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Prenatal exposure to arsenic and lung function in children from the New Hampshire Birth Cohort Study

Antonio J. Signes-Pastor [a], Pablo Martinez-Camblor [b], Emily Baker [c], Juliette Madan [a,d], Margaret F. Guill [d], Margaret R. Karagas [a,*]

[a] Department of Epidemiology, Geisel School of Medicine, Dartmouth College, Lebanon, NH, United States
[b] Biomedical Data Science Department, Geisel School of Medicine, Dartmouth College, Lebanon, NH, United States
[c] Department of Obstetrics & Gynecology, Division of Maternal Fetal Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States
[d] Department of Pediatrics, Geisel School of Medicine, Dartmouth College, Lebanon, NH, United States

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ABSTRACT

Prenatal arsenic exposure is associated with an increased risk of lung cancer along with multiple non-carcinogenic outcomes, including respiratory diseases in arsenic-contaminated areas. Limited epidemiologic data exist on whether *in utero* arsenic exposure influences lung development and subsequent respiratory health. We investigated the association between gestational arsenic exposure and childhood lung function in the New Hampshire Birth Cohort Study. Urinary arsenic speciation including inorganic arsenic (iAs), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and arsenobetaine was measured in maternal urine samples collected during pregnancy and spirometry was performed in offspring at a median age of 7.4 years. Forced vital capacity (FVC), forced expiratory volume in the first second of exhalation (FEV1), and forced expiratory flow between 25% and 75% of FVC (FEF25-75) standardized z-scores were assessed in linear models as dependent variables with the $\log_2$-transformed summation of urinary arsenic species (ΣAs = iAs + MMA + DMA) corrected for specific gravity as an independent variable and with adjustment for maternal smoking status, children's age, sex and height. Among the 358 children in the study, a doubling of ΣAs was associated with a −0.08 (ß) decrease in FVC z-scores (95% confidence interval (CI) from −0.14 to −0.01) and −0.10 (ß) (95% CI from −0.18 to −0.02) decrease in FEV1 z-scores. The inverse association appeared stronger among those mothers with lower secondary methylation index (urinary DMA/MMA), especially among girls. No association was observed for FEF25-75 z-scores. Our results suggest that gestation arsenic exposure at levels relevant to the general US population during the vulnerable period of lung formation may adversely affect lung function in childhood.

1. Introduction

Arsenic is an element ubiquitously present in our water, food and air from both natural and anthropogenic activities. Human exposure to arsenic comes through inhalation, dermal absorption, and ingestion (Al osman et al., 2019). Consumption of contaminated drinking water is the predominant exposure pathway (IARC, 2012). However, ingestion of arsenic from food is also a significant source of exposure of growing concern, particularly for populations non-occupationally exposed and with access to drinking water with relatively low arsenic levels (Nachman et al., 2018).

Inorganic arsenic (iAs), including arsenite (AsIII) and arsenate (AsV), is a well-established toxic chemical form, and its exposure is of major public health concern (ATSDR, 2009; Shih et al., 2019). Chronic iAs exposure is associated with an increased risk of different cancers including skin, lung, and bladder among others (IARC, 2012; Smith et al., 2006). Exposure to iAs is also associated with other health effects among populations exposed to highly contaminated drinking water, in particular, respiratory outcomes (Mazumder, 2007; Olivas-Calderón et al., 2015; Parvez et al., 2013; Ramsey et al., 2013; Recio-Vega et al., 2015; Sanchez et al., 2016; Von Ehrenstein et al., 2005). In arsenic-contaminated areas, fetal and early childhood exposure has been associated with increased risk of lower respiratory tract infections and prevalence of respiratory symptoms (e.g., shortness of breath, chronic cough, and wheeze) during childhood, as well as reduced lung function and mortality from lung cancer, bronchiectasis, and tuberculosis in

* Corresponding author.
E-mail address: margaret.r.karagas@dartmouth.edu (M.R. Karagas).

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adulthood (Dauphiné et al., 2011; Rahman et al., 2011; Raqib et al., 2009; Smith et al., 2006, 2011, 2013). However, the possibility that even relatively low iAs exposure levels early in life may alter both childhood and adulthood respiratory health requires further epidemiologic and mechanistic investigations (Farzan et al., 2016; Hsu et al., 2020; Miller and Marty, 2010; Postma et al., 2015; Steinmaus et al., 2016).

Respiratory abnormalities can be identified from patterns of pulmonary function measured by spirometry such as obstructive or restrictive airflow (Camargo et al., 2014; Martinez-Pitre et al., 2020; Miller and Marty, 2010). A recently published *meta*-analysis and systematic review of studies mainly among highly exposed adult populations reported an association between arsenic exposure and respiratory health, especially in relation to restrictive lung function (Sanchez et al., 2016, 2018). Among school-age children consuming contaminated water in rural Bangladesh, gestational arsenic exposure also related to airflow restrictive patterns with a decrease in forced vital capacity (FVC) and forced expiratory volume in the first second of exhalation (FEV1) (Ahmed et al., 2017). Further, arsenic-induced alterations in inflammatory biomarkers in children in Mexico were related to the development of restrictive lung diseases (Olivas-Calderón et al., 2015; Recio-Vega et al., 2015). In animal models, arsenic in drinking water during pregnancy increased resistance in the peripheral airway and markers of tissue stiffness in the offspring (Lantz et al., 2009; Ramsey et al., 2013).

Ingested iAs is metabolized in the liver through a multistep process via the one-carbon metabolism cycle that results in the formation of monomethylarsonic acid (MMA) followed by dimethylarsinic acid (DMA) that are primarily excreted in urine within a few days (Antonelli et al., 2014; Challenger, 1951; Tseng, 2009). Thus, the sum of iAs and its methylated arsenic species (MMA and DMA) in urine is used as a biomarker of ingested iAs exposure (Powers et al., 2019; Signes-Pastor et al., 2017a). Methylation of iAs is an important mechanism in the metabolism of iAs, and the ratio between urinary MMA/iAs and DMA/MMA can be used as markers of iAs methylation capacity (McCarty et al., 2007; Niedzwiecki et al., 2014). Arsenic easily crosses the placenta and enters the fetus such that maternal blood levels positively correlate with infant cord blood levels (Concha et al., 1998; Hall et al., 2007; Ramsey et al., 2013). Therefore, we investigated arsenic exposure during pregnancy in a general US population, and evaluated maternal arsenic methylation capacity in relation to the pulmonary function among children in the New Hampshire Birth Cohort study (NHBCS) to test the hypothesis that fetal exposure to arsenic affects lung development ultimately impacting lung function in school-aged children.

2. Methods

2.1. Study population

Our study comprised infants enrolled in the NHBCS, a longitudinal pregnancy cohort designed to examine the impacts of toxicants in drinking water and diet on maternal–child health. Since 2009, the NHBCS recruited pregnant women 18–45 years of age at approximately 24–28 weeks of gestation from prenatal clinics in the rural state of New Hampshire. Eligibility criteria include English literacy, the use of a private, unregulated water system at home (e.g., private well), not planning to move during pregnancy and a singleton birth as described previously (Gilbert-Diamond et al., 2016; Karagas et al., 2016; Signes-Pastor et al., 2020). The Committee for the Protection of Human Subjects at Dartmouth College approved this study, and all participants provided written informed consent.

2.2. Samples collection

Mothers provided a spot urinary samples at approximately 24–28 weeks of gestation during the enrollment period in polyethylene sterile containers. Samples were processed and frozen at −80 °C within 24 h until analysis (Karagas et al., 2016). We also collected household tap water samples at enrollment to analyze their arsenic concentrations (Gilbert-Diamond et al., 2016).

2.3. Laboratory analysis

Urine-specific gravity was analyzed using a handheld refractometer with automatic temperature compensation (PAL-10S; ATAGO Co Ltd). The urine samples were thoroughly thawed, centrifuged, and the supernatant pipetted into 0.6 ml vials before arsenic speciation analysis. The Trace Element Analysis Core at Dartmouth College carried out arsenic speciation using anion exchange chromatography inductively coupled plasma mass spectrometry (HPLC-ICP-MS) (Signes-Pastor et al., 2020). It was an Agilent LC 1260 equipped with a Thermo AS7, 2 × 250 mm column and a Thermo AG7, 2 × 50 mm guard column interfaced with an Agilent 8900 ICP-MS in oxygen reaction cell mode to remove polyatomic interferences. We measured concentrations of urinary AsIII, AsV, MMA, DMA, and arsenobetaine (AsB). A gradient mobile phase was prepared starting with 200 mM ammonium carbonate. Authentic standards from SPEX Certiprep and Sigma-Aldrich were used to calibrate the arsenic concentrations under each chromatographic peak. Several NIST reference materials 2669 level I and level II were also analyzed in each analysis batch, with recoveries close to 100%. The arsenic species limit of detection (LOD) ranged from 0.01 to 0.39 μg/L across batches. We calculated the LODs as the mean of the blank concentrations plus three times their standard deviation multiplied by the dilution factor. We did not observe urinary DMA concentrations below the LOD. However, there were 149 (41.6%), 76 (21.2%), 83 (23.2%), and 83 (23.2%) observations with concentrations of AsIII, AsV, MMA, and AsB below the LOD. We applied the value of LOD/$\sqrt{2}$ when concentrations were < LOD (Lubin et al., 2004). Total arsenic in tap water samples was measured with the Agilent 8900 ICP-MS in direct solution acquisition mode with a LOD of 0.04 μg/L.

2.4. Lung function

Children's lung function was assessed with spirometry along with ascertainment of children's age, height and weight. The spirometry was performed according to the American Thoracic Society and European Respiratory Society criteria in a single testing session by trained personnel (Beydon et al., 2007; Crapo et al., 1995). Trained staff performed pulmonary function testing and pre-testing education. All flow-volume curves were *post hoc* inspected for quality assurance by a pediatric pulmonologist (**MG**). The highest measurement obtained of each lung function parameter from a series of three technically acceptable flow-volume curves was used for statistical analysis (Miller et al., 2005). The FVC, FEV1 and forced expiratory flow between 25% and 75% of FVC (FEF25-75) were each measured. In addition, we calculated the ratio FEV1/FVC and the standardized z-scored for FVC, FEV1, and FEF25-75 (Culver et al., 2017; Harris et al., 2018). We computed the z-scores as the absolute values minus predictive values divided by standard deviation of predictive values.

2.5. Covariates

We selected *a priori* based on previous studies and directed acyclic graphs using the DAGitty software: maternal smoking status during pregnancy (never smoker, former smoker, and current smoker), maternal highest attained level of education (<11th grade or high school graduate or equivalent, junior college graduate or some college or technical school, college graduate, and any post-graduate schooling) were collected from self-administered questionnaires, maternal age at enrollment (years, continuous) and maternal body mass index (BMI) calculated using maternal pre-pregnancy weight combined with height (kg/m^2, continuous) were collected from prenatal medical records, and

child's sex from the delivery medical records. As mentioned, child's age (years, continuous), weight (kilograms, continuous), and height at spirometry test (centimeters, continuous) were assessed at the visit (Farzan et al., 2016; Powers et al., 2019; Stick et al., 1996).

2.6. Statistical analysis

We examined urinary iAs (AsIII + AsV), MMA, DMA and the summation of the species (ΣAs = iAs + MMA + DMA) concentrations. They were positively skewed and thus were $\log_2$-transformed for the analyses. Spirometry parameters showed symmetric distributions. For the main statistical analysis, we followed a case-complete approach. A total of 410 children (excluding 9 with missing spirometry parameters) had complete data from the pulmonary function test. We excluded children with spirometry parameter values out of the acceptable range (n = 2), without maternal urinary arsenic species concentrations (n = 2) and specific gravity (n = 21) leaving 385 participants. Our final dataset contained 358 maternal-child pairs after excluding those with missing values in maternal smoking status (n = 27) (**Figure S1**). We evaluated maternal urinary methylation capacity during pregnancy by calculating their primary methylation (PMI = urinary MMA/iAs) and secondary methylation indices (SMI = urinary DMA/MMA) (Niedzwiecki et al., 2014).

We examined the associations between exposures and the outcomes of interest using scatterplots with moving average lowess curves. Graphical inspection showed little evidence of non-linear association between maternal urinary $\log_2$-transformed arsenic concentrations and children's spirometry parameters. Therefore, we conducted linear regression analyses to evaluate the association between *in utero* arsenic exposure and children's standardized z-score spirometry parameters. The FVC, FEV1, and FEF25-75 z-scores were fitted in the models as dependent variables and the $\log_2$-transformed specific gravity-corrected urinary arsenic species concentrations as independent variable adjusting for potentially confounding factors including maternal smoking status, children's age, sex and height. Further analyses included FEV1/FVC as the dependent variable. We performed additional models stratified by maternal methylation capacity using the median PMI and SMI as cutoff values and by sex. As sensitivity analyses to assess the possibility of residual confounding, we ran models restricted to non-smoker mothers and included additional adjustment for maternal age at enrollment, which was weakly correlated with urinary DMA, FEV1 and FVC z-scores (Spearman's ρ = 0.1) but unrelated iAs, MMA, ∑As and the other outcomes, and child's weight, which correlated with with FEV1 z-score and FEV1/FVC (Spearman's ρ = 0.2) but not associated with iAs, MMA, DMA, ∑As or other outcomes (data not shown). A threshold of $\alpha = 0.05$ was used to define associations as statistically significant. We used the R version 4.0 to conduct all statistical analyses and graphics (R Code Team, 2015).

3. Results

The median maternal age of enrollment was 30.7 years, and about 90% were not smokers (n = 322). Maternal medians urinary ΣAs, iAs, MMA, DMA, and AsB were 3.6 μg/L, 0.3 μg/L, 0.3 μg/L, 2.9 μg/L, and 0.8 μg/L, respectively. A total of 46% of children were boys (n = 167). The spirometry test was performed at children's median age of 7.4 years with a median weight and height of 125.0 cm and 25.6 kg, respectively (Table 1). About 80% and 74% of participants with household water arsenic concentrations (n = 350) had water concentrations < 10 μg/L (n = 288) and < 5 μg/L (n = 259), respectively. The value of 10 μg/L is the World Health Organization guideline and the United States Environmental Protection Agency standard for drinking water (US EPA, 2012; WHO, 2011), and the 5 μg/L is the recently established maximum public water arsenic level in the state of New Hampshire (NHDES, 2019).

A doubling of maternal urinary ΣAs was associated with a decrease of −0.08 (ß) in FVC z-score with a 95% confidence interval (CI) ranging

Table 1
Selected characteristics of study mothers and children.

Variables	Original sample (n = 419)	Final sample (n = 358)[φ]	Excluded sample (n = 61)[Ψ]
Maternal characteristics			
Gestational age (weeks)	39 (29, 38.4–40.0, 42)	39.0 (30.9, 38.4–40.0, 42.0)	39.1 (29.0, 38.3–40.0, 42.0)
Age of enrollment	30.8 (18.9, 28.1–33.6, 44.3)	30.7 (19.1, 28.1–33.4, 44.3)	31.9 (18.9, 28.6–34.4, 41.8)
Maternal BMI	24.8 (16.6, 21.9–28.8, 48.3)	24.7 (16.6, 21.8–28.3, 48.3)	26.5 (18.3, 22.7–30.7, 47.3)
Maternal education:			
<11th grade or high school graduate or equivalent	35 (8.8%)	31 (8.7%)	4 (10.5%)
Junior college graduate or some college or technical school	83 (21.0%)	71 (19.8%)	12 (31.6%)
College graduate	162 (40.9%)	152 (42.5%)	10 (26.3%)
Any postgraduate schooling	116 (29.3%)	104 (29.1%)	12 (31.6%)
Parity:			
0	164 (39.5%)	144 (40.7%)	20 (32.8%)
1	157 (37.8%)	132 (37.3%)	25 (41.0%)
>1	94 (22.7%)	78 (22.0%)	16 (26.2%)
Smoking status:			
Never smoker	351 (90.2%)	322 (89.9%)	29 (93.5%)
Former smoker	19 (4.9%)	18 (5.0%)	1 (3.2%)
Current smoke	19 (4.9%)	18 (5.0%)	1 (3.2%)
Urinary arsenic (μg/L):			
iAs (iAsIII + iAsV)	0.26 (0.02, 0.07–0.48, 10.51)	0.25 (0.02, 0.07–0.48, 10.51)	0.39 (0.02, 0.24–0.65, 6.00)
MMA	0.32 (0.01, 0.13–0.55, 3.67)	0.30 (0.01, 0.13–0.54, 3.67)	0.45 (0.02, 0.23–0.71, 2.96)
DMA	3.03 (0.15, 1.39–5.28, 152.7)	2.89 (0.15, 1.30–5.12, 30.84)	3.84 (0.16, 2.29–6.41, 152.7)
AsB	0.88 (0.01, 0.13–5.67, 693.4)	0.80 (0.01, 0.13–5.24, 693.4)	2.03 (0.02, 0.44–8.80, 259.9)
ΣAs	3.76 (0.20, 1.66–6.62, 154.8)	3.64 (0.25, 1.51–6.17, 38.30)	4.57 (0.20, 3.16–7.59, 154.8)
Specific gravity	1.013 (1.001, 1.006–1.019, 1.037)	1.012 (1.001, 1.006–1.019, 1.037)	1.017 (1.004, 1.012–1.022, 1.028)
Marital status			
Married	346 (87.4%)	314 (87.7%)	32 (84.2%)
Single	40 (10.1%)	36 (10.1%)	4 (10.5%)
Divorced	10 (2.5%)	8 (2.2%)	2 (5.3%)
Children's characteristics at spirometry test			
Male/female	199 (47.5%)/ 220 (52.5%)	167 (46.6%)/ 191 (53.4%)	32 (52.5%)/29 (47.5%)
Age (years)	7.4 (4.9, 7.1–7.9, 9.5)	7.4 (4.9, 7.0–7.9, 9.5)	7.6 (5.4, 7.1–8.1, 9.3)
Height (cm)	124.7 (104.6, 121.1–129.1, 142.8)	125.0 (104.6, 121.0–129.0, 152.6)	123.7 (114.5, 121.9–130.6, 142.5)
Weight (kg)	25.7 (13.0, 22.7–29.0, 58.0)	25.6 (13.0, 22.7–29.0, 60.4)	26.0 (19.3, 23.0–28.8, 39.7)
FEV1/FVC	0.9 (0.6, 0.8–0.9, 1.0)	0.9 (0.6, 0.8–0.9, 1.0)	0.9 (0.6, 0.8–0.9, 1.0)
FVC z-score	−0.5 (-6.3, −1.2–0.0, 2.9)	−0.5 (-3.2, −1.2 - −0.1, 3.0)	−0.5 (-5.6, −1.1–0.0, 1.0)
FEV1 z-score	0.4 (-5.5, −0.4–1.0, 4.5)	0.4 (-2.5, −0.4–1.0, 4.6)	0.4 (-5.3, −0.4–1.0, 2.6)
FEF25-75 z-score	−0.3 (-8.4, −2.0–1.2, 8.3)	−0.2 (-8.4, −2.0–1.4, 8.3)	−0.8 (-6.6, −2.0–0.7, 4.9)
Other characteristics			
Tap water As (μg/L):			
<1	198 (50.0%)	175 (50%)	23 (50%)
1–10	129 (32.6%)	113 (32.3%)	16 (34.8%)
>10	69 (17.4%)	62 (17.7%)	7 (15.2%)

[φ] Participants after excluding those with missing values in any spirometry parameters of interest, spirometry values out of acceptable range, missing specific gravity, without maternal urinary arsenic species concentration, maternal smoking status, children's sex, age, and height.

[Ψ] Excluded participants. Continuous values are reported as median (minimum, interquartile range, maximum), and categorical values as relative and absolute frequencies. The total count of missing values in the original sample is 5 in maternal BMI, 23 in education, 4 in parity, 30 in smoking status, 24 in urinary arsenic speciation and specific gravity, 23 in marital status, 3 in child's height, 1 in weight, 1 in FEV1/FVC, 1 in FVC z-score, 3 in FEV1 z-score, 8 in FEF25-75 z-score, and 23 in tap water arsenic. The total count of missing values for the final sample is 1 in maternal BMI, 4 in parity, and 8 in tap water.

from −0.14 to −0.01. We also observed a reduced FVC z-score with maternal urinary iAs and DMA (ß = −0.06, 95% CI from −0.12 to −0.01; ß = −0.07, 95% CI from −0.14 to −0.01, respectively). We found a borderline statistically significant association between urinary MMA concentrations and FVC z-score (ß = −0.05, 95% CI from −0.10 to 0.00). Similarly, a doubling of urinary ΣAs, iAs, MMA, and DMA related to a reduction in FEV1 z-scores (ß = −0.10, 95% CI from −0.18 to −0.02; ß = −0.09, 95% CI from −0.16 to −0.02; ß = −0.07, 95% CI from −0.12 to −0.01; and ß = −0.08, 95% CI from −0.17 to −0.01, respectively). The inverse associations between maternal urinary arsenic and FVC and FEV1 z-scores were stronger among participants with lower SMI. For example, a doubling of urinary MMA related to a reduction in FVC and FEV1 z-scores of ß = −0.18 and 95% CI from −0.29 to −0.07 and ß = −0.20 and 95% CI from −0.33 to −0.06, respectively (Fig. 1). We observed comparable findings when including additional potential

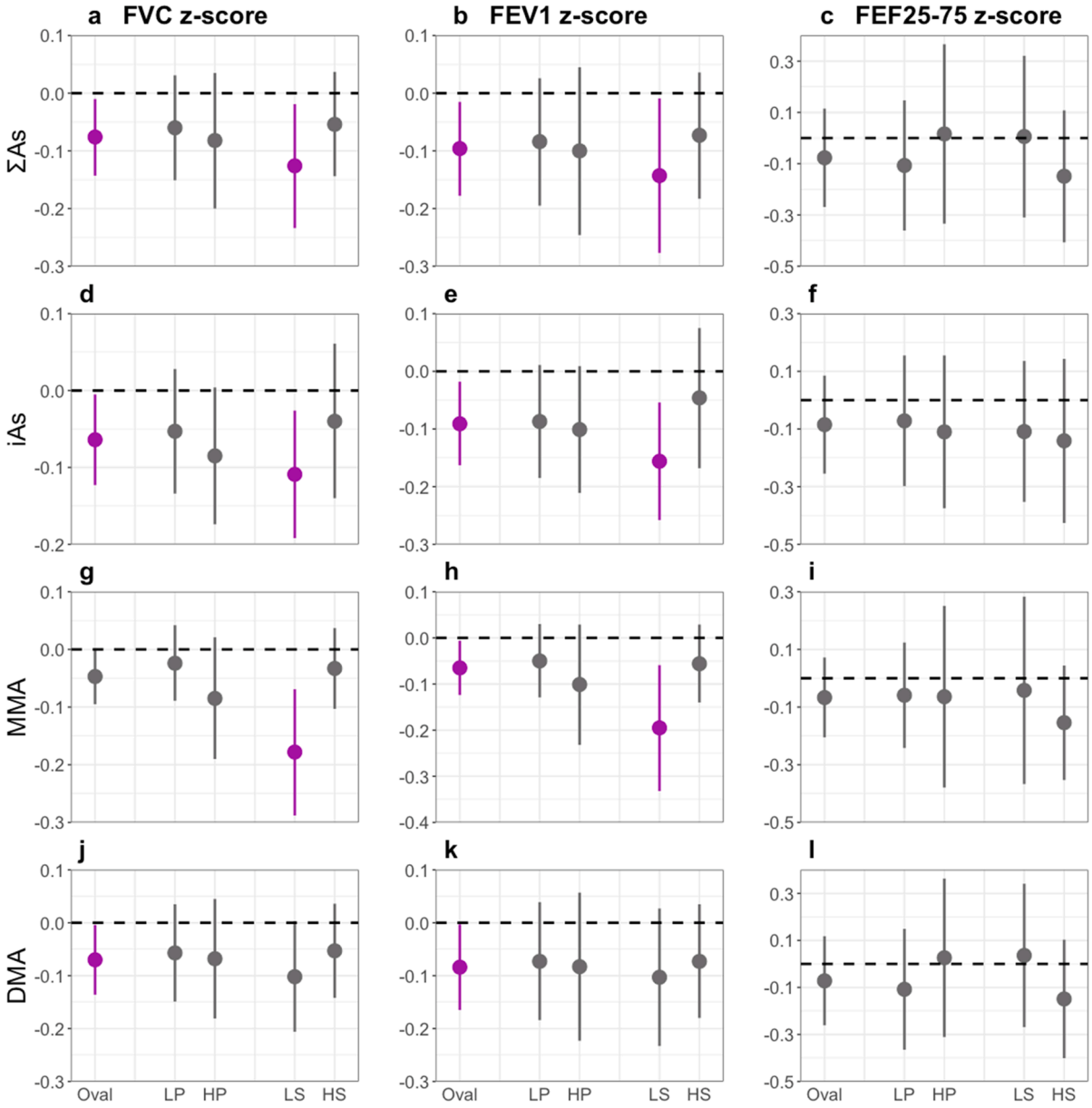

Fig. 1. Association between maternal urinary arsenic species concentration and standardized z-scores from children's spirometry. Oval = overall (n = 358); LP = low primary methylation index (PMI < median; n = 179); HP = high primary methylation index (PMI > median; n = 179); LS = low secondary methylation index (SMI < median; n = 179); HS = high secondary methylation index (SMI > median; n = 179). Linear regression models with spirometry parameters standardized z-score as dependent variables and $\log_2$-transfomed maternal urinary arsenic species concentrations specific gravity corrected as independent variables adjusted for maternal smoking status, children's age, sex, and height. Notice that the scale of the y-axis vary in order to facilitate the visualization of the estimates in each plot.

confounding factors in the models such as maternal age of enrollment and children's weight (**Figure S2**). We had similar results when restricting our analyses to mothers never smoker (**Table S2**). Findings from the stratified analysis by sex were also persistent but suggested somewhat stronger associations among girls (**Figure S3**); however, in the overall regression models, the interaction term between child's sex and maternal urinary arsenic concentrations did not reach statistical significance with a range of *p*-values from 0.281 to 0.933 (**Table S2**). We did not observe any clear association between maternal urinary arsenic species concentrations and children's lung function z-scores in any of the other conducted models using FEV1/FVC as the dependent variable (**Table S1**).

4. Discussion

In this study, we found that maternal gestational urinary arsenic concentrations at levels common to the general US population were associated with reduced children's FVC and FEV1 z-scores. We also found evidence of potential modification of these effects by maternal methylation capacity and sex-specific effects.

A study from Mexico with 358 children of 6–12 years of age exposed to arsenic mainly from drinking water (mean 152.1 μg/L) starting *in utero* and until early childhood and with an average urinary arsenic of 141.2 μg/L, reported a reduced FVC and FEV1. Higher urinary arsenic concentrations were found among children with restrictive spirometry patterns (prevalence of 57%) compared with children with normal patterns (Recio-Vega et al., 2015). The MINIMat cohort in rural Bangladesh investigated the association between maternal urinary ΣAs during pregnancy with an average (range) of 76 (2, 2063) μg/L and lung function in 540 9-year-old children. They reported an inverse association with FVC and FEV1 in volumetric units ($\beta = -12$; 95% CI from −22 to −1.5 ml, and $\beta = -12$; 95% CI from −22 to −1.9 ml, respectively) (Ahmed et al., 2017). In our study population, we did not observe an association between arsenic exposure and FEV1/FVC but a reduced FVC and FEV1 supporting potentially restrictive effects on pulmonary airflow (Sanchez et al., 2018). While our analysis was based on z-scores so are not directly comparable, our exposure levels being far lower than Bangladesh resulted in smaller effect sizes compared to those found in children from the MINIMat cohort (Ahmed et al., 2017).

Arsenic can disrupt the highly complex signaling between embryonic lung tissue of mesenchymal and endodermal origin and can permanently alter lung structure and function in experimental studies (Miller and Marty, 2010). In mice, arsenic exposure during pregnancy at relatively low levels (10 and 100 μg/L) from drinking water caused impaired postnatal lung function in particular abnormal stiffening of the lung parenchyma in the offspring, along with impeded development of the distal airways and alveolar tissue (Ramsey et al., 2013). In humans, the lung formation starts with the development of the lung bud from the fetal foregut at 6 weeks' gestation. Airway generation down to the bronchiolar level are formed by the end of the first trimester of pregnancy. During childhood airways continue to grow, then lung size increases with chest wall growth until adolescence, reaches a plateau at 20–25 years of age and then declines (Merkus et al., 1996). Failure to reach a normal plateau affects airway function (Camargo et al., 2014; Lange et al., 2015; Postma et al., 2015). A prior study suggested sex-specific differences in response to arsenic exposure, such as male mice offspring more susceptible to the effects of arsenic on lung growth and performance than females. However, these lung mechanics alterations were not persistent in adulthood (Ramsey et al., 2013). Our study shows that girls may be more susceptible to the toxic effects of arsenic during gestation on lung function, which could relate to an increased overexpression of genes related to estrogen (Shen et al., 2007). We need further studies to understand the mechanisms by which effects of arsenic may manifest differently in males and females.

In humans, there is large inter-individual variation in methylation capacity of iAs and is characterized by the formation of DMA (60–70%) and MMA (10–20%) excreted in urine along with unmetabolized iAs (10–30%) (Signes-Pastor et al., 2017b; Vahter, 2002). Altered profiles of urinary arsenic species in urine appear to reflect differences in the efficacy of iAs metabolism and are genetically driven (Agusa et al., 2011). There is evidence that this influences individual susceptibility to the adverse effects of iAs including risks of skin, bladder, and lung cancer among highly exposed populations (Chen et al., 2003; López-Carrillo et al., 2014; Steinmaus et al., 2006; Yu et al., 2000). In this study, gestational arsenic exposure related to a reduced lung function in the offspring of women with decreased iAs methylation capacity. On average, we observed a 2.6-fold decrease in FVC and FEV1 z-scores in children whose mother had a low SMI compared to those with a high SMI. An earlier study from the MINIMat cohort also found a stronger inverse association between maternal urinary arsenic and children's FVC and FEV1 among those whose mother had higher percentages of MMA and lower percentages of DMA (Ahmed et al., 2017).

There are limitations in our study. Our study population was healthy overall, and the prevalence of airflow obstruction and restrictive patterns was low. Indeed, <2% of children would be classified with clinical airflow obstruction (FEV1/FVC < 0.70) or restrictive (FVC < 80% predicted together with FEV1/FVC ≥ 0.70) patterns (Powers et al., 2019). We adjusted our primary models for known risk factors selected from a minimally sufficient set of potential confounders; however, residual confounding is still possible. Therefore, we performed sensitive analysis adding in the models maternal age at enrollment and children's weight. The results were consistent with those from the main analyses. AsB is a putative non-toxic form of arsenic excreted in the urine unchanged related to fish/seafood consumption, which may cause exposure misclassification of iAs when total urinary arsenic serves as exposure biomarker (Navas-Acien et al., 2011; Signes-Pastor, et al., 2017a, 2019). In our study population, urinary AsB concentrations with a median < 1 μg/L suggest a limited fish/seafood consumption. However, we measured urinary arsenic speciation and calculated the summation of iAs, MMA and DMA excluding AsB (ΣAs), but did not consider urinary DMA from direct ingestion or from the metabolism of other organosenical compounds (e.g., arsenosugars and arsenolipids) also related to fish/seafood intake (Molin et al., 2015). We used single maternal urine samples; however, urinary arsenic concentrations show temporal stability with consistent patterns of exposure (Signes-Pastor et al., 2021). Our findings suggest sex-related differences in the strength of the effects of gestational arsenic exposure. However, in the sex-stratified analyses we had limited statistical precision, and thus the results need to be interpreted carefully. Also, it is important to recognize that our study did not consider postnatal arsenic exposure, which is expected to be dominated by ingestion of household water and food (Signes-Pastor et al., 2018). Thus, additional studies are needed with repeated postnatal measurements of arsenic exposure.

Our study indicates an association between arsenic exposure at relatively low levels during pregnancy and reduced lung function in childhood that may be important later in life. Additional prospective research is needed to confirm our observations, including potential sex-related and metabolic differences. Our findings support efforts to minimize gestational iAs exposure to reduce the risks of adverse effects on lung formation during this vulnerable window to prevent the potential onset of respiratory diseases throughout the lifespan.

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CRediT authorship contribution statement

Antonio J. Signes-Pastor: Methodology, Visualization. **Pablo Martinez-Camblor:** Methodology. **Emily Baker:** Methodology.

Juliette Madan: Methodology. **Margaret F. Guill: . Margaret R. Karagas:** Conceptualization, Methodology.

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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106673.

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