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Associations of prenatal exposure to polycyclic aromatic hydrocarbons with pubertal timing and body composition in adolescent girls: implications for breast cancer risk

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Abstract

Background: While animal data support an association between prenatal exposure to endocrine disrupting chemicals (EDCs) and altered mammary gland development and tumorigenesis, epidemiologic studies have only considered a few classes of EDCs in association with pubertal growth and development in girls. Polycyclic aromatic hydrocarbons (PAH) are a class of EDCs that have not been rigorously evaluated in terms of prenatal exposure and pubertal growth and development in girls.

Objective: In a New York City birth cohort of Black and Hispanic girls (n=196; recruited 1998-2006), we examined associations of prenatal PAH exposure with self-reported age at growth spurt onset, breast development onset and menarche, and clinical measures of adolescent body composition including body mass index, waist-to-hip ratio, and body fat measured at ages 11-20 years.

Methods: We measured prenatal exposure to PAH using personal air monitoring data collected from backpacks worn by mothers during the third trimester of pregnancy (data available for all 196 girls) and biomarkers of benzo[a]pyrene-DNA adducts in umbilical cord blood (data available for

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Author Contributions

Author Perera designed the original birth cohort study and supervised the collection of the prenatal exposure measures. Author Terry designed and supervised the field activities of the follow-up study conducted in adolescent girls from the original birth cohort. Co-authors Kehm, Miller, Tehranifar, Rundle and Herbstman gave critical input throughout the adolescent field work and follow-up of girls. Authors Terry and Kehm designed the study's analytic strategy. First author Kehm implemented the study's analytic strategy, led the literature review, and prepared the tables, figures and text of the manuscript. Authors Oskar and Zeinomar contributed to the literature review and assisted with data collection and cleaning. All authors contributed to the interpretation of results and editing of the text.

106 girls). We examined associations of prenatal PAH with the timing of pubertal milestones and adolescent body composition (11-20 years) using multivariable linear regression models adjusted for race/ethnicity, household public assistance status at birth, and age at outcome assessment. We also fit models further adjusted for potential mediators, including birthweight and childhood body size (BMI-for-age z-score measured at 6-8 years).

Results: Girls in the highest versus lowest tertile of ambient exposure to PAH, based on a summary measure of eight carcinogenic higher-molecular weight non-volatile PAH compounds ($\Sigma 8$ PAH), had a 0.90 year delay in growth spurt onset (95% confidence interval (CI)=0.25, 1.55; n=196), a 0.35 year delay in breast development onset (95% CI=-0.26, 0.95; n=193), and a 0.59 year delay in menarche (CI=0.06, 1.11; n=191) in models adjusted for race/ethnicity and household public assistance at birth. The statistically significant associations for age at growth spurt onset and menarche were not impacted by adjustment for birthweight or childhood body size. No differences in BMI-for-age z-score, waist-to-hip ratio, or percent body fat were found between girls in the highest versus lowest tertile of ambient $\Sigma 8$ PAH. Results were similar when we evaluated benzo[a]pyrene-DNA adduct levels.

Discussion: Our results suggest that prenatal exposure to PAH might delay pubertal milestones in girls, but findings need to be replicated in other cohorts using prospectively collected data on pubertal outcomes.

Keywords

breast cancer risk; breast development; endocrine disrupting chemicals; menarche; polycyclic aromatic hydrocarbons; prenatal window of susceptibility; pubertal timing

Introduction

Animal data support an association between prenatal exposure to endocrine disrupting chemicals (EDCs) and altered mammary gland development and tumorigenesis (Fenton et al. 2006; Rudel et al. 2011). While some classes of EDCs are shown to accelerate mammary gland development in rodents, others delay development leading to a higher number of terminal end buds (Rudel et al. 2011). The morphological changes in mammary gland development, particularly the effects on terminal end buds, suggest the potential for functional outcomes such as altered pubertal timing, lactational insufficiency, preneoplasia, or increased susceptibility to carcinogens (Rudel et al. 2011). Yet epidemiologic studies have only considered a few classes of EDCs in association with pubertal growth and development in girls (Lee et al. 2019), which may ultimately impact breast cancer risk.

Polycyclic aromatic hydrocarbons (PAH) are a class of EDCs that have not been rigorously evaluated in terms of prenatal exposure and pubertal growth and development in girls. PAH are formed from incomplete combustion of hydrocarbons and are commonly found in particulate air pollution (IARC 1984; Santodonato et al. 1997; Zhang et al. 2016). PAH can cross the placental barrier, and previous epidemiologic studies suggest that the developing fetus may be 10 times more susceptible to PAH-induced DNA damage compared with the mother (Perera et al. 2005). There is mounting epidemiologic evidence linking PAH exposure to increased breast cancer risk (Rodgers et al. 2018), especially for women with

mutations in DNA repair genes (Crew et al. 2007; Shen et al. 2005, 2017; Terry et al. 2004). Yet most of the evidence associating PAH with breast cancer risk comes from studies examining biomarkers of PAH in adult women, such as PAH-DNA adducts in blood and PAH metabolites in urine. Only two studies have evaluated the association of PAH exposure in early life with subsequent breast cancer risk, with both studies measuring exposure in childhood (Nie et al. 2007; Shmuel et al. 2017). One population-based case-control study examined exposure to total suspended particulates (TSP), which is a measure of air pollution that includes PAH, and found that high ($>140 \mu\text{g}/\text{m}^3$) versus low ($<84 \mu\text{g}/\text{m}^3$) concentrations of TSP at birth was associated with increased breast cancer risk in postmenopausal women (odds ratio (OR) = 2.42, 95% confidence interval (CI) = 0.97, 6.09) (Bonner et al. 2005). This study was limited by the use of residential histories and retrospective collection of air monitoring data to evaluate exposure to TSP, as well as lack of direct measures of PAH such as from air monitoring data (TSP is a mixture of PAH and other, potentially carcinogenic, compounds) or biomarkers. Further, the intermediate pathways through which prenatal exposure increases breast cancer risk, such as altered pubertal growth and development, were not evaluated.

In this study, we tested the hypothesis that exposure to PAH during the prenatal window of susceptibility for breast cancer (Terry et al. 2019) is associated with timing of pubertal milestones, including growth spurt onset, breast development onset and menarche, as well as body composition in adolescent girls. We leveraged prospective data from the Columbia Center for Children's Environmental Health (CCCEH) birth cohort (Perera et al. 2002, 2003), and used two complementary approaches to measure prenatal exposure to PAH. We measured ambient levels of pyrene and eight other higher-molecular weight nonvolatile carcinogenic PAH during the third trimester of pregnancy using personal air monitoring data. We also measured biomarkers of benzo[a]pyrene (BaP)-DNA adducts in umbilical cord blood, which indicate both exposure to PAH and individual metabolic difference in detoxification (Herbstman et al. 2012).

Materials and Methods

Study sample

The CCCEH birth cohort was initiated to study the health effects of air pollution in a cohort of non-Hispanic Black and Dominican mothers and children living in a low-income area of New York City (Perera et al. 2002, 2003, 2006). From 1998-2006, women in their third trimester of pregnancy were recruited from prenatal clinics at New York Presbyterian and Harlem Hospitals, as well as satellite clinics. Further details on this birth cohort, including study eligibility and retention, are available elsewhere (Perera et al. 2002, 2006). In 2016, we enrolled 216 of the 285 mother-daughter pairs still active in the CCCEH birth cohort into a follow-up study through the Breast Cancer and the Environment Research Program (BCERP) consortia (Columbia-BCERP Study). For this analysis, 196 girls had complete questionnaire, anthropometric and prenatal air monitoring data. Girls were ages 11-20 years at enrollment into the Columbia-BCERP Study. Informed consent was obtained from girls who were 18 years or older at the Columbia-BCERP Study clinic visit. Informed consent was obtained from mothers of girls under age 18 years at the clinic visit, along with

informed assent from the daughters. This study was approved by the IRB at Columbia University.

PAH exposure assessment

Ambient PAH exposure.—Women wore a small backpack containing a personal air monitor for two consecutive days during the third trimester of pregnancy; the backpack was placed near the bed at night. The personal air sampling pumps operated continuously over this period, collecting vapors and particles $2.5\ \mu\text{g}$ in diameter on a pre-cleaned quartz microfiber filter and a pre-cleaned polyurethane foam cartridge backup. The samples were analyzed at Southwest Research Institute (San Antonio, Texas) for pyrene, a lower-molecule-weight semi-volatile PAH, and eight higher-molecular-weight nonvolatile carcinogenic PAH compounds including benzo[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, BaP, indeno[1,2,3-*cd*]pyrene, dibenz[*a,h*]anthracene, and benzo[*g,h,i*]perylene, as previously described (Tonne et al. 2004). For quality control, each personal monitoring result was assessed for accuracy in flow rate, time, and completeness of documentation.

BaP-DNA adducts.—Prenatal exposure to PAH was also assessed by level of BaP-DNA adducts present in peripheral umbilical cord blood mononuclear cells. BaP is widely used as a representative PAH because concentrations of individual PAH in urban settings are highly correlated (Perera et al. 2004). BaP-DNA adducts in extracted white blood cell DNA were analyzed using a high-performance liquid chromatography-fluorescence method, which detects BaP tetrols released after hydrolysis of DNA adducts during the sample preparation (Alexandrov et al. 1992; Herbstman et al. 2012). This method has a coefficient variation of 12%, and a lower limit of detection of 0.25 adducts per 10^8 nucleotides (Herbstman et al. 2012). BaP-DNA adduct measurements were available for 54% of the sample ($n=106$).

Prior research using the CCCEH birth cohort has found low correlation between PAH in air monitoring during pregnancy and BaP-DNA adducts in umbilical cord blood (Perera et al. 2004), and we found no correlation in our analysis (Spearman correlation (ρ) = 0.04, $P=0.70$). The lack of correlation is likely due to the fact that adducts not only reflect individual exposure, but also susceptibility to adduct formation and repair (Herbstman et al. 2012).

Outcome measures

Timing of pubertal milestones.—At the Columbia-BCERP Study clinic visit, girls self-reported by questionnaire their age at pubertal growth spurt onset (defined as growing taller faster than usual, growth of underarm hair, growth of pubic hair, or skin changes like pimples); breast development onset; and menarche. Girls were asked to report their age at each pubertal milestone using half-year intervals (e.g., 8.5 years). All 196 girls in the analysis reported having experienced onset of pubertal growth spurt and breast development, although three girls could not recall their age at breast development onset. Five girls reported having not yet had their first period.

Adolescent body composition.—Anthropometric measurements were collected at the Columbia-BCERP Study clinic visit when girls were ages 11-20 years. Using standardized

protocols, trained research staff took two measurements each of standing height (using a wall-mounted stadiometer), weight (using the Tanita HD-314 digital weight scale), waist and hip circumference (using a linen tape measure) and percent body fat by bioimpedance (using an Omron Handheld HBF-360C). If the two measurements differed by 10%, a third measurement was taken. The repeated anthropometry measurements (e.g., two measures of weight) were averaged for the analysis. The Centers for Disease Control (CDC) growth charts were used to calculate body mass index (BMI)-for-age z-scores (Kuczmarski et al. 2002). BMI-for-age z-scores were not calculated for two girls who were 20 years at assessment.

Statistical analysis

The 8 non-volatile PAH compounds were significantly intercorrelated (ρ values ranging from 0.45 to 0.94; all p -values < 0.001 by Spearman's rank) (Perera et al. 2003), and we therefore used a summary measure in our analysis ($\Sigma 8$ PAH). We analyzed pyrene separately because it is a semi-volatile PAH compound with markedly higher exposure levels in our sample compared with the individual non-volatile PAH compounds. We categorized these measures of ambient PAH ($\Sigma 8$ PAH and pyrene) into tertiles and evaluated associations with timing of pubertal milestones and adolescent body composition using multivariable linear regression models (all outcomes were modeled as continuous variables). We adjusted models for race/ethnicity (Dominican or Black/African American) and maternal-reported receipt of household public assistance at birth (yes/no). We considered other measures of socioeconomic status, including maternal education and household income at birth, but further adjustment for these measures did not change associations. Therefore, we excluded these variables from the final models for parsimony. We fit models further adjusted for potential mediators including continuous measures of birthweight (grams) and childhood BMI-for-age z-score (ages 6-8 years) defined by standard CDC growth charts, and we examined if these factors operate as effect modifiers rather than mediators of associations between prenatal PAH and pubertal timing. In our analysis of the pubertal timing outcomes, we compared models unadjusted and adjusted for age at Columbia-BCERP study clinic visit (when self-reported pubertal outcomes were assessed). This was done to evaluate whether associations might differ by age at clinic visit based on differential measurement error stemming from a longer period of recalled pubertal timing in older compared with younger girls. All models predicting adolescent body composition were adjusted for age at Columbia-BCERP study clinic, as these outcomes were clinically measured at the visit.

We then examined associations with BaP-DNA adducts categorized as non-detectable (< 0.25 per 10^8 nucleotides), detectable at a level equal to or below the sample median of 0.31 per 10^8 nucleotides, and detectable at a level above the sample median. We used inverse probability weights (IPW) to account for differences between the total sample ($n=196$) and the subsample of girls with umbilical cord blood adduct data ($n=106$). We predicted the inverse probability of having adduct data, given the covariates listed above (e.g., birthweight), age at pubertal milestones, adolescent body composition, and level of prenatal exposure to pyrene and $\Sigma 8$ PAH in ambient air.

Sensitivity analyses

We used multivariable quantile regression to evaluate associations beyond the mean level of the continuous outcomes (Wei et al. 2019). Inferences were consistent between quantile and linear regression models and so we present linear regression results for parsimony. We used multinomial logistic regression to evaluate the three pubertal milestones (onset of growth spurt, onset of breast development, and menarche) in combination. In this analysis, we dichotomized each puberty variable at the sample median and evaluated whether prenatal $\Sigma 8$ PAH was associated with being above the sample median age for one, two, or three pubertal milestones compared with being at or below the median age for all three. We conducted additional sensitivity analyses by restricting models to girls ≥ 15 years at the Columbia-BCERP Study clinic visit ($n=123$); to girls with a BMI <25 kg/m² at the visit ($n=110$); and to girls who were born in a non-smoking household ($n=130$). To further assess differential measurement error based on the age at which pubertal outcomes were recalled, we evaluated models that were adjusted for and stratified by the length of time between age at Columbia-BCERP Study clinic visit and self-reported age of pubertal events. In these models, we considered both unadjusted and age-adjusted measures of the puberty outcomes (age at interview was regressed on age at each pubertal event to obtain age-adjusted residuals).

We also examined models stratified by growth trajectories from birth to childhood (stable, rapid, and slow growth). This analysis was informed by a previous study that found the association between prenatal exposure to maternal smoking (one potential source of PAH exposure) and age at menarche was modified by postnatal growth patterns, with maternal smoking delaying age at menarche in girls with slow weight gain but accelerating age at menarche in girls with rapid weight gain (Houghton et al. 2018). Statistical significance was determined as $P<0.05$ for a two-sided hypothesis test. Analyses were conducted using Stata 15.1 (College Station, Texas) (Stata Corporation 2017).

Results

Sample characteristics

Mean age at the Columbia-BCERP Study clinic visit was 15.5 ± 2.2 years. Mean BMI-for-age z-score, waist-to-hip ratio, and percent body fat at the visit were 0.87 ± 1.1 , 0.75 ± 0.08 , and 29.9 ± 7.8 , respectively. Self-reported mean age at pubertal growth spurt onset, breast development onset, and menarche were 10.7 ± 1.9 years, 10.8 ± 1.7 years, and 11.6 ± 1.5 years, respectively, in the overall sample; the mean ages at each pubertal milestone by age at Columbia-BCERP Study clinic visit are provided in the Supplemental Materials (eTable 1). Self-reported pubertal timing measures were positively correlated (growth spurt-breast development $\rho = 0.57$, $P<0.001$; growth spurt-menarche $\rho = 0.59$, $P<0.001$; breast development-menarche $\rho = 0.46$, $P<0.001$). Birth year was negatively correlated with prenatal exposure to ambient $\Sigma 8$ PAH ($\rho = -0.26$, $P<0.001$), but not with ambient pyrene ($\rho = -0.07$, $P = 0.34$) or BaP-DNA adducts ($\rho = 0.10$, $P = 0.29$). Ambient levels of pyrene and $\Sigma 8$ PAH were positively correlated ($\rho = 0.29$, $P<0.001$). Descriptive characteristics of the study sample by levels of prenatal PAH exposure are available in Table 1. A comparison of

girls with and without umbilical cord blood data is provided in the Supplemental Materials (eTable 2).

Associations of prenatal PAH with timing of pubertal milestones

As shown in Table 2, after adjusting for race/ethnicity and household public assistance at birth, girls in the highest compared with lowest tertile of prenatal exposure to ambient $\Sigma 8$ PAH had a 0.90 year delay in growth spurt onset, which equates roughly with half of a standard deviation (SD) change from the sample mean (Model 1: $\beta = 0.90$, 95% CI = 0.25, 1.55). Further adjustment for birthweight and childhood BMI-for-age z-score did not appreciably alter the association (Model 2: $\beta = 0.93$, 95% CI = 0.29, 1.57), but further adjustment for age at Columbia-BCERP clinic visit reduced the association to a 0.73 year delay (Model 3: $\beta = 0.73$, 95% CI = 0.06, 1.41). Girls with BaP-DNA umbilical cord blood adduct levels above the median had a 0.79 year (95% CI = -0.13, 1.72) delay in growth spurt onset compared with girls with non-detectable adduct levels in the unweighted fully adjusted model and a 0.88 year (95% CI = 0.11, 1.64) delay in the IPW fully adjusted model. Age at onset of growth spurt was not associated with prenatal exposure to ambient pyrene (Supplemental Materials, eTable 3).

We found no difference in age at breast development onset between girls in the highest versus lowest tertile of ambient $\Sigma 8$ PAH in either the minimally adjusted model (Model 1: $\beta = 0.35$, 95% CI = -0.26, 0.95) or in the fully adjusted model (Model 3: $\beta = 0.07$, 95% CI = -0.56, 0.69). However, compared to girls with non-detectable BaP-DNA adduct levels in umbilical cord blood, girls with levels above the median had a 0.59 year (95% CI = -0.22, 1.40) delay in breast development onset in the unweighted fully adjusted model and a 0.74 year (95% CI = 0.03, 1.45) delay in the IPW fully adjusted model. Age at onset of breast development was not associated with prenatal exposure to ambient pyrene (Supplemental Materials, eTable 3).

In models unadjusted for age at Columbia-BCERP clinic visit, girls in the highest compared with lowest tertile of prenatal exposure to ambient $\Sigma 8$ PAH had a 0.60 year delay in menarche, which equates roughly with one-third of a SD change from the sample mean (Model 2: $\beta = 0.60$, 95% CI = 0.08, 1.11). After adjusting for age at Columbia-BCERP clinic visit, this association was attenuated to a 0.38 year delay in menarche and the association was no longer statistically significant (Model 3: $\beta = 0.38$, 95% CI = -0.15, 0.91). We found evidence of additive interaction between prenatal exposure to ambient $\Sigma 8$ PAH and birthweight in models predicting age at menarche ($P = 0.01$; Supplemental Materials eTable 4). As shown in Figure 1, being in the highest versus lowest tertile of $\Sigma 8$ PAH was associated with a 1.16 year (95% CI = 0.14, 2.18) delay in menarche for girls with a birthweight in the 0-25th percentile. Prenatal ambient $\Sigma 8$ PAH was not associated with age at menarche for girls with a birthweight above the 25th percentile. We did not find evidence of additive interaction by childhood BMI percentiles (Supplemental Materials eTable 4) or by childhood growth trajectories (Supplemental Materials eTable 5). Age at menarche was not associated with BaP-DNA adduct levels in umbilical cord blood (Table 2), or with prenatal exposure to ambient pyrene (Supplemental Materials, eTable 3).

In sensitivity analyses, we found generally consistent associations between prenatal ambient PAH and pubertal timing when we restricted the sample to girls 15 years at the Columbia-BCERP Study clinic visit (Supplemental Materials eTable 6); to girls with a BMI <25 kg/m² at the Columbia-BCERP Study clinic visit (Supplemental Materials eTable 7); and to girls born in a non-smoking household (Supplemental Materials eTable 8). Prenatal Σ 8 PAH was consistently associated with delayed pubertal timing in models adjusted for and stratified by the time interval between age at the Columbia-BCERP clinic visit and self-reported age of event (Supplemental Materials eFigure 1). When we evaluated all three pubertal outcomes in combination, we found that girls in the highest versus lowest tertile of prenatal exposure to ambient Σ 8 PAH had 9% (Model 2: OR = 1.09, 95% CI = 0.34, 3.51), 25% (Model 2: OR = 1.25, 95% CI = 0.42, 3.74), and 54% (Model 2: OR = 1.54, 95% CI = 0.51, 4.65) higher odds of being above the sample median age for one, two, or three pubertal milestones, respectively, compared with being at or below the median age for all three milestones (Supplemental Materials eTable 9).

Associations of prenatal PAH with adolescent body composition

Ambient Σ 8 PAH was not associated with BMI-for-age z-score (Model 1: β = 0.14, 95% CI = -0.26, 0.54), waist-to-hip ratio (Model 1: β = -0.14, 95% CI = -0.51, 0.22), or percent body fat (Model 1: β = 0.22, 95% CI = -2.61, 3.05) measured at the Columbia-BCERP Study clinic visit, when comparing girls in the highest versus lowest tertile of exposure (Table 3). No associations were found when we further adjusted for birthweight and childhood BMI-for-age z-score. We found no differences in body composition between girls with BaP-DNA cord blood adduct levels above the median compared with non-detectable levels in either the unweighted or IPW models. However, BMI-for-age z-score was higher for the middle compared with lowest tertile of ambient Σ 8 PAH (Model 2: β = 0.30, 95% CI = 0.04, 0.55), as well as for the middle compared to lowest level of BaP-DNA adducts in the unweighted (Model 2: β = 0.45, 95% CI = 0.11, 0.79) and IPW (Model 2: β = 0.46, 95% CI = 0.10, 0.83) models. Adolescent body composition at the Columbia-BCERP Study clinic visit did not vary by tertiles of ambient pyrene (Supplemental Materials eTable 10).

Discussion

We found evidence suggesting that prenatal exposure to PAH is associated with delayed puberty in girls. Specifically, we found that high (>2.95 ng/m³) versus low (<1.75 ng/m³) levels of ambient exposure to higher-molecular-weight nonvolatile PAH compounds (i.e., Σ 8 PAH) was associated with a 10.8-month delay in pubertal growth spurt onset and a 7.1-month delay in menarche after adjusting for race/ethnicity and household public assistance at birth. We also found that a high level of umbilical cord blood BaP-DNA adducts (>0.31 adducts/10⁸ nucleotides) was associated with a 6-month or longer delay in onset of both pubertal growth spurt and breast development. When we evaluated all three pubertal timing milestones in combination, girls exposed to high versus low levels of ambient Σ 8 PAH were more likely to be delayed for multiple pubertal events, although confidence intervals were wide for these estimates.

There are several known endocrine disrupting properties of PAH that could delay the timing of pubertal milestones. Several studies have shown that PAH compounds can act as antiestrogens and/or antiandrogens by interacting directly with estrogen receptors or androgen receptors (Bolden et al. 2017; Sahay et al. 2018). For example, benzo[a]anthracene, BaP, fluoranthene, and chrysene have been shown to inhibit androgenic activity (Boden et al. 2017; Vinggaard et al. 2000). PAH are also shown to bind to the aryl hydrocarbon (Ah) receptor, triggering induction of Ah-responsive genes and resulting in widespread anti-estrogenic responses including an increase in the metabolism of estradiol and a decrease in the nuclear estrogen receptor (Arcaro et al. 1999; Bolden et al. 2017; Chaloupka et al. 1993; Paulik et al. 2016).

This is the first study to prospectively examine associations of prenatal PAH (measured by personal air monitoring and umbilical cord blood adducts) with pubertal timing in girls. However, a previous study examined associations of prenatal exposure to particulate matter 10 μm in diameter (measured using monitoring stations located near residences during pregnancy) with pubertal timing in a large population-based birth cohort of boys and girls in Hong Kong. Consistent with our findings, this study found that prenatal exposure to particulate matter was associated with later pubertal stage at age 11 in girls (based on the highest Tanner stage for breast or pubic hair development). (Huang et al. 2017). No association was found in boys, which may support the endocrine-disrupting effects of air pollution in early life (Huang et al. 2017). In contrast, a US-based cohort study found that higher traffic exposure during childhood (ages 6-8 years) was associated with several months earlier onset of breast and pubic hair development in girls (McGuinn et al. 2016). These contradictory findings may suggest that the relationship between environmental exposures and pubertal timing is dependent on the time window of exposure (e.g., prenatal versus early childhood).

Several prior studies have examined associations of maternal smoking during pregnancy with pubertal timing in daughters, with mixed results. While some studies have associated maternal smoking during pregnancy with accelerated pubertal onset in daughters, including earlier breast development (Brix et al. 2018; Maisonet et al. 2010), other studies have found no association (Fried et al. 2001; Windham et al. 2017). A 2015 meta-analysis of 17 epidemiologic studies concluded that prenatal exposure to maternal smoking is associated with accelerated menarche, but found strong heterogeneity of effects between birth years (Yermachenko et al. 2015). We previously found that age at menarche was accelerated in girls with rapid weight gain between birth and 4 years who were exposed to intrauterine maternal smoking and delayed in those with slow weight gain who were exposed to intrauterine maternal smoking (Houghton et al. 2018). These findings again suggest that the relationship between environmental exposures and pubertal growth and development is complex and likely dependent on the timing of exposures.

Although maternal smoking during pregnancy is one potential source of prenatal exposure to PAH, our findings are not directly comparable with the smoking literature because we considered PAH in isolation of the other chemicals found in cigarettes. Our cohort was restricted to girls whose mothers were non-smokers during pregnancy. We also conducted a sensitivity analysis restricted to girls born in non-smoking households ($n=130$), which

produced results consistent with our main findings. Our study thus provides novel insight into the impact of prenatal exposure to PAH on pubertal timing in girls, independent of other carcinogens found in cigarettes.

We did not find evidence of an association between prenatal PAH and adolescent (ages 11-20 years) body composition in girls, including measures of BMI-for-age z-score, waist-to-hip ratio, and percent body fat. Previous studies using the full CCCEH birth cohort of girls and boys have examined the association of prenatal exposure to ambient PAH with BMI-for-age z-scores at earlier ages in childhood (5-14 years) (Rundle et al. 2012, 2019). These studies found a statistically significant positive association between prenatal exposure to ambient PAH and BMI z-scores at ages 5 years (highest versus lowest tertile: $\beta = 0.39$, 95% CI = 0.08, 0.70) and 7 years ($\beta = 1.93$, 95% CI = 0.33, 3.54) (Rundle et al. 2012). However, when BMI z-score trajectories from ages 5 to 14 years were examined across tertiles of prenatal PAH in the full CCCEH birth cohort of girls and boys, trajectories were found to converge as children aged, with no differences in BMI by age 11 years (Rundle et al. 2019). Our results suggest that this convergence in BMI trends across levels of prenatal exposure to PAH persists into late adolescence.

This current study has several notable strengths including the use of prospectively collected data from a birth cohort, as well as multiple measurements of prenatal PAH capturing both external dose (personal air monitoring backpacks) and biologically effective dose (BaP-DNA adducts) (Herbstman et al. 2012). We were limited by the use of self-reported measures of pubertal timing milestones, although prior research suggests that self-assessment is a valid and reliable method for evaluating sexual maturation in children (Baird et al. 2017; Chavarro et al. 2017; Gilger et al. 1991). For example, Gilger et al. found high test-retest reliability coefficients (range: 0.73-0.97) for recalled age at onset of pubertal milestones in a sample of college students (Gilger et al. 1991). This study also found that the magnitude of the test-retest and intraclass correlations for recalled timing of pubertal milestones in monozygotic versus dizygotic twins followed theoretical expectations for a trait demonstrating significant genetic influence (Gilger et al. 1991). Further, retrospective self-reports from family members across three different generations followed the expected secular trend of a cross-generational decrease in the age of sexual maturation (Gilger et al. 1991). However, this study by Gilger et al. sampled girls in the 1980s, when childhood obesity rates were much lower in the United States (Anderson & Butcher, 2006). Therefore, the accuracy of reporting may have been better in this previous study compared with more recent studies, given that the reliability of self-reported puberty has been found to be lower in obese girls compared with non-obese girls (Bonat, 2002). In our study, higher childhood BMI-for-age z-score, a well-established predictor of pubertal timing (Biro et al. 2013, 2018), was associated with earlier age at growth spurt onset ($P = 0.01$), breast development onset ($P = 0.05$) and menarche ($P = 0.03$), independent of BMI at the Columbia-BCERP Study clinic visit, supporting the validity of our measures.

The pubertal outcomes were reported at the Columbia-BCERP Study clinic visit after they occurred, and we found that age at the Columbia-BCERP Study clinic visit was positively correlated with self-reported age at growth spurt onset ($\rho = 0.21$, $P = 0.01$), breast development onset ($\rho = 0.19$, $P = 0.01$), and menarche ($\rho = 0.21$, $P < 0.01$) (see

Supplement Materials eTable 1). Therefore, we evaluated the impact of adjusting for age at clinic visit for the three pubertal outcomes (age at growth spurt onset, breast development and menarche). We found that associations were attenuated after adjusting for age at Columbia-BCERP Study clinic visit, although only age at menarche resulted in a different inference. Therefore, it is possible that differential measurement error accounts for some of the observed associations, especially given that the statistically significant beta coefficients were somewhat modest in magnitude (less than one SD from the mean). However, we also recognize that controlling for age at clinic visit, which comes after the pubertal events, could be an over adjustment, especially given that prenatal PAH exposure levels were shown to vary by birth year. We found no evidence to support that associations between prenatal PAH and delayed pubertal timing were driven by differential measurement error stemming from a longer time interval between age at the clinic visit and self-reported age at the pubertal event (Supplemental Materials eFigure 1).

We were also limited by the fact that personal air monitoring was only conducted over a 48-hour period during the third trimester of pregnancy, and this short period of exposure assessment may not be representative of long-term exposures throughout pregnancy. However, an indoor air monitoring sub-study conducted in the CCCEH cohort showed that residential indoor PAH exposure levels were fairly stable during the last 6-8 weeks of pregnancy, and home indoor PAH levels were found to be correlated with those in the personal air monitoring samples (Rundle et al. 2012). We also did not adjust for exposure to PAH during childhood in analyses, which could theoretically be correlated with the mother's exposure levels during pregnancy. Therefore, we cannot be certain that the prenatal period is the critical window of exposure, given that we might be indirectly observing the effects of early childhood exposures on subsequent growth and development trajectories (Rundle et al. 2012).

Conclusions

Our findings support the need for continued research on whether prenatal exposure to PAH is associated with delayed pubertal development in girls. In particular, epidemiologic studies using prospectively collected clinical measurements of pubertal timing and serial measurements of PAH exposure throughout childhood are warranted. This work will help to elucidate the impact of exposure to EDCs and other environmental pollutants during early life windows of susceptibility on breast cancer risk and other health outcomes across the life course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BaP	benzo[α]pyrene
BCERP	Breast Cancer and the Environment Research Program
BMI	body mass index
CCCEH	Columbia Center for Children's Environmental Health
CI	confidence interval
EDCs	endocrine disrupting chemicals
IPW	inverse probability weights
PAH	Polycyclic aromatic hydrocarbons
SD	Standard deviation

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Figure 1.

Predicted Mean Age at Menarche by Tertiles of Prenatal Exposure to $\Sigma 8$ PAH in Ambient Air and Birthweight Percentiles for Girls from the Columbia Center for Children's Environmental Health (CCCEH) Birth Cohort in the Columbia Breast Cancer and the Environment Research Program (Columbia-BCERP) Study.

Beta coefficients (β s), 95% confidence intervals (CIs), and predicted means are estimated from linear regression models adjusted for age at Columbia-BCERP Study clinic visit, race/ethnicity and household public assistance at birth. Models were stratified by birthweight percentile categories of 0-25th percentile (n=53), 25-50th percentile (n=52), 50-75th percentile (n=45), and 75-100th percentile (n=38). The sample includes girls from the Columbia Center for Children's Environmental Health (CCCEH) Birth Cohort (recruited from a low-income area of New York City in 1998-2006) who were enrolled in the Columbia Breast Cancer and the Environment Research Program (Columbia-BCERP) Study in 2016. Girls were classified into percentiles of birthweight using standard growth charts from the Centers for Disease Control.

Table 1.

Characteristics of Girls from the Columbia Center for Children's Environmental Health (CCCEH) Birth Cohort in the Columbia Breast Cancer and the Environment Research Program (Columbia-BCERP) Study (N=196).

Characteristic	Tertiles of Maternal Exposure to Ambient Σ8 PAH during Pregnancy			Benzo[a]pyrene-DNA Adducts in Umbilical Cord Blood		
	Low Tertile (< 1.75 ng/m ³) n=65	Medium Tertile (1.75-2.95 ng/m ³) n=65	High Tertile (> 2.95 ng/m ³) n=66	Non-Detectable n=55	Median Level of 0.31 per 10 ⁸ Nucleotides n=26	> Median Level of 0.31 per 10 ⁸ Nucleotides n=25
Age at Columbia-BCERP Study clinic visit, years	14.6±2.2	15.6±2.1	16.2±2.0	16.4±2.0	14.7±2.2	16.2±1.8
<i>Measures self-reported by mother at enrollment</i>						
Race/ethnicity, n (%)						
Dominican	42 (33.6)	37 (29.6)	46 (36.8)	30 (47.6)	19 (30.2)	14 (22.2)
Non-Hispanic Black	23 (32.4)	28 (39.4)	20 (28.2)	25 (58.1)	7 (16.3)	11 (25.6)
Household public assistance at birth, n (%)						
Yes	29 (30.2)	33 (34.3)	34 (35.4)	31 (52.5)	12 (20.3)	16 (27.1)
No	36 (36.0)	32 (32.0)	32 (32.0)	24 (51.1)	14 (29.8)	9 (19.2)
<i>Measures obtained from medical record</i>						
Birthweight, grams	3,290.6±440.2	3,363.6±457.2	3,312.3±511.0	3,412.5±411.4	3,313.1±445.5	3,480.6±551.7
<i>Clinical measurements at childhood follow-up visit (ages 6-8 years)</i>						
BMI-for-age z-score	0.65±1.14	0.80±1.30	0.75±1.13	0.76±1.25	0.69±1.28	0.60±1.33
<i>Clinical measurements at Columbia-BCERP Study visit (ages 11-20 years)</i>						
BMI-for-age z-score	0.67±1.10	1.11±1.00	0.83±1.16	0.78±1.17	1.02±0.98	0.85±1.27
Waist-to-hip ratio	0.75±0.06	0.74±0.08	0.74±0.11	0.75±0.06	0.74±0.11	0.77±0.08
Percent body fat	29.1±7.2	31.0±7.7	29.7±8.3	29.9±8.1	29.6±8.1	31.1±9.0
<i>Measures self-reported by girl at Columbia-BCERP Study visit (ages 11-20 years)</i>						
Age at growth spurt onset, years	10.3±1.9	10.7±2.1	11.1±1.7	10.7±1.8	10.8±2.3	11.5±1.9
Age at breast development, years	10.6±1.6	10.6±1.9	11.0±1.7	11.0±1.9	10.5±1.8	11.6±1.4
Age at menarche, years	11.2±1.4	11.7±1.4	11.8±1.6	11.9±1.7	11.5±1.4	12.1±1.2

Note: BMI = body mass index; SD = standard deviation. P-values are reported from analysis of variance test for continuous measures and chi-squared test for categorical measures.

Table 2.

Linear Regression Results for the Association of Prenatal Exposure to PAH with Pubertal Timing in Girls from the Columbia Center for Children's Environmental Health (CCCEH) Birth Cohort in the Columbia Breast Cancer and the Environment Research Program (Columbia-BCERP) Study (N=196).

Teriles of Maternal Exposure to Ambient Σ8 PAH during Pregnancy				Benzo[a]pyrene-DNA Adducts in Umbilical Cord Blood			
				Unweighted Sample		Weighted Sample ^a	
	Low Tertile < 1.75 ng/m ³ β (95% CI)	Medium Tertile 1.75-2.95 ng/m ³ β (95% CI)	High Tertile > 2.95 ng/m ³ β (95% CI)	Non-Detectable Level β (95% CI)	Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)	Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)	Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)
Age at onset of growth spurt ^b							
Model 1 ^c	0.00 (ref.)	0.42 (−0.23, 1.07)	0.90 (0.25, 1.55)	0.00 (ref.)	0.19 (−0.74, 1.12)	0.80 (−0.13, 1.73)	0.00 (−1.02, 1.02)
Model 2 ^d	0.00 (ref.)	0.46 (−0.18, 1.11)	0.93 (0.29, 1.57)	0.00 (ref.)	0.10 (−0.82, 1.03)	0.79 (−0.13, 1.71)	−0.10 (−1.11, 0.90)
Model 3 ^e	0.00 (ref.)	0.34 (−0.32, 1.00)	0.73 (0.06, 1.41)	0.00 (ref.)	0.22 (−0.76, 1.20)	0.79 (−0.13, 1.72)	0.08 (−1.01, 1.17)
Age at onset of breast development ^f							
Model 1 ^c	0.00 (ref.)	−0.06 (−0.67, 0.55)	0.35 (−0.26, 0.95)	0.00 (ref.)	−0.60 (−1.45, 0.25)	0.62 (−0.23, 1.48)	−0.60 (−1.41, 0.21)
Model 2 ^d	0.00 (ref.)	−0.03 (−0.63, 0.57)	0.37 (−0.23, 0.97)	0.00 (ref.)	−0.67 (−1.49, 0.14)	0.59 (−0.22, 1.41)	−0.71 (−1.44, 0.02)
Model 3 ^e	0.00 (ref.)	−0.22 (−0.83, 0.38)	0.07 (−0.56, 0.69)	0.00 (ref.)	−0.51 (−1.37, 0.35)	0.59 (−0.22, 1.40)	−0.48 (−1.40, 0.43)
Age at menarche ^g							
Model 1 ^c	0.00 (ref.)	0.45 (−0.08, 0.98)	0.59 (0.06, 1.11)	0.00 (ref.)	−0.52 (−1.25, 0.21)	0.13 (−0.62, 0.88)	−0.64 (−1.30, 0.02)
Model 2 ^d	0.00 (ref.)	0.46 (−0.06, 0.98)	0.60 (0.08, 1.11)	0.00 (ref.)	−0.56 (−1.29, 0.16)	0.12 (−0.62, 0.86)	−0.69 (−1.38, 0.00)
Model 3 ^e	0.00 (ref.)	0.34 (−0.18, 0.85)	0.38 (−0.15, 0.91)	0.00 (ref.)	−0.38 (−1.14, 0.38)	0.09 (−0.64, 0.83)	−0.45 (−1.09, 0.18)

^aWeights were constructed based on the inverse probability of having umbilical cord blood adduct data given age at Columbia-BCERP Study clinic visit, race/ethnicity, household public assistance at birth, birthweight, childhood BMI-for-age z-score (6-8 years), age at growth spurt onset, age at breast development onset, age at menarche, adolescent BMI-for-age z-score (11-20 years), adolescent waist-to-hip ratio (11-20 years), adolescent percent body fat (11-20 years), and tertiles of prenatal exposure to Σ8 PAH and pyrene in ambient air.

^bSample size = 196 for models assessing Σ8 PAH in ambient air; sample size = 106 for models assessing umbilical cord blood adducts.

^cModel 1 is adjusted for race/ethnicity and household public assistance at birth.

^dModel 2 is further adjusted for birthweight and childhood BMI-for-age z-score (ages 6-8 years).

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Model 3 is further adjusted for age at Columbia-BCERP Study clinic visit.
Sample size = 193 for models assessing $\Sigma 8$ PAH in ambient air; sample size = 104 for models assessing umbilical cord blood adducts.
Sample size = 191 for models assessing $\Sigma 8$ PAH in ambient air; sample size = 104 for models assessing umbilical cord blood adducts.

Linear Regression Results for the Association of Prenatal Exposure to PAH with Adolescent Body Composition in Girls from the Columbia Center for Children's Environmental Health (CCCEH) Birth Cohort in the Columbia Breast Cancer and the Environment Research Program (Columbia-BCERP) Study (N=196).

Table 3.

	Teriles of Maternal Exposure to Ambient Σ8 PAH during Pregnancy				Benzo[a]pyrene-DNA Adducts in Umbilical Cord Blood			
	Low Tertile < 1.75 ng/m ³ β (95% CI)	Medium Tertile 1.75-2.95 ng/m ³ β (95% CI)	High Tertile > 2.95 ng/m ³ β (95% CI)	Non-Detectable Level β (95% CI)	Unweighted Sample Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)	Unweighted Sample Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)	Weighted Sample Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)	Weighted Sample Median Level of 0.31 per 10 ⁸ Nucleotides β (95% CI)
BMI-for-age z-score ^b								
Model 1 ^c	0.00 (ref.)	0.43 (0.04, 0.82)	0.14 (-0.26, 0.54)	0.00 (ref.)	0.44 (-0.14, 1.03)	0.09 (-0.46, 0.64)	0.40 (-0.13, 0.93)	0.10 (-0.52, 0.73)
Model 2 ^d	0.00 (ref.)	0.30 (0.04, 0.55)	0.09 (-0.17, 0.35)	0.00 (ref.)	0.45 (0.11, 0.79)	0.17 (-0.15, 0.48)	0.46 (0.10, 0.83)	0.16 (-0.16, 0.48)
Waist-to-hip ratio ^{e,f}								
Model 1 ^c	0.00 (ref.)	-0.13 (-0.49, 0.23)	-0.14 (-0.51, 0.22)	0.00 (ref.)	-0.11 (-0.59, 0.38)	0.14 (-0.32, 0.60)	-0.31 (-1.20, 0.57)	0.08 (-0.31, 0.47)
Model 2 ^d	0.00 (ref.)	-0.17 (-0.52, 0.18)	-0.16 (-0.52, 0.19)	0.00 (ref.)	-0.13 (-0.60, 0.33)	0.20 (-0.25, 0.64)	-0.36 (-1.31, 0.59)	0.12 (-0.26, 0.50)
Percent body fat ^g								
Model 1 ^c	0.00 (ref.)	1.74 (-1.02, 4.50)	0.22 (-2.61, 3.05)	0.00 (ref.)	1.01 (-3.17, 5.18)	1.28 (-2.67, 5.22)	1.03 (-3.04, 5.10)	1.60 (-2.88, 6.09)
Model 2 ^d	0.00 (ref.)	0.89 (-1.09, 2.88)	-0.34 (-2.37, 1.69)	0.00 (ref.)	1.37 (-1.39, 4.12)	1.87 (-0.73, 4.47)	1.74 (-1.24, 4.72)	2.04 (-0.67, 4.75)

^aWeights were constructed based on the inverse probability of having umbilical cord blood adduct data given age at Columbia-BCERP Study clinic visit, race/ethnicity, household public assistance birth, birthweight, childhood BMI-for-age z-score (6-8 years), age at growth spurt onset, age at breast development onset, age at menarche, adolescent BMI-for-age z-score (11-20 years), adolescent waist-to-hip ratio (11-20 years), adolescent percent body fat (11-20 years), and tertiles of prenatal exposure to Σ8 PAH and pyrene in ambient air

^bSample size = 194 for models assessing Σ8 PAH in ambient air; sample size = 106 for models assessing umbilical cord blood adducts.

^cModel 1 is adjusted for age at Columbia-BCERP Study clinic visit, race/ethnicity and household public assistance at birth.

^dModel 2 is further adjusted for birthweight and childhood BMI-for-age z-score (ages 6-8 years).

^eSample size = 196 for models assessing Σ8 PAH in ambient air; sample size = 106 for models assessing umbilical cord blood adducts.

^fWaist-to-hip ratio is standardized so that the beta coefficient for a one-unit change in exposure reflects a one standard deviation change in waist-to-hip ratio.

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Sample size = 196 for models assessing PAXH in ambient air; sample size = 106 for models assessing umbilical cord blood adducts.