in knowledge, investigations are needed to assess the potential effects of prenatal phthalate mixture exposure on lung function and to determine if these relationships vary by sex.

While research on phthalate exposure among the Mexican population has been growing [5,44–46], epidemiological data examining the single and mixed effects of phthalate exposure during pregnancy on respiratory health in Mexico is lacking. Moreover, despite the recognized impact of phthalates on human health and their widespread presence in human environments, Mexico has not yet implemented regulations governing the use of phthalates in commercial products. To bridge this knowledge gap, we leveraged data from the PROGRESS (Programming Research in Obesity, GRowth, Environment and Social Stress) cohort in Mexico City. Our study aimed to assess the sex-specific individual and mixed effects of prenatal phthalate metabolites exposure on lung function parameters in children aged 8–13 years. We hypothesized that prenatal exposure to individual phthalates and their mixtures would be associated with lung function in children, with potential differences based on sex.

2. Material and methods

2.1. Study population

Pregnant women receiving healthcare and prenatal services from the Mexican Social Security Institute (Instituto Mexicano del Seguro Social - IMSS) were recruited into the PROGRESS study between July 2007 and February 2011 [47]. Inclusion criteria for the study were: participants had to be less than 20 weeks pregnant, at least 18 years old, intending to reside in Mexico City for the next three years, accessible via telephone, and have no history of kidney or heart disease, daily alcohol consumption, or usage of steroids or anti-epilepsy drugs. Out of the initial cohort, 681 mother-child dyads are being actively followed, with 476 meeting the necessary criteria for analysis (Supplemental Fig. S1). We did not

find any differences in baseline characteristics between the included versus excluded participants (Supplemental Table S1). The study was approved by the institutional review boards at the Mexican National Institute of Public Health and the Icahn School of Medicine at Mount Sinai. All participating women provided written informed consent, and starting at 7 years of age, children also gave their assent to take part in the study.

2.2. Prenatal phthalate metabolite quantification

Urine samples were collected from participants during visits in the 2nd and 3rd trimesters using specimen cups free of phthalates. Subsequently, 2 mL aliquots of these samples were stored at a temperature of –80 °C, and shipped on dry ice to the Centers for Disease Control (CDC) in December 2017. The analysis of samples was conducted at the CDC using solid-phase extraction followed by reversed-phase high-performance liquid chromatography, coupled with isotope dilution tandem mass spectrometry [48,49]. In addition to following standard analytical quality control protocols, the reliability of the data was further validated by analyzing 92 blinded replicate samples of purchased anonymous adult urine (Bioreclamation IVT) that were randomly inserted and analyzed alongside the study samples [5]. The coefficients of variation across all metabolites spanned from 2.1 % to 16.5 %, with the median coefficient being 8.1 % [50].

Concentrations of 15 phthalate metabolites were quantified. To manage the complexity of the data and address correlations among metabolites from the same parent compound, molar sums were used when possible. Molar sums were derived for four phthalate parent compounds [$\sum$DEHP = MEHP (mono-2-ethylhexyl phthalate) + MEHHP (mono-2-ethyl-5-hydroxyhexyl phthalate) + MEOHP (mono-2-ethyl-5-oxohexyl phthalate) + MECPP (mono-2-ethyl-5-carboxypentyl phthalate), $\sum$DiNP = MONP (monooxononyl phthalate) + MCOP (mono (carboxyisooctyl) phthalate), $\sum$DiBP = MHiBP (monohydroxyisobutyl phthalate) + MiBP (mono-isobutyl phthalate), and $\sum$DBP = MBP (mono-n-butyl phthalate) + MHBP (mono-hydroxybutyl phthalate)]. We also assessed concentration of MECPTP (mono-2-ethyl-5-carboxypentyl terephthalate), MCNP (mono (carboxy-isononyl) phthalate), MCPP (mono-3-carboxypropyl phthalate), MBzP (monobenzyl phthalate), and MEP (monoethyl phthalate). Depending on the specific metabolite, the LOD (limit of detection) for the samples ranged from 0.2 to 1.2 ng/mL. For values below the LOD, the instrument-reported value was used instead of imputation, as per Schisterman et al. (2006) [51], which may offer more insight than LOD based imputation methods, and previous analysis in this population have shown that it does not significantly alter the observed associations between phthalate exposure and other cardiometabolic risk factors when compared to imputation techniques [45]. Urine specific gravity was measured with a digital handheld refractometer (AR200, Reichert Technologies, Buffalo, NY), and missing specific gravity values were imputed with a median value of 1.016 (N = 4), the robustness of this approach within this cohort has been discussed previously by Wu et al. (2020) [5]. After adjusting for specific gravity using the dilution standardization formula, concentrations of all metabolites were $\log_2$-transformed for subsequent analysis [52,53].

2.3. Measurement of childhood lung function

Spirometric testing was conducted on children either at their homes or in the study clinic by a trained field nurse or physician, adhering to the American Thoracic Society guidelines [54]. We used a portable MedGraphics™ PC-based USB spirometer with real-time flow-volume plots for the tests [54,55]. Children's height was recorded after measurement using a fixed stadiometer prior to testing. Flow was gauged using a heated screen pneumotachograph (PT) (flow range 0 ± 20 L/s, accuracy 0.2 to 12 L/s ± 2 %), and the volume was determined through digital integration [56]. The spirometer, equipped with a heated screen pneumotachograph, was calibrated with a 3-liter syringe before each session, taking into account ambient temperature, humidity, and air pressure.

Eligibility for testing has been previously described [56]. In brief, participants had to be free of acute respiratory symptoms for the past three weeks and withhold asthma medications prior to testing. We recorded a minimum of three and a maximum of eight maneuvers. Parameters of interest were, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), $FEF_{25–75\ \%}$, and FEV_1/FVC ratio. FEV_1 and/or FEV_1/FVC are measures of global airway obstruction; $FEF_{25–75\ \%}$ is an indicator of small airway function [57]. A pediatric pulmonologist reviewed all tests to ensure acceptability and reproducibility. Spirometry parameters were transformed into age, height and sex standardized z-score, with a mean of 0 and a standard deviation (SD) of 1.

2.4. Covariates

In our models, we adjusted for covariates that have been previously associated with prenatal phthalate exposure and childhood lung function, with careful consideration to ensure they did not form part of the causal pathways. Covariate selection was informed by previous studies [9,21] and a causal diagram using a directed acyclic graph (DAG) (Supplemental Fig. S2). The covariates included are maternal age at the time of enrollment (measured continuously in years), maternal pre-pregnancy body mass index (BMI) (kg/m^2), prenatal ETS (environmental tobacco smoke) exposure (yes/no), primiparity (yes/no), and maternal education level at the time of enrollment, categorized as no more than high school, high school graduate, and more than high school. In this study, prenatal ETS exposure was defined as a report of anyone smoking inside the home during either the 2nd or 3rd trimester of the pregnancy.

2.5. Statistical analysis

Descriptive statistics were used to assess the distributional properties of demographic data, and the results were presented as mean (± SD) or frequency (percentage, %). Pearson correlation coefficients were calculated to assess the relationship between phthalate concentrations in the 2nd and 3rd trimesters. An overview of the statistical methods used to assess associations of phthalates exposure and lung function outcomes is shown in Supplemental Fig. S3. To evaluate the sex-specific joint effects of the phthalates mixture on our outcomes, we used a sex-stratified weighted quantile sum (WQS) regression model, as outlined by Busgang et al. (2022) [58]. This model generates a weighted index that estimates the mixed effect of a mixture on an outcome and identifies chemicals of concern. The weights, which represent the relative contribution of each metabolite to the overall association within the mixture, are expressed as percentages that collectively sum to one hundred. For sex-specific effects we included an interaction term, WQS*sex, and employed stratified weights specific to each sex. This allowed the effect of the WQS index to vary between sex, resulting in distinct slopes, magnitudes, and ranks for the estimated weights in males and females. Relative weights in our analysis were computed by dividing the average weight of each chemical by the total weight within each respective stratum, such as females or males, with each sum amounting to 100 % [59]. We tested joint effects in the negative direction. In addition to using 100 bootstrap sampling, we employed a validation technique with 100 repeated holdouts, partitioning the data randomly (40/60 %) with replacement in each iteration [60]. This provided a distribution of estimates and chemical weights across different data partitions. The mean estimates, along with their 95 % confidence intervals (CIs), are reported, though p-values for the estimates are not provided. Instead, significance in our study was determined based on the criterion that at least 97.5 % of the beta coefficients had to be either below or above the null effect, a method described by Tanner et al. (2019) [60]. Additionally, we evaluated the number of holdouts resulting in an estimate below or above

Table 1
Overall and sex-stratified maternal and child characteristics of participating in the PROGRESS study.

	Overall Sample $N = 476$	Males $N = 256$	Females $N = 220$
Characteristic	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
Maternal age at enrollment (years)	27.5 (5.41)	27.6 (5.30)	27.2 (5.53)
Maternal pre-pregnancy BMI (kg/m^2)	26.5 (4.21)	26.8 (4.02)	26.5 (4.21)
Maternal education			
< High school	190 (39.9)	109 (42.6)	81 (36.8)
High school	179 (37.6)	87 (34.0)	92 (41.8)
> High school	107 (22.5)	60 (23.4)	47 (21.4)
Parity			
0	294 (61.8)	166 (64.8)	128 (58.2)
≥ 1	182 (38.2)	90 (35.2)	92 (41.8)
Prenatal ETS exposure			
Yes	143 (30.0)	82 (32.0)	61 (27.7)
No	333 (70.0)	174 (68.0)	159 (72.3)
Child age at spirometry (years)	10.8 (1.86)	10.9 (1.83)	10.7 (1.89)
Child height at spirometry (cm)	145 (12.71)	147 (13.50)	144 (11.60)
FEV_1 z-score[a]	− 0.01 (1.00)	− 0.01 (1.06)	− 0.01 (0.94)
FVC z-score[a]	− 0.01 (1.00)	− 0.02 (1.01)	− 0.01 (0.99)
FEV_1/FVC ratio	86.88 (6.31)	85.80 (6.14)	88.13 (6.30)
$FEF_{25-75\ \%}$ z-score[a]	0.00 (1.01)	0.00 (1.04)	0.00 (0.97)

Abbreviations: PROGRESS, Programming Research in Obesity, Growth, Environment and Social Stress; BMI, body mass index; SD, standard deviation; ETS, environmental tobacco smoke; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; $FEF_{25-75\ \%}$, forced expiratory flow between 25 % and 75 %.
[a] Adjusted for age, sex, and height.

the null effect. For each chemical, the ''Busgang criteria'' was applied to ascertain its contribution to the observed effects. A chemical was considered a ''probable'' contributor if at least 90 % of the holdouts exceeded the 1/c threshold (where c is the number of chemicals), and a ''possible'' contributor if this was true for at least 50 % of the holdouts, as per Busgang et al. (2022) [58]. All models included adjustments for select covariates: maternal age, BMI, ETS, education, and parity.

We also applied hierarchical Bayesian kernel machine regression (BKMR), stratified by sex, to detect potential linear and non-linear associations and interactions among exposures. BKMR employs kernel machine regression to evaluate a non-parametric high-dimensional exposure–response function [61]. Phthalate metabolites were categorized into two groups based on their parent phthalate molecular weight within a single kernel: low molecular weight (including DiBP, DBP, and MEP) and high molecular weight (comprising DEHP, MECPTP, DiNP, MCNP, MCPP, and MBzP) [62]. We used the hierarchical variable selection method, running 50,000 iterations, to determine the posterior inclusion probability (PIP) of exposures with high correlations. The PIP was used to quantify the importance of exposures with a range of 0 to 1, a PIP of 1 is equivalent to 100 % of the multiple iterations including that metabolite. Univariate exposure–response functions, which depict the relationship of concentrations of a single phthalate with lung function parameter while holding the remaining phthalates in the mixture constant at their median value, were examined to assess linearity. Subsequently, we assessed the overall association of the mixture by estimating the effect of a simultaneous quantile increase in all mixture components, compared to median concentrations. All of these analyses were shown using graphical outputs. The probability of each group (e.g.,high or low molecular weight) and the specific biomarker within each group were indicated by the group probabilities of inclusion (group PIP) and conditional PIP, which offer estimates of the frequence with which each group and individual biomarker are included in the BKMR models. A

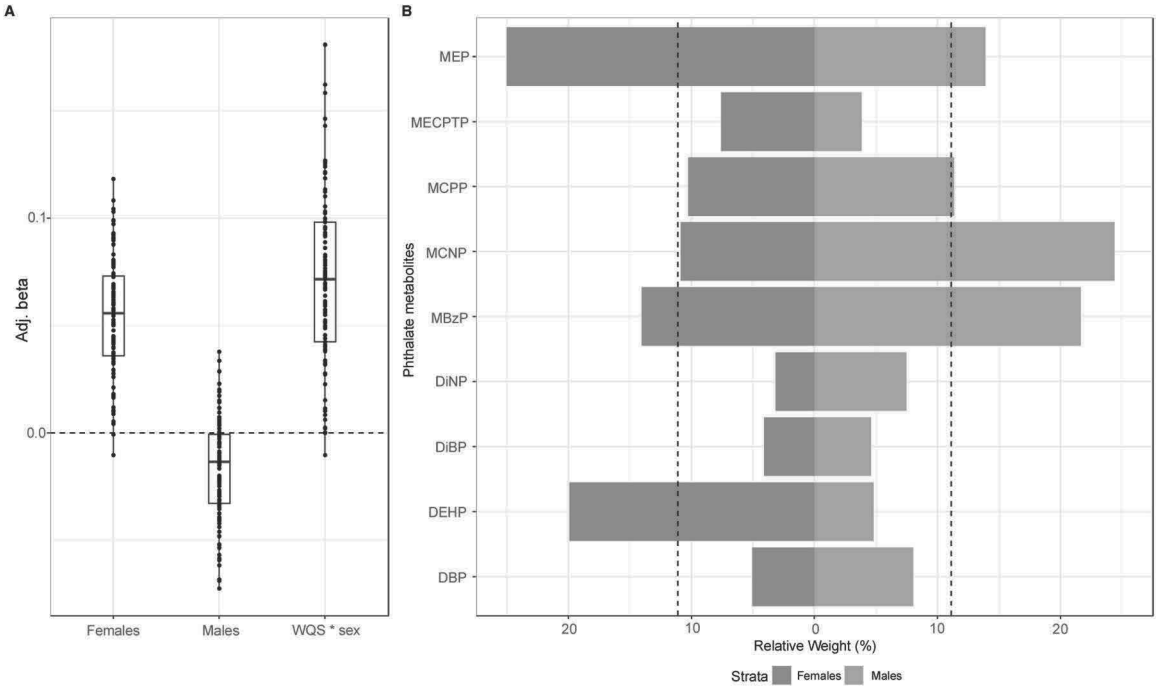

Fig. 1. Mean adjusted betas (A) and sex-specific relative weights (B) from a WQS (negative constraint) linear regression model with 100 repeated holdouts between **2nd trimester phthalates mixture and FEV_1 z-score**. The model was adjusted for maternal age, BMI, ETS, education, parity. (A) Illustrates the distribution of the adjusted betas across the 100 repeated holdouts where each dot represents the estimate from each holdout. (B) Illustrates the mean estimated relative weight for each chemical of the phthalate mixtures across the 100 repeated holdouts. The relative weight is the percentage of weight attributable to each chemical in the phthalate mixtures within the total weight of each strata (males and females). The dotted line represents the threshold (11.1 %) for chemicals of concern. Chemicals with relative weights above this threshold in at least 50 % of the repeated holdouts were considered chemicals of concern. Abbreviations: FEV_1 = forced expiratory volume in 1 s; BMI = body mass index; ETS = environmental tobacco smoke; Notes: All chemicals were $\log_2$ transformed to reduce skewness in the distribution of the concentrations.

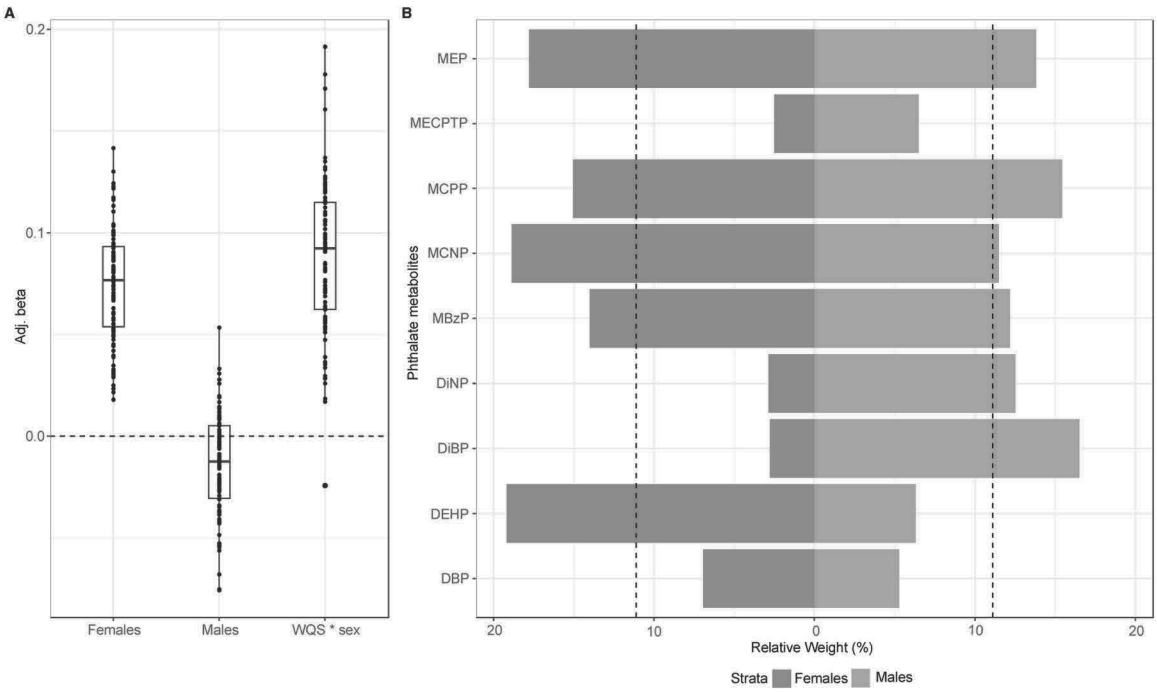

Fig. 2. Mean adjusted betas (A) and sex-specific relative weights (B) from a WQS (negative constraint) linear regression model with 100 repeated holdouts **between 2nd trimester phthalates mixture and FVC z-score**. The model was adjusted for maternal age, BMI, ETS, education, parity. (A) Illustrates the distribution of the adjusted betas across the 100 repeated holdouts where each dot represents the estimate from each holdout. (B) Illustrates the mean estimated relative weight for each chemical of the phthalate mixtures across the 100 repeated holdouts. The relative weight is the percentage of weight attributable to each chemical in the phthalate mixtures within the total weight of each strata (males and females). The dotted line represents the threshold (11.1 %) for chemicals of concern. Chemicals with relative weights above this threshold in at least 50 % of the repeated holdouts were considered chemicals of concern. Abbreviations: FVC = forced vital capacity; BMI = body mass index; ETS = environmental tobacco smoke; Notes: All chemicals were $\log_2$ transformed to reduce skewness in the distribution of the concentrations.

conventional threshold of 0.5 was employed to confirm ''important'' predictors [63].

We also modeled the adjusted associations of the 2nd and 3rd trimester phthalate concentrations with lung function parameters, fitting separate models for each phthalate metabolite and stratifying by sex. Estimates represent the change in mean z-score of FVC, FEV_1, and $FEF_{25–75\ \%}$ and FEV_1/FVC ratio, per doubling of phthalate concentrations. All statistical analyses were performed using R software, version 4.2.1 (R Project for Statistical Computing). The "gWQS" and "bkmr" R packages were employed for the WQS and BKMR analyses, respectively [64,65]. A p-value of 0.05 (two-tailed) was set as the threshold for statistical significance.

3. Results

3.1. Study participant characteristics

Table 1 presents the characteristics of the mother and child dyads included in our overall sample and stratified by sex. Most participant characteristics and outcomes did not vary by sex. A slightly higher proportion of mothers of male children had less than high school education (42.6 vs 36.8 for female children). About 30.0 % of the mothers reported prenatal exposure to ETS in the overall sample, with a lower proportion of mothers of female children (27.7 %) exposed compared to mothers of male children (32.0 %). The average child age at spirometry was 10.8 years (SD = 1.86) for the overall sample, with similar ages for male (10.9 years, SD = 1.83) and female (10.7 years, SD = 1.89) children. Mean child height at spirometry was 145 cm (SD = 12.71) overall, with male children slightly taller (147 cm, SD = 13.5) than female children (144 cm, SD = 11.6).

MEP exhibited the highest concentrations in maternal urine during both the 2nd and 3rd trimesters, with DEHP showing the second highest concentrations in both trimesters (Supplemental Table S2). The correlations between single metabolites and their sums ranged from moderate to high (0.17–0.85) and are shown in Supplemental Fig. S4. The strongest correlations were found between MCPP and other phthalate metabolites.

3.2. Sex-stratified mixture analysis

In WQS analyses, we initially fit the complex model including both the interaction term and stratified weights in the negative directions (Supplemental Table S3–S10). We found evidence of an interaction between 2nd trimester phthalates mixture and sex on FEV_1 and FVC z-scores. In female children, the phthalates mixture effect was related to higher FEV_1 (mean β = 0.054, 95 %CI: 0.005, 0.104) while it was associated with lower FEV_1 in male children (mean β = −0.017, 95 %CI: −0.066, 0.026) (Fig. 1A and Supplemental Table S3). We saw a similar pattern in which the 2nd trimester phthalates mixture effect was associated with higher FVC z-score in female children (mean β = 0.074, 95 % CI: 0.024, 0.124) and with lower FVC in male children (mean β = −0.014, 95 %CI: −0.065, 0.030) (Fig. 2A and Supplemental Table S4). In FEV_1 models, MEP and MBzP were important contributors to the association in both strata. For FVC models, DEHP and MCNP were the top contributors to the mixture effect in female children, while DiBP and MCPP were the top contributors for the male stratum (Fig. 2B). We did not identify evidence of a sex-specific association for the 3rd trimester phthalates mixture concentrations and any lung function parameters.

Sex-specific BKMR analysis was employed to evaluate the joint effects of phthalates mixture on lung function parameters. The PIPs for the two groups (group PIPs) and (conditional PIPs) obtained from the sex-specific BKMR model for the four lung function parameters in two trimesters are shown in Supplemental Table S11. In Figs. 3–6, we did not find evidence of an overall effect of the phthalate mixture in stratified BKMR results. However, most of the stratified models showed similar patterns to what we saw with WQS analysis with higher 2nd trimester

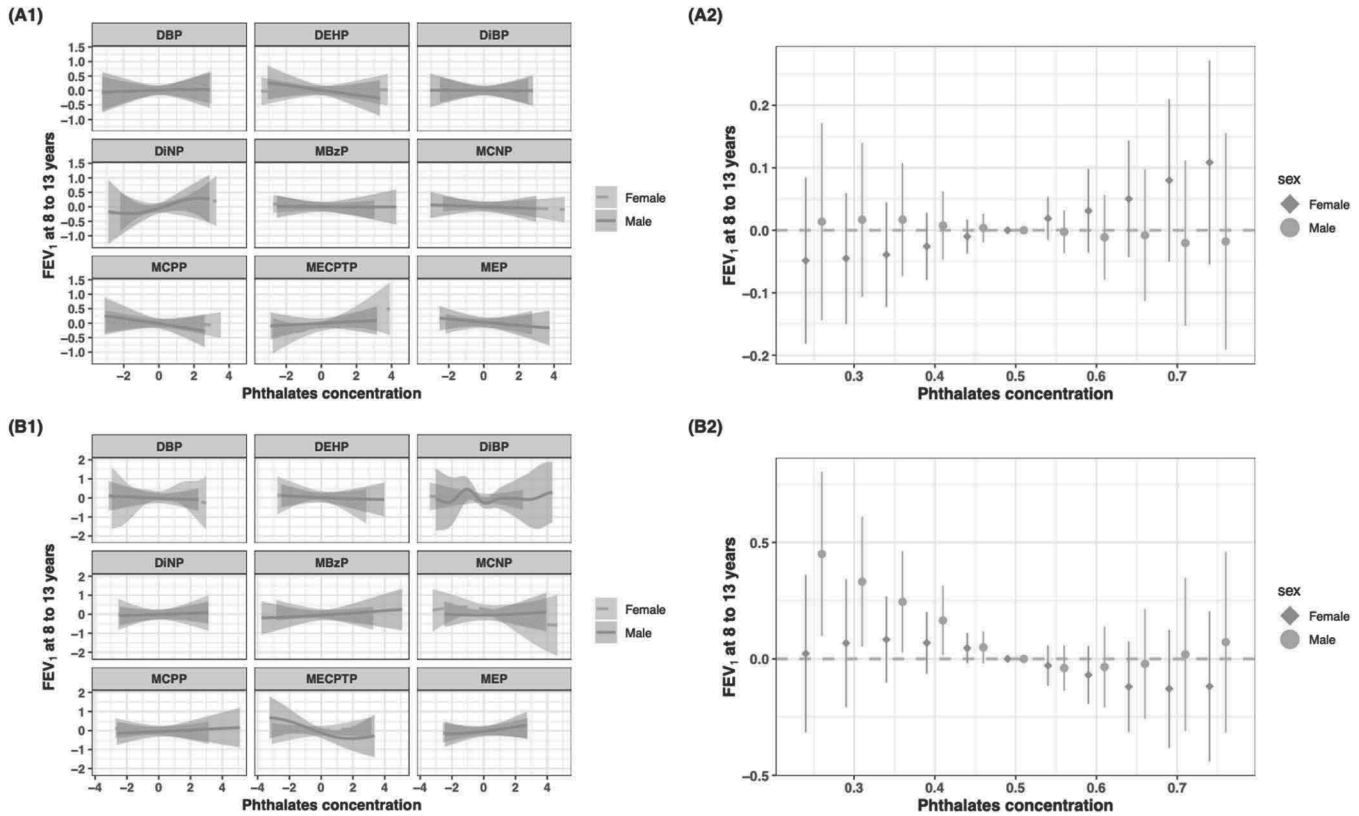

Fig. 3. BKMR mixture associations of the 2nd (A) and 3rd (B) phthalate metabolites with sex-specific FEV_1 at ages 8 to 13 years. The models are adjusted for maternal age, BMI, ETS, education, and parity. A1 and B1. Exposure-response relationships for each phthalate metabolite while holding all other metabolites at their median concentrations. A2 and B2. Overall association of the phthalates mixture at different concentration percentiles compared to the 50th percentile and their 95 % credible intervals. FEV_1, forced expiratory volume in 1 s. DEHP, di(2-ethylhexyl) phthalate; DiNP, diisononyl phthalate; DiBP, diisobutyl phthalate; DBP, dibutyl phthalate; MECPTP, mono-2-ethyl-5-carboxypentyl terephthalate; MCNP, mono(carboxy-isononyl) phthalate; MCPP, mono-3-carboxypropyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate.

phthalate mixture showing a pattern of positive associations in the female stratum and negative associations in the male stratum.

3.3. Sex-specific associations of individual phthalates with lung function

In individual regression models with phthalates modeled as continuous variables we found some evidence of sex-specific associations between metabolite concentrations and lung function parameters (Supplemental Fig. S5−S6). In male children, 2nd trimester MEP exposure was negatively related to $FEF_{25–75\,\%}$ z-score ($\beta = -0.09$, 95 % CI: −0.15, −0.02). In female children, we found that exposure to several phthalate metabolites during the 2nd trimester was related to higher lung function parameters. Specifically, DEHP was associated with FEV_1 ($\beta = 0.10$, 95 % CI: 0.01, 0.20) and FVC ($\beta = 0.11$, 95 % CI: 0.01, 0.21); DiNP was also associated with FEV_1 ($\beta = 0.09$, 95 % CI: 0.01, 0.17) and FVC ($\beta = 0.10$, 95 % CI: 0.01, 0.18); and DBP was associated with FVC ($\beta = 0.10$, 95 % CI: 0.01, 0.19). MECPTP exposure was related to FEV_1 ($\beta = 0.14$, 95 % CI: 0.06, 0.22), FVC ($\beta = 0.11$, 95 % CI: 0.03, 0.20), and $FEF_{25–75\,\%}$ ($\beta = 0.10$, 95 % CI: 0.02, 0.19). MCPP was also associated with FVC ($\beta = 0.11$, 95 % CI: 0.01, 0.21). In models examining 3rd trimester phthalate levels, we did not observe any significant association with lung function parameters in male or female children.

4. Discussion

This study examined the sex-specific associations of prenatal exposure to phthalate metabolites, as measured in maternal urine during the 2nd and 3rd trimesters, on lung function parameters in children aged 8 to 13 years. We found evidence that the 2nd trimester phthalates mixture exposure was related to lung function outcomes in a sex-specific manner with increased FEV_1 and FVC z-scores in female children, and lower z-scores in male children. We did not observe a similar pattern for 3rd trimester measures. Overall, our study indicates that prenatal exposure to phthalate may be associated with childhood lung function in a manner that is dependent on the sex of offspring and the trimester of exposure.

Our study contributes to the growing body of evidence on the impacts of prenatal phthalate exposure on childhood lung function. Earlier research identified patterns of associations between higher prenatal exposure to phthalates and lower childhood lung function parameters, although most findings did not attain statistical significance [39,41]. Some studies identified specific individual phthalate metabolites associated with reduced lung function [32,42,43]. Interestingly, we found certain phthalate metabolites to be significantly related to lung function during the 2nd trimester but not the 3rd, a pattern not previously reported due to the scarcity of studies with repeated maternal urine phthalate measurements. For example, we observed that the 2nd trimester MEP exposure was negatively associated with $FEF_{25–75\,\%}$ in male children which is in line with results from one U.S. birth cohort study [32]. However, given the numerous tests performed in the analyses of individual phthalate exposure and lung function associations, the possibility of false positive results cannot be ruled out, and the findings should be interpreted with caution. With regard to the mixture effect of prenatal phthalates exposure on lung function, our study found the 2nd trimester phthalates mixture was associated with higher lung function parameters in female children. These results are not consistent with most prior studies, with the exception of Adgent et al. (2020), which is the only study that reported protective effects of phthalates

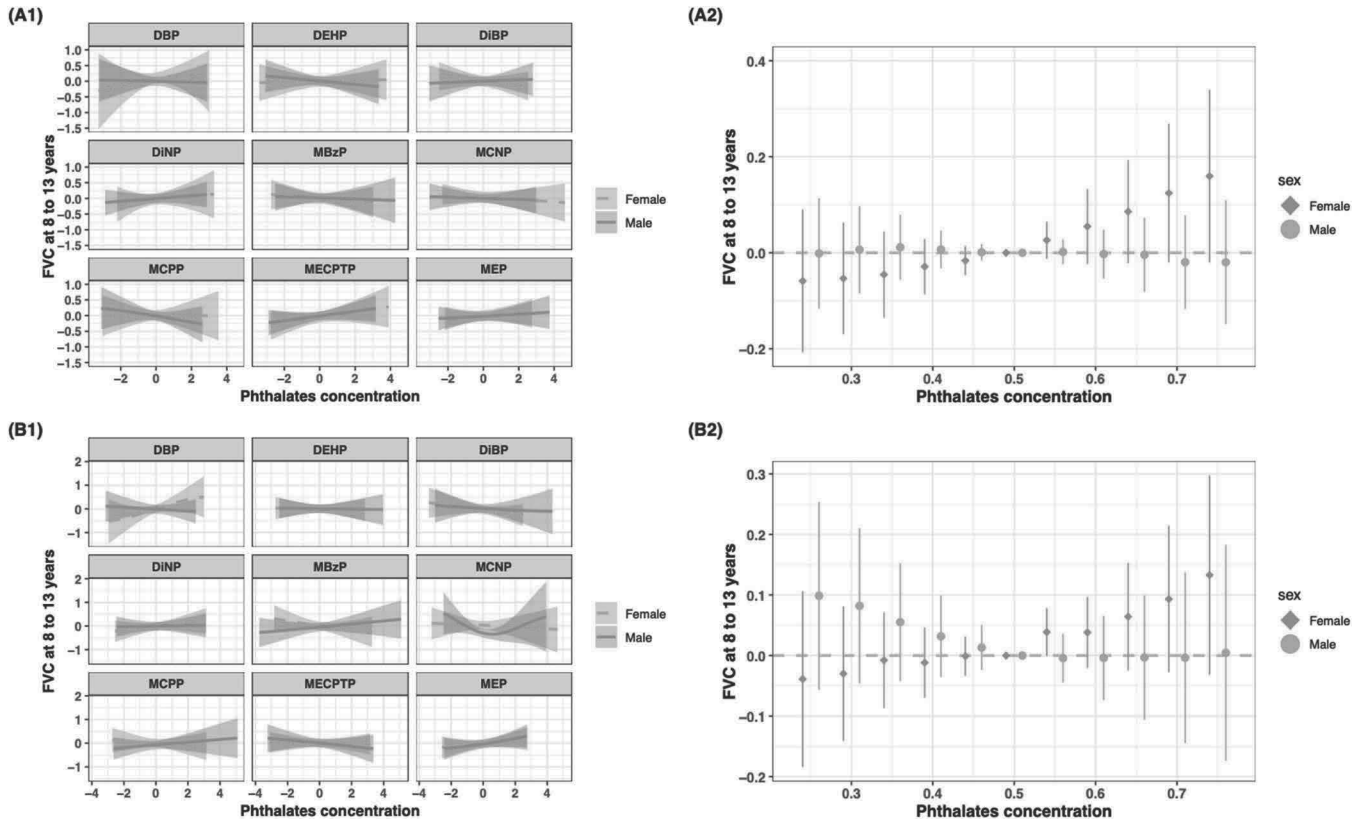

Fig. 4. BKMR mixture associations of the 2nd (A) and 3rd (B) phthalate metabolites with sex-specific FVC at ages 8 to 13 years. The models are adjusted for maternal age, BMI, ETS, education, and parity. A1 and B1. Exposure-response relationships for each phthalate metabolite while holding all other metabolites at their median concentrations. A2 and B2. Overall association of the phthalates mixture at different concentration percentiles compared to the 50th percentile and their 95 % credible intervals. FVC, forced vital capacity. DEHP, di(2-ethylhexyl) phthalate; DiNP, diisononyl phthalate; DiBP, diisobutyl phthalate; DBP, dibutyl phthalate; MECPTP, mono-2-ethyl-5-carboxypentyl terephthalate; MCNP, mono(carboxy-isononyl) phthalate; MCPP, mono-3-carboxypropyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate.

mixture for current wheeze, current asthma and ever asthma in girls in sex-stratified mixture analyses [18]. Notably, MBzP, identified as the primary contributor to the mixture effect on FEV_1 and FVC in our study, was also reported as the 2nd strongest contributing metabolite in the only prior study employing a mixture analytical method [42], but this analysis did not examine sex-specific mixture associations.

Variations in urinary concentrations of specific metabolites may account for some of the discrepancies observed across studies. Notably, our study population exhibited higher concentrations of DEHP, DBP, and MEP exposure compared to other cohort studies conducted in the U. S. [66], China [67], Canada [68], France [69], and Puerto Rico [70]. Compared to a similar cohort of pregnant women in Mexico (ELEMENT) enrolled between 1997 and 2005, our study participants also showed elevated levels of most phthalate metabolites, including MBzP and those derived from DBP, DiBP, and DEHP [71,72]. These data indicates that exposure levels are strongly influenced by the geographic region and specific demographic characteristics of the study population. Moreover, increasing evidence has consistently linked gestational exposure to phthalate and higher risk of childhood respiratory diseases in a sex-specific manner [37,38,40,73]. However, the relationship of prenatal phthalates exposure with childhood lung function remains less well-established, with limited and inconsistent findings across studies. The discrepancies in the literature regarding the impact of phthalates on lung function and other respiratory outcomes may be attributed to several factors. With the exception of aforementioned biomarker concentrations variation, differences in chemical use patterns across countries, developmental timing of exposures, the metabolites quantified, timing of follow-up, or other population characteristics may also play important roles. To address these differences, future research should involve multi-cohort studies across diverse populations, incorporating repeated measurements of phthalates levels during pregnancy and childhood, as well as repeated measurements of lung function outcomes in children.

The development and maturation of the lungs exhibit an intricate and dynamic pattern of sexual dimorphism influenced by various factors. Notably, the differences in lung physiology between males and females have significant clinical implications. The disparity in lung development in utero between male and female fetuses manifests as early as 16 to 24 weeks of gestation [74]. Female fetuses have smaller airways and a lower number of respiratory bronchioles compared to their male counterparts; however, their maturation rate is more rapid. Surfactant, a crucial compound facilitating proper lung function, is produced earlier in females than in males, enabling a faster lung maturation process [75]. The estrogen produced by the placenta stimulates the production of surfactant and the development of alveoli [76]. In contrast, androgens derived from the testes, such as testosterone, act to suppress surfactant production, an exposure that female fetuses do not experience [77]. The developmental stage of the lungs may explain why phthalate exposure during pregnancy, particularly in the second trimester, can lead to postnatal lung function differences between male and female children.

Prenatal phthalates exposure may influence childhood lung function through multiple biological mechanisms, with sex-specific effects. One potential mechanism is endocrine disruption, particularly of sex hormones [78,79]. Phthalates can interfere with the synthesis, metabolism, and signaling of estrogen and androgen [80]. As androgens are crucial for lung development, prenatal phthalates exposure may have a greater impact on lung function in boys by inhibiting androgen receptors [81].

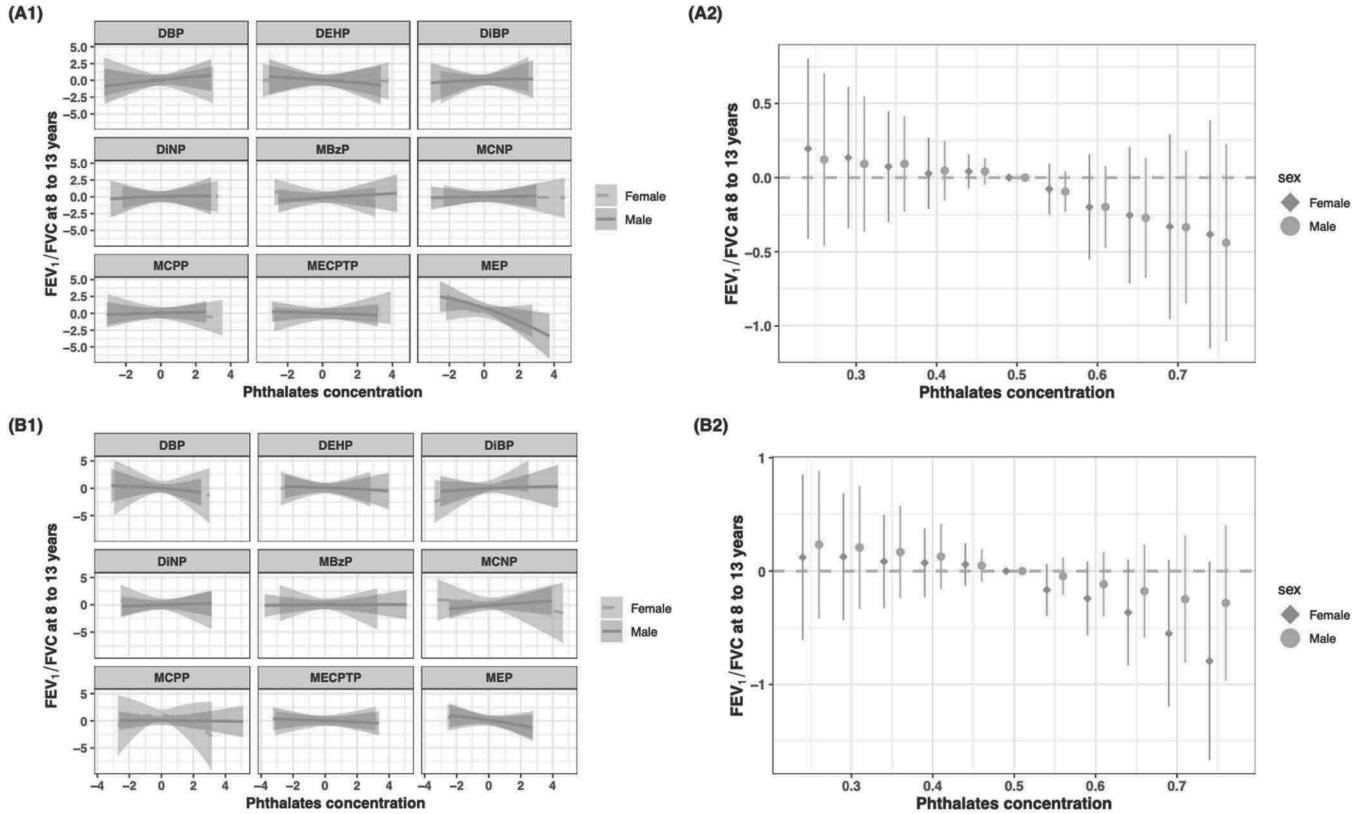

Fig. 5. BKMR mixture associations of the 2nd (A) and 3rd (B) phthalate metabolites with sex-specific EFV_1/FVC at ages 8 to 13 years. The models are adjusted for maternal age, BMI, ETS, education, and parity. A1 and B1. Exposure-response relationships for each phthalate metabolite while holding all other metabolites at their median concentrations. A2 and B2. Overall association of the phthalates mixture at different concentration percentiles compared to the 50th percentile and their 95 % credible intervals. DEHP, di(2-ethylhexyl) phthalate; DiNP, diisononyl phthalate; DiBP, diisobutyl phthalate; DBP, dibutyl phthalate; MECPTP, mono-2-ethyl-5-carboxypentyl terephthalate; MCNP, mono(carboxy-isononyl) phthalate; MCPP, mono-3-carboxypropyl phthalate; MBzP, monobenzyl phthalate; MEP, mono-ethyl phthalate.

Another mechanism is immune modulation. Phthalates possess immunotoxic properties and can alter the balance of T cell subsets, promoting a Th2-type immune response [32]. This may lead to increased airway inflammation and hyperresponsiveness [34,82]. Sex differences in immune modulation may be related to the regulation of immune responses by sex hormones [83,84]. Epigenetic modifications may also play a role in the sex-specific effects of prenatal phthalates exposure on lung development [85]. Phthalates exposure can induce changes in DNA methylation and histone modifications, affecting gene expression [86,87]. These epigenetic alterations may be particularly important in mediating sex-specific responses to environmental exposures during lung development [88,89]. Furthermore, oxidative stress is another potential mechanism. Phthalates exposure can induce the generation of reactive oxygen species (ROS), leading to oxidative damage and inflammatory responses [90,91], compromised fetal lung development and reduced alveolarization [92]. Estrogen has antioxidant properties and can mitigate oxidative stress [93], which may partially explain why females are less affected by phthalates exposure.

In addition, there are also some reports of protective effects of prenatal phthalate exposure. For example, Shin et al. (2014) reported that maternal DEHP exposure reduced airway inflammation and mucus production in offspring in an animal study, suggesting potential protective effects [94]. Similarly, Merrill et al. (2024) found sex-specific patterns in the association of prenatal DEHP exposure with upper respiratory infections and epigenetic age with some protective effects reported in females [85]. This evidence may explain our findings of higher lung function parameters in females in association with 2nd trimester phthalates mixture exposure. Taken together, prenatal phthalates exposure may influence childhood lung function through endocrine disruption, immune modulation, epigenetic modifications, and oxidative stress. The sex-specific effects observed may be attributed to the differential roles of sex hormones in these biological mechanisms. Further research is needed to elucidate the complex interplay between these mechanisms and the sexual dimorphism in the impact of prenatal phthalates exposure on lung development and function.

The strengths of this study include its prospective design and the inclusion of a relatively large sample from a population that has received limited attention in previous research. By measuring phthalates in two prenatal samples, we were able to evaluate the longitudinal association of prenatal exposure with lung function in childhood. We obtained high quality lung function in childhood, overread by a pediatric pulmonologist. We were able to examine phthalate associations individually and as a mixture using validated WQS and BKMR methods. Additionally, using stratified WQS models we were able to obtain sex specific associations and weights. We observed significant associations for metabolites that are widely prevalent, either present in personal care products [95] or used as plasticizers and not regulated in Mexico.

We also acknowledge some limitations. The findings from our study, which was conducted among Mexican women, may have limited generalizability to pregnant populations of other ethnic or demographic backgrounds. The limited number of individual urine samples (two) collected from pregnant women may not fully capture their personal phthalate exposure due to variability between trimesters, potentially resulting in misclassification. However, our study is an improvement over previous studies that have used a single spot urine sample collected in pregnancy and are in line with previous research showing that more than one sample is needed to accurately classify exposure [66,96,97]. In addition, personal monitoring or biomarker analysis in other biological

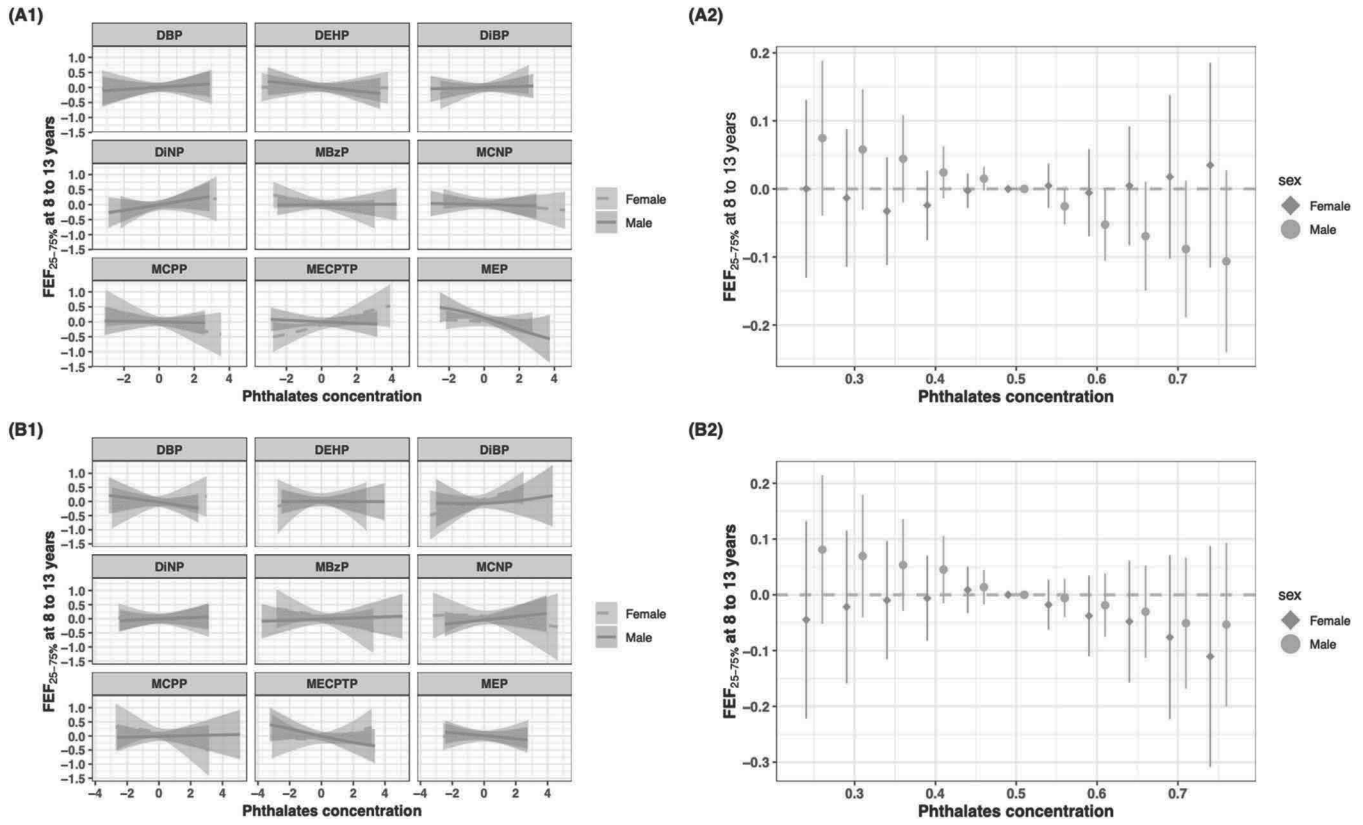

Fig. 6. BKMR mixture associations of the 2nd (A) and 3rd (B) phthalate metabolites with sex-specific $FEF_{25-75\,\%}$ at ages 8 to 13 years. The models are adjusted for maternal age, BMI, ETS, education, and parity. A1 and B1. Exposure-response relationships for each phthalate metabolite while holding all other metabolites at their median concentrations. A2 and B2. Overall association of the phthalates mixture at different concentration percentiles compared to the 50th percentile and their 95 % credible intervals. $FEF_{25-75\,\%}$, forced expiratory flow between 25 % and 75 %; DEHP, di(2-ethylhexyl) phthalate; DiNP, diisononyl phthalate; DiBP, diisobutyl phthalate; DBP, dibutyl phthalate; MECPTP, mono-2-ethyl-5-carboxypentyl terephthalate; MCNP, mono(carboxy-isononyl) phthalate; MCPP, mono-3-carboxypropyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate.

matrices (e.g., blood, hair) will enrich our understanding of phthalates exposure. As with any observational study, residual confounding remains a possibility. While we adjusted for several covariates in our statistical analysis, other important factors, such as unmeasured socio-demographic or environmental variables (e.g., housing conditions and indoor/outdoor air quality), may have influenced our results. These factors could potentially mediate or modify the relationship between phthalate exposure and lung function. Finally, we fitted a large number of models, and it is conceivable that some results may have arisen by chance. Rather than adjusting for multiple comparisons, we chose to concentrate on the patterns of association across the analysis, particularly in light of concerns about type II error following such adjustments.

5. Conclusions

Our findings add to the growing literature on sex-differences in susceptibility to endocrine disrupting chemicals. In our mixture analysis, we observed sexually dimorphic associations between a phthalate mixture measured during the 2nd trimester with higher FEV_1 and FVC z-scores in female children and lower FEV_1 and FVC z-scores in male children. The widespread exposure to phthalates and the established connection between childhood lung function and adult respiratory health highlight the public health significance of these findings, as impaired lung function in early life may have long-term consequences, and it may be benefit for pregnant women to reduce their exposure to products containing phthalates and their alternatives during pregnancy. Studies examining the programming of sex differences in response to prenatal exposure to endocrine disrupting chemicals could provide valuable insights into the growth and development of the lungs.

Environmental implications

Our findings underscore the potential risks of prenatal phthalate exposure on childhood lung function and highlight the need for stricter regulations to limit the use of these chemicals. Understanding mixture and sex-specific effects of phthalate exposure may provide unique insights into mechanisms and better inform public health interventions.

Funding

This work was supported by the National Institute of Child Health and Human Development grant T32HD049311 (Alcala, CS) and the Excellence in Doctoral Education and Training Enhancement Program for visiting research role at the Icahn School of Medicine at Mount Sinai (Hu, C-Y). The National Institute of Environmental Health Sciences grants, R00ES027496 and R01ES033245 (Rosa MJ, PI). The PROGRESS project has been supported by the following grants; R01ES014930, R01ES013744, R24ES028522, P30ES023515 (Wright RO, PI) and R01ES021357 (Baccarelli A and Wright RO, MPI). This work was also supported in part through the computational and data resources and staff expertise provided by Scientific Computing and Data at the Icahn School of Medicine at Mount Sinai and supported by the Clinical and Translational Science Award (CTSA) grant UL1TR004419 from the National Center for Advancing Translational Sciences.

CRediT authorship contribution statement

Rosalind J. Wright: Writing – review & editing, Supervision, Project administration, Funding acquisition. **Cheng-Yang Hu:** Writing – review

& editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Kecia N. Carroll:** Writing – review & editing, Project administration. **Cecilia S. Alcala:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Maria José Rosa:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hector Lamadrid-Figueroa:** Writing – review & editing, Project administration. **Allan C. Just:** Writing – review & editing, Project administration. **Chris Gennings:** Writing – review & editing, Project administration, Methodology. **Martha María Téllez-Rojo:** Writing – review & editing, Project administration. **Robert O. Wright:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Marcela Tamayo-Ortiz:** Writing – review & editing, Project administration. **Adriana Mercado-Garcia:** Writing – review & editing, Project administration. **Nadya Rivera Rivera:** Writing – review & editing, Project administration.

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.

Data Availability

The data that has been used is confidential.

Acknowledgments

We are grateful to the PROGRESS participants and staff at the National Institute of Public Health/Ministry of Health of Mexico and the National Institute of Perinatology. We thank the ABC (American British Cowdray Medical Center) in Mexico for providing some of the needed research facilities. We also extend our special thanks to Drs. Stefano Renzetti and Katherine Svensson for their invaluable advice and guidance on the application of repeated holdout Weighted Quantile Sum methods in our study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.134863.

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