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Polycyclic aromatic hydrocarbon (PAH) exposure during pregnancy and child anthropometry from birth to 10 years of age: Sex-specific evidence from a cohort study in rural Bangladesh

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) have endocrine disrupting properties and they cross the placental barrier, but studies on gestational exposure and child anthropometry are inconclusive. We aimed to elucidate the impact of early gestational PAH exposure on anthropometry from birth to 10 years of age in 1295 mother-child pairs from a nested sub-cohort of the MINIMat trial in Bangladesh. Several PAH metabolites [1-hydroxyphenanthrene (1-OH-Phe), Σ2-,3-hydroxyphenanthrene (Σ2-,3-OH-Phe), 4-hydroxyphenanthrene (4-OH-Phe), 1-hydroxypyrene (1-OH-Pyr), Σ2-,3-hydroxyfluorene (Σ2-,3-OH-Flu)] were quantified in spot urine collected around gestational week 8 using LC-MS/MS. Child weight and height were measured at 19 occasions from birth to 10 years. Multivariable-adjusted regression models were used to assess associations of maternal PAH metabolites (log_2-transformed) with child anthropometry. The median concentration of 1-OH-Phe, Σ2-,3-OH-Phe, 4-OH-Phe, 1-OH-Pyr and Σ2-,3-OH-Flu was 1.5, 1.9, 0.14, 2.5, and 2.0 ng/mL, respectively. All maternal urinary PAH metabolites were positively associated with newborn weight and length and all associations were more pronounced in boys than in girls (p interaction for all <0.14). In boys, the strongest associations were observed with Σ2-,3-OH-Phe and Σ2-,3-OH-Flu for which each doubling increased mean birth weight by 41 g (95% CI: 13; 69 and 12; 70) and length by 0.23 cm (0.075; 0.39) and 0.21 cm (0.045; 0.37), respectively. Maternal urinary PAH metabolites were not associated with child anthropometry at 10 years. In longitudinal analysis, however, maternal urinary PAH metabolites were positively associated with boys' weight-for-age (WAZ) and height-for-age Z-scores (HAZ) from birth to 10 years, but only the association of 4-OH-Phe with HAZ was significant (B: 0.080 Z-scores; 95% CI 0.013, 0.15). No associations were observed with girls' WAZ or HAZ. In conclusion, gestational PAH exposure was positively associated with fetal and early childhood growth, especially in boys. Further studies are needed to confirm causality and to explore long-term health effects.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are byproducts generated during incomplete combustion or pyrolysis of organic materials and during various industrial processes. In low- and middle-income settings, exposure occurs primarily via indoor burning of fossil fuels for heating or cooking (Shen et al., 2013). Other exposure sources include food, either through external pollution or because of cooking practices, contamined drinking water, tobacco smoking, soil and household dust (Falco et al., 2003; Srogi, 2007). PAHs are metabolized in the body and excreted via urine, and both ingestion and exposure via inhalation have been shown to lead to excretion of hydroxylated metabolites of PAHs in urine (Alghamdi et al., 2015; Strickland et al., 1996). Exposure to PAHs has been linked to various adverse health effects, including cancer,

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cardiovascular disease, and diabetes (Kim et al., 2013; Poursafa et al., 2017; Stallings-Smith et al., 2018). In addition, there is evidence suggesting that PAHs have endocrine disrupting properties (Zhang et al., 2016), and that especially low-molecular weight PAHs can cross the placental barrier (Zhang et al., 2017), raising concern for the impact on fetal development and child health. In experimental animal studies, prenatal PAH exposure has been observed to lead to teratogenic effects (Kim et al., 2013).

In a meta-analysis including 11 epidemiological studies, there was no significant association of prenatal PAH exposure, assessed either via air monitoring, PAH-DNA adducts in cord blood or concentrations of 1-hydroxypyrene (1-OH-Pyr) in maternal urine, with size at birth (Yang et al., 2020). In the four studies exploring the association of 1-OH-Pyr in maternal urine and birth weight, the summary OR was 1.00 (95% CI: 0.97, 1.03) (Al-Saleh et al., 2013; Niwa et al., 2011; Polanska et al. 2014a, 2014b; Suzuki et al., 2010). A few epidemiological studies have also explored associations of several other maternal urinary PAH metabolites with birth anthropometry with varying results (Huang et al., 2020; Huo et al., 2019; Polanska et al. 2014a, 2014b). In a prospective Polish study, neither 1-OH-Pyr or any of the other eight PAH metabolites measured in maternal urine in the second trimester were associated with either birth weight or length (Polanska et al. 2014a, 2014b). In a cross-sectional Chinese study, the sum of several PAH metabolites in maternal urine was inversely associated with birth weight, but not birth length (Huo et al., 2019). On the contrary, in another Chinese study which merely assessed correlations, maternal urinary 2-hydroxyfluorene (2-OH-Flu) was positively correlated with birth weight, while no correlation was observed with the other nine PAH metabolites in maternal urine (Huang et al., 2020). Additionally, we identified only one epidemiological study exploring the link between prenatal PAH exposure and continued childhood growth (Rundle et al., 2019), in which increased prenatal airborne PAH exposure was associated with higher childhood body mass index (BMI) Z-scores up to the age of 5 years, but the BMI trajectories converged at 11 years of age. Thus, based on the inconclusive and sometimes very limited data available, there is a need for more large-scale prospective studies assessing the impact of maternal exposure to PAHs during pregnancy on fetal as well as continued childhood growth.

The aim of the present study was to explore associations of several different gestational urinary PAH metabolites with size at birth, and with child anthropometry from birth to 10 years in boys and girls in a longitudinal mother-child cohort in rural Bangladesh. We hypothesize that prenatal PAH exposure can increase oxidative stress (Shamsedini et al., 2022) and alter endocrine signaling (Zhang et al., 2016; Drwal et al., 2019) and thereby hamper fetal and child growth.

2. Materials and methods

2.1. Study design and participants

This prospective birth cohort study was carried out in Matlab, a rural subdistrict located about 50 km south-east of the capital Dhaka in Bangladesh, where the International Centre for Diarrhoeal Disease Research in Bangladesh (icddr,b) has been running a Health and Demographic Surveillance System (HDSS) since 1966 in addition to providing health services to the population. The cohort was initially nested into the Maternal and Infant Nutrition Intervention, Matlab trial (MINIMat trial, reg#ISRCTN16581394), which enrolled 4436 pregnant women from November 2001 throughout October 2003. In total, 3625 live infants were born in the MINIMat trial for which the design and procedures have been reported elsewhere (Persson et al., 2012). In short, eligibility criteria for enrollment in the MINIMat trial included no severe illness, viable fetus, gestational age of less than 14 weeks by ultrasound examination, and consent for participation. Once enrolled, the pregnant women were randomly allocated to six different groups, receiving one of the three allotted micronutrient supplements (30 mg iron and 400 μg folate, 60 mg iron and 400 μg folate, or a multiple micronutrient supplement containing 15 different micronutrients including iron and folate), in combination with early [around gestational week (GW) 14] or usual timed food supplementation (around GW20).

Out of the 3267 MINIMat mothers who had a singleton birth with measured birth anthropometry (Fig. S1), we randomly selected a subsample of 1295 in which different PAH metabolites were measured in urine collected in early pregnancy, around GW8, between 2001 and 2003. The multivariable-adjusted models of maternal urinary PAH metabolites and birth anthropometry included 1294 and 1293 mother-child dyads for birth weight and length, respectively, the discrepancy occurred due to missing information on either maternal BMI (n = 1) or birth length (n = 1). Out of these children, 1202 also had their height and weight measured at several time points during infancy and childhood until 10 years of age (data collected 2011–2012). Comparing mothers who were included in the present study of gestational PAH exposure (n = 1295) with those who were not (n = 1972), we observed that the included mothers were slightly lighter, had acquired a marginally lower grade of education, and had a slightly lower household socioeconomic status than mothers for whom PAH exposure data was unavailable (Table S1).

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethical Review Committee at icddr, b in Bangladesh, and by the Regional Ethical Review Board in Stockholm, Sweden. The participating women were enrolled after providing written informed consent and they were informed that they could withdraw from the study at any time.

2.2. PAH metabolites in urine

PAH metabolites in urine can serve as biomarkers of internal dose from recent exposure (Strickland et al., 1996). Urinary 1-OH-Pyr, a metabolite of pyrene, is a classical biomarker of PAH exposure; however, metabolites of other PAHs, such as phenanthrene and fluorene have also been associated with adverse health outcomes (Alhamdow et al. 2020, 2021) and should therefore also be considered, particularly for exposure assessment of low molecular weight PAHs. We measured monohydroxylated metabolites of phenanthrene (1-OH-Phe, 2-OH-Phe, 3-OH-Phe, and 4-OH-Phe), fluorene (2-OH-Flu and 3-OH-Flu) and pyrene (1-OH-Pyr). However, as the peaks of 2-OH-Phe and 3-OH-Phe as well as 2-OH-Flu and 3-OH-Flu could not be separated, they were analyzed and reported as single peaks (Σ2-,3-OH-Phe and Σ2-, 3-OH-Flu). The measurements were performed in spot urine samples which had been collected in the women's homes around GW8 using a urine collection cup. Thereafter, the urine was transferred to a 20 mL acid washed polyethylene container (Zinsser Analytic GmbH, Germany), which was transported to the central hospital in Matlab and stored at −70 °C until being transported frozen to Sweden.

The urinary metabolites were analyzed using liquid chromatography – mass spectrometry (QTRAP6500+, Sciex, Framingham, MA, USA) at Lund University, Sweden, and the analytical method has been described in detail previously (Alhamdow et al. 2020, 2021; Krais et al., 2021). Prior to the analysis, urine samples were thawed and shaken before pipetting 0.2 mL of each sample into a 96-well plate hydrolyzed by β-glucuronidase. Thereafter, deuterium-labelled internal standards (D_9-1-OH-Phe, D_9-2-OH-Phe, D_9-4-OH-Phe, D_9-1-OH-Pyr, D_9-2-OH-Flu) were added. Analytical method details are presented in Table S2. Blank controls and two quality control (QC) urine samples were analyzed with every analytical batch in duplicates. The limit of detection (LOD) was calculated from water blanks and defined as three times the standard deviation of the concentration corresponding to the peak at the same retention time as the individual compounds. Equally, the limit of quantification (LOQ) was calculated as 10 times the standard deviation. The LOD was 0.02, 0.01, 0.01, 0.12, and 0.01 ng/mL for 1-OH-Phe, Σ2-, 3-OH-Phe, 4-OH-Phe, 1-OH-Pyr, and Σ2-,3-OH-Flu, respectively. The

LOQ was 0.02, 0.02, 0.04, 0.28, 0.03 ng/mL for 1-OH-Phe, Σ2-, 3-OH-Phe, 4-OH-Phe, 1-OH-Pyr, and Σ2-,3-OH-Flu, respectively. The laboratory participates in G-EQUAS inter-laboratory exercise for the analysis of 1-OH-Pyr coordinated by the University of Erlangen-Nuremberg, Germany.

The metabolite concentrations were adjusted for specific gravity using the following formula: metabolite concentration × (average specific gravity in the study sample (1.012) − 1)/(individual specific gravity − 1). The specific gravity was measured using a refractometer (EUROMEX RD712 Clinical Refractometer, EUROMEX Holland, Anhem, The Netherlands).

2.3. Outcomes

Weight and length of newborns delivered at health clinics in Matlab were measured by the attending nurse (Persson et al., 2012). For newborns delivered at home (60%), a birth notification system was established to ensure accurate anthropometric assessment by trained health workers as described elsewhere (Arifeen et al., 2000; Persson et al., 2012). Birth weight was measured with daily calibrated electronic scales (UNICEF Uniscale; SECA, Hamburg, Germany; precision: 10 g), and birth length was measured with a locally made, wooden infantometer (precision: 1 mm) (Persson et al., 2012).

Child weight and height/length were measured by trained nurses once a month during the child's first year of life, every third month during the second year and thereafter at 5 and 10 years of age. Weight was measured using a daily calibrated digital scale (TANITA HD-318; Tanita Corporation). Height was measured with a collapsible length board (precision: 0.1 cm) until the child was 1.5 years of age, and thereafter it was measured with a regularly calibrated free-standing stadiometer Seca214 Height Measure (Leicester). Weight-for-age and height-for-age Z-scores (WAZ and HAZ) were calculated using the World Health Organization (WHO) international reference values for child growth (de Onis et al., 2007; WHO, 2006). Underweight and stunting were classified as WAZ and HAZ below −2, respectively.

2.4. Covariates

Data on the women's background characteristics [age, weight, height, parity, education, household socioeconomic status (SES), smoking and cooking indoors] and information about gestational age and child sex were collected within the MINIMat trial. The women's weight and height around GW8 were used to calculate their early pregnancy BMI (kg/m^2). Parity was categorized as primiparous or multiparous. Maternal education was defined as the number of completed years of formal schooling and it was categorized into three groups (no education, 1–5 years, or ≥6 years). Family SES was estimated through a wealth index, based mainly on ownership of several durable household assets, created using principal components analysis (Saha et al., 2008) and was categorized into quintiles. The date of the last menstrual period was subtracted from the date of the birth to obtain newborn gestational age (weeks).

2.4.1. Statistical analyses

The statistical analyses were conducted using STATA (version 16; STATA Corp, College Station, TX, USA) and a p value < 0.05 (two-sided) was considered to be statistically significant. Bivariate associations were assessed using Spearman's rank correlation coefficient (rho), Kruskal-Wallis test or Pearson's χ^2 test, depending on the type of data. The urinary concentrations of PAH metabolites were not normally distributed, and they were therefore log$_2$-transformed in all statistical models. The correlations of different urinary PAH metabolites (1-OH-Phe, Σ2-,3-OH-Phe, 4-OH-Phe, 1-OH-Pyr, and Σ2-,3-OH-Flu) with size at birth (weight and length) and WAZ and HAZ from birth to 10 years of age were evaluated by scatter plots with Lowess lines.

Associations between urinary concentrations of PAH metabolites (log$_2$-transformed) and size at birth (birth weight and length) were evaluated using multivariable-adjusted linear regression models as the scatter plots did not indicate any nonlinear associations. The associations between different PAH metabolites and birth size were modelled in separate models because there was a high correlation between different PAH metabolites. The three metabolites of phenanthrene (1-OH-Phe, Σ2-,3-OH-Phe, 4-OH-Phe) were included in the models both as a sum of hydroxylated phenanthrene metabolites (ΣOH-Phe) and separately. The models were adjusted for covariates which were correlated with the outcomes and any of the exposure biomarkers in the bivariate analyses (Table S3) and were statistically significant in the models. The chosen covariates were maternal BMI (continuous; kg/m^2), maternal education (0, 1–5, ≥6 years), parity at enrollment (primiparous or multiparous), household SES (quintiles), and newborn sex. We did not adjust for maternal erythrocyte concentrations of arsenic and cadmium, as exposure to these metals was not found to be associated with the PAH metabolites (Table S3). As our previous studies have indicated sex-specific associations of maternal metal exposure with size at birth (Kippler et al., 2012) and child anthropometry (Gardner et al., 2013; Malin Igra et al., 2021), we explored potential multiplicative interactions between urinary PAH metabolites and newborn sex [urinary metabolite (log$_2$-transformed)*sex]. Thereafter, we repeated the regression analyses stratified by newborn sex.

As a secondary step, we assessed sex stratified associations between the maternal urinary PAH metabolites (log$_2$-transformed) during pregnancy and the children's weight and height at 10 years, to see if any association with size at birth persisted until 10 years. The models were adjusted similarly to the models mentioned above for birth size as outcome. Finally, we also assessed sex stratified associations between maternal urinary PAH metabolites (log$_2$-transformed) during pregnancy and WAZ and HAZ from birth to 10 years of age using multivariate linear regression. Each child was considered as a separate cluster using a robust, clustered variance-covariance matrix estimator. The regression models were adjusted for child age (months), maternal BMI at GW8 (kg/m^2), maternal education (0, 1–5, ≥6 years) and parity at enrollment (primiparous or multiparous). We modelled time as a splined variable (at ages 2, 6, 12, 24, and 52 months) based on beta coefficient significance in combination with BIC (Bayesian Information Criterion) and AIC (Akaike Information Criterion).

3. Results

3.1. General characteristics

The general background characteristics of the 1295 studied pregnant women are presented in Table 1. Approximately 36% of the women were illiterate, and one-third had a BMI <18.5 kg/m^2. Thirty percent were primiparous and about 50% had 1-2 children. None of the women reported smoking during pregnancy and about 15% reported that they cooked indoors. The average gestational age at birth was 38.7 weeks (range 30–44 weeks) and 8% of the newborns were delivered before GW37. The mean birth weight was 2684 g and 31% of the newborns weighed less than 2500 g. The mean (±SD) birth weight and length were significantly higher in boys (2713 ± 412 g and 47.9 ± 2.27 cm) than in girls (2653 ± 372 g and 47.6 ± 1.95 cm; p < 0.05). At 10 years, the mean weight was significantly but marginally higher in boys (23.4 ± 3.6 kg) than in girls (23.1 ± 4.2 kg), while mean height in boys (126.4 ± 5.8 cm) and in girls (126.3 ± 5.9 cm) did not differ. The proportion of boys and girls being underweight (WAZ < −2) at 10 years was 41% and 45%, respectively; 27% of the boys and 30% of the girls were categorized as stunted (HAZ < −2).

3.2. Maternal urinary PAH metabolites and influencing factors

All urinary PAH metabolites were detected in the 1295 pregnant women in early pregnancy (Table 2); the median concentration and

Table 1
Characteristics of the mothers and their newborns.

Characteristics	n	Mean or percentage	SD	Median	Range
Mothers					
Age (years)	1295	25.9	6.0	25	13–44
Weight at GW8 (kg)	1294	45	6.7	44	25–90
Height (cm)	1295	150	5.2	150	135–169
BMI at GW8 (kg/m^2)	1294	20	2.6	19.6	13–35
<18.5	385	30			
>18.5	909	70			
Education	1295				
Illiterate (%)	473	37			
1–5 years (%)	305	24			
6 or more years (%)	517	40			
Socioeconomic status (quintiles, %)	1295	22/24/20/17/17			
Parity	1295				
Primiparous (%)	391	30			
Multiparous (%)	904	70			
Erythrocyte As (μg/kg) at GW14	1205	7.7	8.1	4.4	0.0078–87
Erythrocyte Cd (μg/kg) at GW14	1205	1.1	0.69	0.91	0.064–5.1
Indoor cooking	1281				
Yes (%)	194	15			
No (%)	1087	85			
Newborns					
Sex (boys/girls)	1295				
Boys (%)	660	51			
Girls (%)	635	49			
Gestational age (weeks)	1295	38.7	1.7	39	30–44
Weight (g)	1295	2684	394	2676	1250–4249
Length (cm)	1294	47.6	2.13	47.8	37.9–58.45

Abbreviations: SD, standard deviation; GW, gestational week; As, arsenic; Cd, cadmium.

Table 2
Concentrations of urinary metabolites (specific gravity adjusted) of polycyclic aromatic hydrocarbons (PAH) in 1295 MINIMat women during early pregnancy (on average gestational week 8).

PAH metabolites (ng/mL)[a]	Mean ± SD	Median	5th-95th percentile	Range
Phenanthrene metabolites				
ΣOH-Phe	4.53 ± 4.09	3.45	0.79–11.60	0.16–44.26
1-OH-Phe	1.89 ± 1.87	1.45	0.24–4.84	0.01–24.21
Σ2-,3-OH-Phe	2.43 ± 2.89	1.85	0.44–6.30	0.11–21.27
4-OH-Phe	0.19 ± 0.18	0.14	0.02–0.50	0.00–2.32
Pyrene metabolite				
1-OH-Pyr	3.17 ± 2.82	2.45	0.27–8.66	0.01–30.05
Fluorene metabolite				
Σ2-,3-OH-Flu	2.75 ± 2.68	2.00	0.54–7.77	0.05–26.27

Abbreviations: PAH: polycyclic aromatic hydrocarbons; SD, standard deviation; ΣOH-Phe: sum of hydroxylated phenanthrene metabolites; 1-OH-Phe, 1-hydroxyphenanthrene; Σ2-,3-OH-Phe, Σ2-,3-hydroxyphenanthrene; 4-OH-Phe, 4-hydroxyphenanthrene; 1-OH-Pyr, 1-hydroxypyrene; Σ2-,3-OH-Flu, Σ2-,3-hydroxyfluorene.
[a] Adjusted for average specific gravity (1.012).

associated 5th-95th percentiles of 1-OH-Phe, Σ2-,3-OH-Phe, 4-OH-Phe, 1-OH-Pyr, and Σ2-,3-OH-Flu were 1.45 ng/mL (0.24–4.84), 1.85 ng/mL (0.44–6.30), 0.14 ng/mL (0.02–0.50), 2.45 ng/mL (0.27–8.66), and 2.00 ng/mL (0.54–7.77). In bivariate analysis, the urinary metabolites were highly correlated with each other (rho between 0.77 and 0.89; $p < 0.001$), while they were not correlated with the concentrations of arsenic and cadmium in maternal erythrocytes at GW14 (Table S3).

There was a very weak correlation between most of the PAH metabolites and maternal age, BMI, education, parity and household socioeconomic status (Table S3). PAH metabolite concentrations did not differ between mothers who reported to practice indoor cooking and those who did not (p-values for Mann-Whitney *U*-tests >0.27). The median concentration of urinary Σ2-,3-OH-Phe was slightly higher in mothers who were pregnant with boys [median 2.0 ng/mL (5th-95th percentiles 0.54–6.1)] than in those pregnant with girls [1.7 ng/mL (0.36–7.2); p-value = 0.0099].

3.3. Maternal urinary PAH metabolites and size at birth

In the multivariable-adjusted linear regression analyses (Table 3), all maternal urinary PAH metabolites (ΣOH-Phe, 1-OH-Phe, Σ2-,3-OH-Phe, 4-OH-Phe, 1-OH-Pyr, and Σ2-,3-OH-Flu) were positively associated with birth weight. The strongest estimate was found in relation to maternal urinary Σ2-,3-OH-Phe, for which a doubling was associated with a mean increase in birth weight of 25 g (95% CI 7.4; 43 g; p = 0.006). Likewise, ΣOH-Phe and Σ2-,3-OH-Phe were positively associated with birth length (Table 3). A doubling of maternal urinary Σ2-,3-OH-Phe was associated with a mean increase in birth length of 0.12 cm (95% CI 0.022; 0.22 cm; p = 0.016).

There were indications of a multiplicative interaction between the different PAH metabolites and newborn sex in relation to both birth weight (p for all 0.045–0.11) and birth length (p for all 0.007–0.046; Table 3). Stratification by newborn sex indicated that positive associations of maternal urinary PAH metabolite concentrations with birth weight and length were only present in boys, while no associations were observed in girls (Table 4). In relation to both birth weight and length, the strongest estimates were observed with Σ2-,3-OH-Phe and Σ2-,3-OH-Flu. In boys (Table 4), a doubling of maternal urinary Σ2-,3-OH-Phe and Σ2-,3-OH-Flu was associated with a mean increase in birth weight of 41 g (95% CI: 13–96 g) and 41 g (95% CI: 12–70 g), respectively. For birth length, the corresponding estimates were 0.23 cm (95% CI: 0.075–0.39 cm) and 0.21 cm (95% CI: 0.045–0.37 cm), respectively.

3.4. Maternal urinary PAH metabolites and child anthropometry from birth to 10 years of age

There was no association between maternal urinary PAH metabolites and the children's weight and height at 10 years in either boys or girls (Table 5). Nonetheless, in multivariate linear regression models modelling maternal urinary PAH metabolites in relation to the children's WAZ and HAZ at 19 time points from birth up until 10 years of age the results were similar to those observed in relation to the newborns' anthropometry (Table 6). In boys, all the maternal urinary PAH metabolites were positively associated with WAZ from birth to 10 years of age, but none of the associations were statically significant (p for all 0.084–0.14). The estimates were of similar size (B ranging between 0.045 and 0.052 Z-scores). Likewise, all maternal urinary PAH metabolites were positively associated with the boys' HAZ from birth to 10 years of age (Table 5). The estimates varied between 0.045 and 0.080 (p for all 0.018–0.16) and the association with 4-OH-Phe was statically significant (Table 6). A doubling of maternal urinary 4-OH-Phe was associated with a mean increase in HAZ of 0.080 Z-scores (95% CI: 0.013–0.15; p = 0.018).

4. Discussion

To our knowledge, this is the first study to measure levels of several hydroxylated PAH metabolites in pregnant women's urine in a resource limited setting in Bangladesh, with the purpose of evaluating whether levels of these metabolites impacted fetal and child growth. Findings indicate that pregnant women residing in the rural subdistrict Matlab from 2001 throughout 2003 were exposed to elevated levels of PAHs,

Table 3
Multivariable-adjusted linear regression analysis of maternal urinary PAH metabolites (ng/mL, log_2-transformed) in early pregnancy with size at birth [weight (n = 1294) and length (n = 1293)].

Urinary metabolites (ng/mL, log_2)	Birth weight				Birth length			
	Crude model	Adjusted model[a]			Crude model	Adjusted model[a]		
	B (95% CI)	B (95% CI)	p[b]	p_{int}[c]	B (95% CI)	B (95% CI)	p[b]	p_{int}[c]
ΣOH-Phe	25 (6.8; 44)	22 (4.7; 40)	0.013	0.089	0.11 (0.015; 0.21)	0.10 (0.0043; 0.20)	0.041	0.026
1-OH-Phe	19 (3.8, 35)	15 (−0.15, 30)	0.052	0.14	0.084 (−0.0010, 0.17)	0.062 (−0.021, 0.14)	0.14	0.046
Σ2-,3-OH-Phe	26 (7.5, 44)	25 (7.4, 43)	0.006	0.11	0.12 (0.024, 0.22)	0.12 (0.022, 0.22)	0.016	0.036
4-OH-Phe	19 (4.1, 34)	15 (0.33, 29)	0.045	0.11	0.083 (0.0034, 0.16)	0.064 (−0.014, 0.14)	0.11	0.007
1-OH-Pyr	15 (0.16, 30)	16 (2.2, 31)	0.024	0.095	0.043 (−0.037, 0.12)	0.044 (−0.034, 0.12)	0.27	0.040
Σ2-,3-OH-Flu	22 (3.6, 41)	21 (2.6, 38)	0.025	0.045	0.084 (−0.016, 0.18)	0.080 (−0.018, 0.18)	0.11	0.020

Abbreviations: CI, confidence interval; ΣOH-Phe: sum of hydroxylated phenanthrene metabolites; 1-OH-Phe, 1-hydroxyphenanthrene; Σ2-,3-OH-Phe, 2-,3-hydroxyphenanthrene; 4-OH-Phe, 4-hydroxyphenanthrene; 1-OH-Pyr, 1-hydroxypyrene; Σ2-,3-OH-Flu, 2-,3-hydroxyfluorene.
[a] Adjusted for maternal BMI at gestational week 8 (continuous; kg/m^2), household socioeconomic status (quintiles), parity (primiparous or multiparous), and maternal education level (0, 1–5, >6 years) at enrollment, and newborn sex.
[b] p-value for adjusted model.
[c] p-value for multiplicate interaction between maternal urinary PAH metabolites (log_2-transformed) and newborn sex.

Table 4
Multivariable-adjusted linear regression analysis of maternal urinary PAH metabolites (ng/mL, log_2-transformed) in early pregnancy with size at birth (weight and length) by newborn sex.

Urinary metabolites (ng/mL, log_2)	Birth weight (g)				Birth length (cm)			
	Boys (n = 659)		Girls (n = 635)		Boys (n = 658)		Girls (n = 635)	
	B (95% CI)[a]	p	B (95% CI)[a]	p	B (95% CI)[a]	p	B (95% CI)[a]	p
ΣOH-Phe	39 (11; 68)	0.007	8.8 (−13; 31)	0.44	0.23 (0.064; 0.39)	0.006	0.0097 (−0.11; 0.13)	0.87
1-OH-Phe	29 (2.3, 55)	0.033	6.1 (−12, 24)	0.51	0.17 (0.020, 0.32)	0.026	−0.00098 (−0.097, 0.095)	0.98
Σ2-,3-OH-Phe	41 (13, 69)	0.004	11 (−11, 34)	0.33	0.23 (0.075, 0.39)	0.004	0.029 (−0.091, 0.15)	0.63
4-OH-Phe	28 (4.3, 52)	0.021	4.5 (−13, 22)	0.62	0.19 (0.059, 0.33)	0.005	−0.023 (−0.12, 0.070)	0.63
1-OH-Pyr	33 (9.1, 56)	0.007	6.2 (−11, 24)	0.49	0.15 (0.017, 0.28)	0.027	−0.020 (−0.11, 0.073)	0.67
Σ2-,3-OH-Flu	41 (12, 70)	0.006	4.8 (−18, 27)	0.68	0.21 (0.045, 0.37)	0.013	−0.012 (−0.13, 0.11)	0.84

Abbreviations: CI, confidence intervals; ΣOH-Phe: sum of hydroxylated phenanthrene metabolites; 1-OH-Phe, 1-hydroxyphenanthrene; Σ2-,3-OH-Phe, Σ2-,3-hydroxyphenanthrene; 4-OH-Phe, 4-hydroxyphenanthrene; 1-OH-Pyr, 1-hydroxypyrene; Σ2-,3-OH-Flu, Σ2-,3-hydroxyfluorene.
[a] Adjusted for maternal BMI at gestational week 8 (kg/m^2), household socioeconomic status (quintiles), parity (primiparous or multiparous), and maternal education level (0, 1–5, >6 years) at enrollment.

Table 5
Multivariable-adjusted linear regression analysis of maternal urinary PAH metabolites (ng/mL, log_2-transformed) in early pregnancy with weight and height at 10 years by child sex (n = 586 boys and n = 616 girls).

Urinary metabolites (ng/mL, log_2)	Weight at 10 y (kg)				Height at 10 y (cm)			
	Boys		Girls		Boys		Girls	
	B (95% CI)[a]	p	B (95% CI)[a]	p	B (95% CI)[a]	p	B (95% CI)[a]	p
ΣOH-Phe	−0.027 (−0.29; 0.23)	0.84	0.015 (−0.23; 0.26)	0.91	0.053 (−0.38; 0.49)	0.81	−0.022 (−0.38; 0.34)	0.91
1-OH-Phe	−0.056 (−0.30; 0.19)	0.65	0.036 (−0.16; 0.24)	0.73	0.048 (−0.35; 0.45)	0.82	0.084 (−0.21; 0.38)	0.58
Σ2-,3-OH-Phe	−0.010; −0.26; 0.24)	0.94	−0.029 (−0.28; 0.22)	0.82	0.033 (−0.39; 0.45)	0.88	−0.13 (−0.50; 0.23)	0.48
4-OH Phe	0.018 (−0.20; 0.23)	0.87	0.051 (−0.15; 0.25)	0.61	0.15 (−0.21; 0.51)	0.42	0.062 (−0.23; 0.35)	0.68
1-OH Pyr	0.047 (−0.17; 0.26)	0.67	−0.0010 (−0.19; 0.19)	0.99	0.10 (−0.26; 0.46)	0.58	−0.062 (−0.34; 0.22)	0.67
Σ2-,3-OH Flu	0.085 (−0.18; 0.35)	0.53	−0.025 (−0.27; 0.22)	0.84	0.099 (−0.34; 0.54)	0.66	−0.097 (−0.45; 0.26)	0.59

Abbreviations: CI, confidence intervals; ΣOH-Phe: sum of hydroxylated phenanthrene metabolites; 1-OH-Phe, 1-hydroxyphenanthrene; Σ2-,3-OH-Phe, Σ2-,3-hydroxyphenanthrene; 4-OH-Phe, 4-hydroxyphenanthrene; 1-OH-Pyr, 1-hydroxypyrene; Σ2-,3-OH-Flu, Σ2-,3-hydroxyfluorene.
[a] Adjusted for maternal BMI at gestational week 8 (kg/m^2), household socioeconomic status (quintiles), parity (primiparous or multiparous), and maternal education level (0, 1–5, >6 years) at enrollment.

mostly likely both via inhalation and ingestion. Interestingly, in contrast to our hypothesis, increasing concentrations of gestational urinary PAH metabolites were associated with increased newborn weight and length, and associations were clearly more pronounced in boys than in girls. This positive trend also persisted in relation to the boys' WAZ and HAZ from birth up to 10 years, although the lack of associations of gestational urinary PAH metabolites with the boys' weight and height at 10 years of age suggests that the impact was diminished with increasing age.

Unlike in the present study of non-smoking Bangladeshi women where the median concentration of 1-OH-Pyr was 2.45 ng/mL, epidemiological studies in Europe, Japan and Saudi Arabia with much lower median exposure levels (1-OH-Pyr ranging between 0.12 and 0.59 ng/mL (Table S4)] did not report any associations of gestational urinary PAH metabolites with birth weight or length (Al-Saleh et al., 2013; Niwa et al., 2011; Polanska et al. 2014a, 2014b; Suzuki et al., 2010), especially not after adjusting for tobacco smoking which is a well-known source of PAHs and an important determinant of fetal growth restriction (Al-Saleh et al., 2013). Furthermore, two cross-sectional Chinese studies of pregnant women conducted six years apart in an e-waste recycling and reference area reported conflicting results. During this time the gestational urinary 1-OH-Pyr concentrations increased 2-fold (median 1.76 and 0.84 ng/mL to 71 and 54 ng/mL) (Huang et al.,

Table 6
Linear regression models of maternal urinary PAH metabolites (ng/mL, log_2-transformed) during pregnancy with weight-for-age Z-scores (WAZ) and height-for-age Z-scores (HAZ) from birth to 10 years of age (19 measurements) by child gender (n = 586 boys and n = 616 girls).

Urinary metabolites (ng/mL, log_2)	WAZ				HAZ			
	Boys		Girls		Boys		Girls	
	B (95% CI)[a]	p	B (95% CI)[a]	p	B (95% CI)[a]	p	B (95% CI)[a]	p
ΣOH-Phe	0.052 (−0.0073; 0.11)	0.085	−0.0051 (−0.054; 0.044)	0.84	0.062 (−0.0030; 0.13)	0.061	0.0021 (−0.047; 0.051)	0.93
1-OH-Phe	0.045 (−0.012; 0.10)	0.13	0.0012 (−0.039; 0.042)	0.95	0.052 (−0.011; 0.11)	0.1	0.010 (−0.031; 0.051)	0.64
Σ2-,3-OH-Phe	0.047 (−0.0090; 0.10)	0.099	−0.0088 (−0.058; 0.041)	0.73	0.060 (−0.0016; 0.12)	0.056	−0.0038 (−0.052; 0.045)	0.88
4-OH-Phe	0.052 (−0.0071; 0.11)	0.084	−0.0019 (−0.042; 0.038)	0.93	0.080 (0.013; 0.15)	0.018	0.0051 (−0.034; 0.045)	0.80
1-OH-Pyr	0.047 (−0.0066; 0.10)	0.085	−0.0020 (−0.040; 0.036)	0.92	0.045 (−0.012; 0.10)	0.12	−0.0092 (−0.050; 0.031)	0.66
Σ2-,3-OH-Flu	0.045 (−0.015; 0.11)	0.14	−0.024 (−0.073; 0.025)	0.33	0.049 (−0.019; 0.12)	0.16	−0.012 (−0.061; 0.037)	0.62

Abbreviations: CI, confidence interval; ΣOH-Phe: sum of hydroxylated phenanthrene metabolites; 1-OH-Phe, 1-hydroxyphenanthrene; Σ2-,3-OH-Phe, Σ2-,3-hydroxyphenanthrene; 4-OH-Phe, 4-hydroxyphenanthrene; 1-OH-Pyr, 1-hydroxypyrene; Σ2-,3-OH-Flu, Σ2-,3-hydroxyfluorene.

[a] Adjusted for age of the child in months (5 splines), maternal BMI at gestational week 8 (kg/m^2), parity (primiparous or multiparous), household socioeconomic status (quintiles) and maternal education level (0, 1-5, >6 years) at enrollment.

2020; Huo et al., 2019). In the initial study of 257 pregnant women, in which exposure levels were slightly lower than in the present study, the total sum of urinary PAH metabolites was inversely associated with birth weight after adjustment for multiple confounders (Huo et al., 2019). In the latter study of 163 pregnant women, findings were partly in accordance with ours, as gestational urinary 2-OH-Flu was positively correlated with birth weight and the remaining nine urinary PAH metabolites showed the same trend (Huang et al., 2020), although lack of confounder adjustment renders results uncertain. Nevertheless, it cannot be excluded that the diverse findings among studies may be due to the presence of non-monotonic dose-response relationships for prenatal PAH exposures and birth outcomes as indicated in the study by Huo and co-workers (Huo et al., 2019). Furthermore, unlike in the present study, none of the other studies explored potential sex-differences which may have attenuated the associations.

We report for the first time that positive associations of gestational urinary PAH metabolites with boys' weight and height seem to persist into childhood, but that they appear to be attenuated towards prepubertal age. The continued impact of prenatal PAH exposure on child growth is supported by one previous U.S. study, comprising 535 African American and Hispanic children, in which children in the third tertile of prenatal exposure to airborne PAHs had significantly higher BMI z-scores than those in the first exposure tertile (0.35 z-score units; 95% CI: 0.09, 0.61) at the age of 5 years. Similarly to our study, the trajectories in the American study also converged with increasing age and the difference was no longer evident at 11 years of age (Rundle et al., 2019). In contrast to our findings, however, they did not observe any clear difference by child sex, but they did report a high prevalence of obesity during childhood (Rundle et al. 2012, 2019), which is not prevalent in our children (1 and 5 children with WAZ>2 at 5 and 10 years, respectively). In support of these findings, experimental studies of mice exposed to benzo(*a*)pyrene have reported decreased lipolytic response and higher weight gain (Irigaray et al., 2006), and exposure to a mixture of airborne PAHs resulted in higher fat accumulation, possibly through higher expression of peroxisome proliferator-activated receptor γ (PPARγ) (Yan et al., 2014). On the other hand, experimental studies have thus far not been able to confirm that phenanthrene, of which some metabolites were measured herein, may act as an obesogen (Guo et al., 2021).

Our sex-specific associations are more indicative of altered hormonal signaling as the underlying mode of action. Accordingly, increased concentrations of hydroxylated PAH metabolites throughout pregnancy have been associated with increased levels of corticotropin-releasing hormone (CRH), estriol, progesterone, and triiodothyronine (T3), and decreased levels of testosterone (Cathey et al., 2020). Interestingly, the positive associations with CRH were more pronounced in women carrying male fetuses as opposed to female fetuses (Cathey et al., 2020), albeit increased CRH levels have foremost been associated with onset of parturition and fetal growth restriction (Goland et al., 1993), not increased fetal growth. Several epidemiological studies have reported that increased T3 levels in the mothers are associated with increased birth weight (Johns et al., 2018; Zhang et al., 2019), but the underlying mechanisms by which T3 affects fetal weight are unknown and sex differences have not been documented. On the other hand, studies in the general population have reported that certain hydroxylated PAH metabolites were positively associated with T3 in females, while other PAH metabolites were inversely associated with T4 in males (Jain, 2016). Thus, a negative impact on maternal T4 and/or increased fetal T4 levels cannot be excluded which, in turn, have been associated with increased birth weight in males only (Janssen et al., 2017; Shields et al., 2011). Additionally, increasing concentrations of PAHs in cord blood have been correlated with increased expression of insulin-like growth factor 1 (IGF-1) and IGFBP-3 in placenta (Xu et al., 2013), which are important determinants of fetal growth with documented sexually dimorphic effects (Geary et al., 2003).

Unfortunately, we could not identify any sources of the women's PAH exposure, which is needed to be able to establish effective public health interventions. We only had information on whether the women cooked indoors or not but we did not observe any difference in PAH metabolites based on this, despite that at the time of sampling (2001–2003) all households had traditional stoves, which have poor combustion capacity, require more time for cooking, and can produce a lot of smoke (Zaman et al., 2017). Probably, there is a need for more detailed data regarding indoor cooking and heating to be able to detect differences in the exposure. Diet is likely another important exposure source. Rural Bangladeshi populations consume mostly cereals such as rice, pulses, vegetables, and eat fish on occasion, while foods like meat, eggs and milk are only consumed a couple of times per month (Haque et al., 2014). Food preparation involves the use of various types of cooking oils and takes place several times per day (Hossain and Salehuddin, 2012). Indeed, elevated concentrations of some PAHs have been detected in certain vegetables and edible oils on the Bangladeshi market and in seafood from coastal areas in Bangladesh (Habibullah-Al-Mamun et al., 2019; Hossain and Hoque, 2011; Hossain and Salehuddin, 2012). In addition, during high temperature cooking practices such as frying and deep-frying, which are commonly used methods of cooking in this area, additional PAH compounds may be created (Sampaio et al., 2021).

The main strengths of this study include the prospective population-based design in a cohort of pregnant women who did not consume alcohol or smoked tobacco, the use of biomarkers in assessing individual

exposure to PAHs, and the large sample size which enabled us to explore sex differences. This study also has several limitations. First, the exposure was only measured once in early pregnancy, and therefore variations in exposure due to pregnancy-related physiological changes cannot be excluded. However, results from an earlier study in Puerto Rico with repeated exposure assessment only indicate moderate variations in exposure during pregnancy (Cathey et al., 2020). Secondly, we only measured hydroxylated urinary metabolites from three parent PAH compounds. On the other hand, exposure to different environmental PAHs does not occur in isolation, which is supported by the strong correlation between metabolites, and it is therefore likely that the metabolites analyzed in the current study are reflective of overall exposure (Hansen et al., 2008). We had information on multiple potential confounders, although the information concerning indoor cooking (only yes/no) was most likely not detailed enough to be informative about the exposure. We also lacked data on women's dietary intake and on exposure to environmental tobacco smoking, previously shown to be a determinant of PAH exposure as well as birth outcomes (Al-Saleh et al., 2013; Huo et al., 2019). However, if environmental tobacco smoking had been an important confounder, the prenatal PAH exposure-anthropometry associations would most likely have been negative (Misra and Nguyen, 1999). Still, it is important to note that residual or unmeasured confounding cannot be excluded.

5. Conclusions

Our findings indicate that elevated gestational exposure to PAHs may increase fetal growth in male fetuses, while female fetuses seem to be less affected. Additionally, the impact of gestational exposure to PAHs on boys' growth persisted during early childhood but seemed to level out at the age of 10 years. Further epidemiological studies are needed to confirm the present findings and potential long-term effects on child health and development, especially since prenatal exposure to PAHs has previously been associated with several adverse outcomes such as obesity, metabolic risk indicators, and altered immune and cognitive function later in life (Drwal et al., 2019). Furthermore, additional experimental studies are needed to explore the underlying modes of action for the sex-specific findings.

Author contribution

Syed Moshfiqur Rahman: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition; Annachiara Malin Igra: Formal analysis, Data curation, Writing – original draft, Writing – review & editing; Julie Y. Essig: Investigation, Writing – review & editing; Eva-Charlotte Ekström: Conceptualization, Writing – review & editing; Kristian Dreij: Writing – review & editing; Mercedes Trask: Writing – original draft, Writing – review & editing; Christian Lindh: Investigation, Writing – review & editing; Shams El Arifeen: Conceptualization, Writing – review & editing; Anisur Rahman: Conceptualization, Writing – review & editing; Annette M. Krais: Investigation, Writing – review & editing; Maria Kippler: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition

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.

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Appendix A. Supplementary data

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