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Prenatal exposure to polycyclic aromatic hydrocarbons and cognition in early childhood

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Ethical Approval

ECHO PATHWAYS research activities were approved by the University of Washington Human Subjects Division (#STUDY00000638).

CRediT authorship contribution statement

Bob Sun: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review and editing. **Erin R Wallace:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review and editing. **Yu Ni:** Formal analysis, Writing – review and editing. **Christine T. Loftus:** Conceptualization, Methodology, Writing – review and editing. **Adam Szpiro:** Methodology, Writing – review and editing. **Drew Day:** Methodology, Writing – review and editing. **Emily S. Barrett:** Writing – review and editing. **Ruby HN Nguyen:** Writing – review and editing. **Kurunthachalam Kannan:** Resources, Formal analysis. **Morgan Robinson:** Resources, Formal analysis. **Nicole R. Bush:** Funding acquisition, Writing – review and editing. **Sheela Sathyanarayana:** Funding acquisition, Writing – review and editing. **Alex Mason:** Funding acquisition, Writing – review and editing. **Shanna H. Swan:** Funding acquisition, Writing – review and editing. **Leonardo Trasande:** Funding acquisition, Writing – review and editing. **Catherine J. Karr:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – review and editing. **Kaja Z. LeWinn:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108009.

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Abstract

Background: Epidemiological evidence for gestational polycyclic aromatic hydrocarbon (PAH) exposure and adverse child cognitive outcomes is mixed; little is known about critical windows of exposure.

Objective: We investigated associations between prenatal PAH exposure and child cognition in a large, multi-site study.

Methods: We included mother–child dyads from two pooled prospective pregnancy cohorts (CANDLE and TIDES, N = 1,223) in the ECHO-PATHWAYS Consortium. Seven urinary mono-hydroxylated PAH metabolites were measured in mid-pregnancy in both cohorts as well as early and late pregnancy in TIDES. Child intelligence quotient (IQ) was assessed between ages 4–6. Associations between individual PAH metabolites and IQ were estimated with multivariable linear regression. Interaction terms were used to examine effect modification by child sex and maternal obesity. We explored associations of PAH metabolite mixtures with IQ using weighted quantile sum regression. In TIDES, we averaged PAH metabolites over three periods of pregnancy and by pregnancy period to investigate associations between PAH metabolites and IQ.

Results: In the combined sample, PAH metabolites were not associated with IQ after full adjustment, nor did we observe associations with PAH mixtures. Tests of effect modification were null except for the association between 2-hydroxynaphthalene and IQ, which was negative in males (β_{males} = −0.67 [95%CI:−1.47,0.13]) and positive in females ($\beta_{females}$ = 0.31 [95%CI: −0.52,1.13])($p_{interaction}$ = 0.04). In analyses across pregnancy (TIDES-only), inverse associations with IQ were observed for 2-hydroxyphenanthrene averaged across pregnancy (β = −1.28 [95%CI: −2.53,−0.03]) and in early pregnancy (β = −1.14 [95%CI:−2.00,−0.28]).

Significance: In this multi-cohort analysis, we observed limited evidence of adverse associations of early pregnancy PAHs with child IQ. Analyses in the pooled cohorts were null. However, results also indicated that utilizing more than one exposure measures across pregnancy could improve the ability to detect associations by identifying sensitive windows and improving the reliability of exposure measurement. More research with multiple timepoints of PAH assessment is warranted.

Keywords

Polycyclic aromatic hydrocarbons; Neurodevelopment; Prenatal

1. Introduction

Accumulating epidemiological evidence suggests that prenatal exposure to polycyclic aromatic hydrocarbons (PAHs), a prevalent environmental toxicant resulting from the incomplete combustion of fossil fuels and other organic materials, is associated with adverse neurocognitive development. Predominant sources of PAH exposure include inhalation of ambient air pollution, smoking, and from diet through consuming grilled or barbequed meats(Agency for Toxic Substances and Disease Registry (ATSDR), 1995). Neurodevelopmental deficits in children associated with prenatal PAH exposure have included differences in attention, behavior, and cognition(Jedrychowski et al., 2015; Perera et al., 2014). Hypothesized mechanisms for neurotoxic effects include disruption of pathways that regulate neuronal differentiation, synapse formation, and synapse plasticity(McCallister et al., 2008; Deanna D Wormley et al., 2004), epigenetic modifications (Herbstman et al., 2012), endocrine disruption(Takeda et al., 2004), oxidative stress and neuroinflammation(Saunders et al., 2006), and impairment of long-term potentiation of hippocampus, critical to learning and memory (D. D. Wormley et al., 2004).

Several previous studies have specifically investigated associations between prenatal PAH exposure and childhood IQ(Edwards et al., 2010; Perera et al., 2012, 2009). Two of these studies, conducted in New York City, and Krakow, Poland, demonstrated lower childhood IQ (Perera et al., 2009) or nonverbal reasoning ability (Edwards et al., 2010) associated with prenatal PAH exposure measured in persona. In contrast a third study in Chongqing, China of prenatal PAHs measured in cord blood showed no association with child IQ (Perera et al., 2012). Measures of prenatal PAH exposure via personal air monitoring have the benefit of capturing longer periods of exposure than PAHs measured in urine, are limited to airborne sources, and do not capture exposure by routes such as dietary intake. This is important, as diet is estimated to contribute up to 70–90% of total PAH exposure, but with substantial geographic and temporal variability(Agency for Toxic Substances and Disease Registry (ATSDR), 1995; Skupinska et al., 2004; Suzuki and ´ Yoshinaga, 2007). Furthermore, previous work largely aggregates measures of various PAH compounds into a single exposure assessment, whether by constructing a composite of PAH concentrations in air, or by measuring PAHs in cord blood at birth. This does not allow for evaluating associations of individual PAH metabolites, or co-exposure to multiple PAH metabolites, which may have different neurodevelopmental toxicities that are not apparent in single-pollutant models. Further, the use of a single exposure metric may be prone to misclassification error as it does not account for intraindividual variability and may not reflect patterns of exposure over pregnancy; nor does it allow for the exploration of windows of vulnerability to prenatal PAH exposure.

Another gap in the current literature is the limited research on child or pregnancy-related factors that might modify adverse associations between PAH and child cognition or other neurodevelopmental endpoints. Studies of prenatal exposures to similar toxicants such $PM_{2.5}$ and child IQ show differences in outcomes by child sex, with inverse associations more prominent in boys than girls (Chiu et al., 2016; Lertxundi et al., 2019). Brain development differs between males and females and sex hormones are believed to interact with the neuroendocrine and immune systems in modulating the fetus' response to stressors

(McCarthy et al., 2017). We also hypothesized that maternal body composition could interact with PAH exposure on fetal brain development. PAHs are lipophilic and accumulate in fatty tissue(Pastor-Belda et al., 2019), and studies of other lipophilic environmental contaminants demonstrate that they are transferred from adipose tissue to placenta (Kapraun et al., 2022), potentially exposing fetuses of women with higher body mass to higher exposure to PAHs even given the same level of environmental exposure.

Our study adds to the existing literature by estimating the associations between prenatal exposure to PAH and childhood cognition at age 4–6 years in a large, diverse, multi-site U.S. sample, with robust adjustment for potential confounders. We measured PAHs in mid-pregnancy urine, which captures all routes of PAH exposure. We hypothesized that higher prenatal PAH exposure would be associated with lower childhood IQ. We also use contemporary mixtures methods to estimate associations between mixtures of PAH metabolites and early childhood cognition. We assessed whether sex or pre-pregnancy body mass index modified associations between prenatal PAH and childhood IQ. Finally, in a subset of participants, we evaluated multiple time points of prenatal exposure to PAH in relation to childhood IQ to better estimate associations across pregnancy and to explore periods during which the fetus may be more susceptible to the impacts of PAH exposure.

2. Subjects and methods

2.1. Design and participants

The current investigation is part of the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) PATHWAYS Consortium, which pooled data from three pre-existing cohorts (LeWinn et al., 2022). Two cohorts of the ECHO PATHWAYS Consortium had mid-pregnancy PAH data and were included in this analysis: the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study, in Memphis, TN; and The Infant Development and Environment Study (TIDES) in San Francisco, CA, Minneapolis, MN, Rochester, NY, and Seattle, WA. Design, recruitment, and data collection for CANDLE and TIDES have been previously described(LeWinn et al., 2022). In brief, CANDLE enrollment of pregnant mothers occurred between 2006 and 2011. Participant follow-up included two prenatal study visits in mid and late pregnancy, biospecimen collection, and ongoing postnatal follow up of mothers and offspring. Mother-child pairs were followed prenatally and at regular intervals with clinic and home visits and telephone surveys, including clinic visits at approximately 4 years of age. The TIDES study recruited mothers between 2010 and 2012, with three prenatal study visits occurring in early, mid, and late pregnancy that included biospecimen collection and maternal surveys. Mother-child pairs were followed with questionnaires and a clinic visit at approximately 6 years of age. For the current study, CANDLE and TIDES participants were included if they were singleton births with a mid-pregnancy prenatal urinary PAH measure and a measure of IQ. We excluded children born less than 34 weeks of pregnancy, as well as children of mothers who smoked during pregnancy, as the relationship between children born prematurely and of mothers who smoke and child IQ is well-established in the literature (Herrmann et al., 2008; Soleimani et al., 2014). Maternal prenatal smokers were defined using self-reported smoking at any point in pregnancy, or had urinary cotinine

levels of greater than 200 ng/ml measured in mid or late pregnancy(Schick et al., 2017). The CANDLE study was approved by the institutional review board (IRB) of the University of Tennessee Health Sciences Center. TIDES was approved by the IRBs of the University of California, San Francisco, University of Minnesota, University of Rochester Medical Center, and University of Washington. The current analysis was conducted by ECHO PATHWAYS and was approved by the University of Washington IRB.

2.2. Exposure assessment

For CANDLE participants, urine collection occurred in mid-pregnancy, at a mean of 23.0 weeks (SD = 3.0). In TIDES, collection occurred once each in early-, mid-, and late-pregnancy, with mid-pregnancy samples used in the main analyses. Early pregnancy urinary measures were taken, on average, at 10.9 weeks' gestation (SD = 2.4); mid-pregnancy, at a mean of 20.8 weeks (SD = 3.8); and late-pregnancy, at a mean of 32.7 weeks (SD = 3.1). The methods for the extraction and processing of urinary hydroxy-PAHs (OH-PAHs) has been published previously(Guo et al., 2013). Briefly, extraction of OH-PAHs from urine was performed by liquid–liquid extraction followed by LC-MS/MS analysis (Guo et al., 2013). A Waters Acquity I-Class UPLC system (Waters; Milford, MA, USA) was used for chromatographic separation of PAHs, connected with an Acquity UPLC BEH C18 column (50 × 2.1 mm, 1.7 μm, Waters; Milford, MA, USA). The identification and quantification of PAH metabolites was performed on an ABSCIEX 5500 triple quadrupole mass spectrometer (Applied Biosystems; Foster City, CA, USA). The laboratory participated in several external quality assurance schemes to validate OH-PAHs assay successfully(Kannan et al., 2021). Individual urinary OH-PAH metabolites were included in this analysis if they were detected in at least 70% of the pooled TIDES and CANDLE study sample. These include 1-hydroxypyrene, 1- and 2-hydroxynaphthalene, 1/9-, 2-, and 3-hydroxyphenanthrene, and 2/3/9-hydroxyfluorene. In addition, we analyzed the molar sums of the hydroxynaphthalene and hydroxyphenanthrene metabolites for separate analyses. For OH-PAH measured below the limit of detection (LOD), we substituted the value of $\mathrm{LOD}/\sqrt{2}$.

2.3. Outcome

Child cognition was assessed using a validated measure of IQ in each cohort. In CANDLE, IQ was measured at approximately age 4 years using the Stanford-Binet Intelligence Scales, Fifth Edition (SB-5). The SB-5 included 10 subtests addressing five cognitive factors, including knowledge, fluid reasoning, quantitative reasoning, visual-spatial processing, and working memory. The IQ score in the SB-5 has excellent internal consistency and test–retest reliability (0.98 and 0.92, respectively)(Sattler, 2018). In TIDES, the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V), was administered at approximately 6 years(Raiford, 2018). For the WISC-V, IQ was derived from five subtests and included Vocabulary (Verbal Comprehension), Block Design (Visual Spatial), Matrix Reasoning (Fluid Reasoning), Digit Span (Working Memory), and Coding (Processing Speed). This combination represents one primary subtest from each index scale. IQ was calculated using the Tellegen and Briggs formula(Wechsler, 2003). Reliability and validity coefficients for this five-subtest version are 0.945 and 0.934 respectively (Sattler, 2018). This approach is comparable to prior studies(Mollon et al., 2018) which have utilized an abbreviated four-subtest version of the WISC-IV to assess child cognition. IQ scores from both the SB-5

and WISC-V were standardized to age in 3-month intervals to a mean score of 100 and a standard deviation of 15. While the specific tests used to capture the different cognitive domains may vary between SB-5 and WISC-V, performance on the instruments is highly correlated in typically developing children and they provide a standardized metric of overall cognitive performance (Roid, 2003). This approach is similar to prior studies which sought to examine child IQ across different instruments (Kullar et al., 2019; Lanphear et al., 2005; Ni et al., 2022). All examiners were thoroughly trained on the administration and scoring of the SB-5 or WISC-V by licensed psychologists. They participated in didactic instruction and guided practice, inter-rater reliability exercises, as well as weekly supervision by psychologists post-training. Overall reliability equal to or greater than 90% was required for the examiners to administer the measure independently. To identify potential data entry and scoring errors, we used logic checks (e.g., comparing raw scores to expected standardized scores) and reviewed outliers (i.e., scores significantly above or below the normative mean).

2.4. Other variables

Mothers reported on their own and their child's characteristics at prenatal and postnatal study visits, including child race, marital status, pre-pregnancy body mass index (BMI), maternal education attainment, household size, smoking and tobacco use during pregnancy and in the postnatal period, length of breastfeeding and family income. Family income was adjusted for regional price differences and inflation using established econometric methods from the U.S. Bureau of Economic Analysis (BEA)(Bureau of Economic Analysis, 2021). Medical record abstraction was used to collect information on infant sex, gestational age, and birthweight. Child secondhand tobacco smoke exposure was reported at the child's age 4–6 visit by maternal survey. Mothers were asked if they, the child's father, child's caregiver or care provider, or any other person living in the home with the child smoked (Yes/No). Child opportunity was measured using the Education and Social and Economic domains of the Child Opportunity Index, linked to maternal address at enrollment(Acevedo-Garcia et al., 2014). Maternal IQ was assessed at the age 4–6 visit using the Wechsler Abbreviated Scale of Intelligence (WASI) short form in both cohorts(Axelrod, 2002).

2.5. Statistical analysis

We described the demographics of the study sample overall as well as for the component CANDLE and TIDES cohorts. For descriptive summaries of OH-PAH metabolites, we standardized raw PAH values to the median study sample urinary specific gravity (SG) to account for urinary dilution, as follows:

$$PAH_{standard} = PAH_{raw} \times \frac{SG_{median} - 1}{SG_{observed} - 1}$$

Where $PAH_{standard}$ represents the standardized PAH value, PAH_{raw} represents the raw PAH value, SG_{median} represents the median specific gravity for the PAH metabolites, and $SG_{observed}$ represents the specific gravity for the PAH metabolite(Levine and Fahy, 1945). To assess the relationship between OH-PAH and IQ, we used multivariable linear regression, with separate models for each individual urinary metabolite (and the hydroxynaphthalene and hydroxyphenanthrene sums). Unless specified, all analyses were restricted to participants

without missing covariate data. Consistent with prior studies of urinary measures of prenatal PAH exposure and health outcomes(Ferguson et al., 2017) (Abid et al., 2014; Ferguson et al., 2017), we used raw, log-transformed OH-PAH metabolite concentrations in the multivariable linear regressions and an adjustment term for specific gravity was included to account for urinary dilution. Estimates and 95% CI were multiplied by ln (2) to calculate change in IQ per 2-fold increase in OH-PAH metabolite or parent compound sum. We took a staged approach to covariate adjustment to examine the influence of increasing adjustment on effect estimates. Potential confounders were determined *a priori* and defined as factors either directly or indirectly associated with prenatal PAH exposure and child IQ. We also identified selected precision variables with well-established relationships with child IQ although not likely to be associated with prenatal PAH exposure(Lewinn et al., 2020). Supplemental Fig. 1 shows a Directed Acyclic Graph for covariate selection and regression model development. A “minimal” model adjusted for study site (five categories), child sex (binary), child age (continuous), analysis batch (four categories), specific gravity (continuous), and an interaction between specific gravity and cohort to account for urinary dilution in each cohort’s OH-PAH measures. A “full” model, considered the main analysis, additionally adjusted for maternal education (four categories), maternal IQ (continuous), maternal age (continuous), marital status (binary, married or living as married vs. not), birth order (binary, first born vs. not), prenatal urinary cotinine (continuous), secondhand smoke exposure (binary, any vs. none), breastfeeding practice (binary, none vs. any), an interaction between household income and household count, each of the education and economics domains of the Child Opportunity Index (continuous), and child race (three categories). Race and ethnicity are conceptualized as important social constructs that, in this analysis, may capture unmeasured confounding due to exposures inequitably distributed by race and associated with both exposure to air pollution and EF (e.g., other toxic exposures like lead). Finally, an “extended” model additionally included gestational age (continuous) and birthweight (continuous), potential confounders that were not included in the full model because they may also lie on the causal pathway.

2.6. Sensitivity analyses

We conducted a number of sensitivity analyses. To evaluate alternate methods of accounting for urinary dilution, we standardized individual OH-PAHs as well as urinary cotinine to SG via the above formula rather than adjusting for SG as a covariate. We substituted below LOD OH-PAH values by censored likelihood multiple imputation (CLMIClick or tap here to enter text.)(Boss et al., 2019), using fixed effects *meta*-analysis rather than our primary pooling approach since differences in OH-PAH distributions across cohorts precluded fitting pooled CLMI models. To compare with our primary analysis’s exclusion of participants with missing covariates (i.e. complete case analysis), we imputed missing covariates using the method of multiple imputation by chained equations. To assess whether our results might be driven by heterogeneous associations across study sites or cohort, we performed a series of “full” regressions leaving one study site out in turn as well as repeating the main analyses by study cohort. To exclude the influence of participants with intellectual disability, who may have underlying neurodevelopmental differences linked to their level of cognition, we repeated our analyses after restricting our sample to participants with IQ above 70. As a final sensitivity analyses, we repeated analyses using more parsimonious adjustment models with

covariate adjustment comparable to prior cohort studies of prenatal PAH exposure and IQ in New York and Krakow (Edwards et al., 2010; Perera et al., 2009).

2.7. Secondary analyses

As a secondary analysis, we examined the associations between mixtures of OH-PAH metabolites and early childhood IQ by weighted quantile sum (WQS) regression(Carrico et al., 2015; Czarnota et al., 2015). OH-PAH levels were standardized to specific gravity via the formula above and transformed into deciles. We estimated weighted sums of individual OH-PAH metabolites to comprise the WQS score. To improve the sensitivity to detect the associations between the WQS score and IQ in multivariable linear regression models, we used bootstrap resampling methods to estimate index weights, using 1000 bootstrap samples for each analysis. We separately tested for positive or negative associations between the OH-PAH mixture and IQ. Estimates were adjusted for all covariates in the “full” model. To correct for potential Type 1 error, for any full sample WQS analysis that resulted in a 95% CI that did not include the null, we estimated a permutation test p-value (Day et al., 2022).

To investigate possible effect modification by child sex and maternal pre-pregnancy BMI, we used multivariable linear regression and added an interaction term between each modifier and OH-PAH metabolite. We estimated stratum-specific associations and corresponding 95% CI in each group and evaluated evidence of effect modification using p-values for interaction with a significance threshold of 0.05. Pre-pregnancy BMI was dichotomized as overweight/obese (≥25 kg/m2) vs. not (less than25 kg/m2). All estimates were adjusted for covariates in the “full” model.

2.8. Analyses across pregnancy

In the study sample from the TIDES cohort that had OH-PAH measures from all three periods of pregnancy, we examined associations of pregnancy-averaged OH-PAH exposures and IQ as well as estimating period-specific associations to explore the possibility of differing susceptibility to PAH exposure at different points in pregnancy. 1-Hydroxypyrene and 2/3/9-hydroxyfluorene were excluded from these TIDES-only analyses due to the high proportion of samples below LOD in the participant sample. We calculated pregnancy-average OH-PAH metabolite concentrations over the three periods of pregnancy and examined associations with IQ. In addition, for each of the three periods in pregnancy, we separately performed multivariable linear regression. We then examined OH-PAHs during each period in pregnancy with and without mutual adjustment for the other two periods to assess the independent association of OH-PAH at a particular window in pregnancy on childhood IQ. All regressions were performed with the “full” model described above.

All analyses were completed in R version 3.6.5 (R Development Core Team). *P*-values less than 0.05 were deemed statistically significant.

3. Results

The inclusion of enrolled CANDLE and TIDES participants in the analytic sample is illustrated in Fig. 1. Of the 2,403 participants enrolled in CANDLE and TIDES, 1,375 had both prenatal PAH measures and child IQ. After excluding 118 prenatal smokers and 34

children born prior to 34 weeks, the study sample comprised 838 CANDLE participants and 385 TIDES participants, for a total of 1,223. Participants in the analytic sample were similar across sociodemographic and maternal characteristics to the study population at enrollment (Supplemental Table 1). Descriptive characteristics of the analytic sample are presented in Table 1. Compared to child participants in CANDLE, those in TIDES were more often reported to be White (69% TIDES, 29% CANDLE), more likely to ever breastfeed (93% TIDES, 68% CANDLE), and less likely to be exposed to second hand smoke (2% TIDES, 25% CANDLE); they had higher income households on average ($105 k ± 58 k TIDES, $42 k ± 29 k CANDLE) with fewer household members. Mothers in TIDES were more educated (80% with some college or beyond, 46% in CANDLE), more likely to be married (87%, 59% CANDLE), and less often overweight or obese (44%, 61% CANDLE) (Table 1).

3.1. Distribution of prenatal urinary OH-PAHs and IQ

The distribution of OH-PAH values in the analytic sample and by cohort, standardized to SG, are described in Supplemental Table 2. The proportion of sample below LOD was highest for 1-hydroxypyrene and 2/3/9-hydroxyfluroene and lowest for 2-hydroxynapthalene (Supplemental Table 2). Urinary OH-PAH concentrations were higher in CANDLE than TIDES participants for all metabolites with the exception of 3-hydroxyphenanthrene and 1-hydroxypyrene (Supplemental Table 2). OH-PAHs exhibited moderate-to-strong pairwise correlations (Supplemental Table 3). Child IQ averaged 102.9 (standard deviation 15.6) in the pooled study sample.

3.2. Associations between urinary OH-PAHs and IQ

In minimally adjusted models, we observed significant inverse associations between several individual OH-PAH metabolites and IQ, most notably for 2-hydroxynapthalene, 1-hydroxypyrene, and 2/3/9-hydroxyfluorene. None of these associations persisted after full or extended adjustment for covariates and there were no meaningful differences between the results of the full and expanded adjustment models (Fig. 2).

3.3. Sensitivity analyses

Estimates were similar when OH-PAH values were standardized to specific gravity to account for urinary dilution rather than by including specific gravity as a covariate (Supplemental Fig. 2); 1-hydroxynaphthalene was positively associated with IQ ($\beta = 0.61$, 95% CI: 0.02, 1.22; $p = 0.04$). Other sensitivity analyses, including using CLMI to impute OH-PAH values below LOD, restricting the study sample to those with IQ over 70, imputation of missing covariates, leave-one-out analyses (exclusion of individual study sites one at a time) and by study cohort, and using more parsimonious adjustment were also similar to the main analyses (Supplemental Figs. 3–7).

3.4. Secondary analyses

In secondary analyses of OH-PAH mixtures using WQS, we did not observe any association, either positive or negative, between a mixture of OH-PAHs and IQ (Table 2). Estimates of effect modification by child sex are provided in Fig. 3. There was no evidence of association between OH-PAHs and IQ in either males or females and there was no statistical

evidence for effect modification by sex with the exception of 2-hydroxynapthalene, which was associated with lower IQ in males (β_{males} = −0.67, 95% CI: −1.5, 0.13), but not associated with IQ in females ($\beta_{females}$ = 0.31, 95% CI: −0.52, 1.1) (*p*-value for interaction = 0.04) (Fig. 3). We observed no evidence for effect modification by maternal pre-pregnancy BMI (Fig. 3).

3.5. Associations between urinary PAHs and IQ across pregnancy

There were 356 TIDES participants who had prenatal OH-PAHs measured in all three periods of pregnancy and IQ data in childhood. The distribution of prenatal PAH metabolite concentrations averaged over all of pregnancy and by period of pregnancy are provided in Supplemental Table 4. Intraclass correlation coefficients for PAH metabolites across pregnancy ranged from 0.29 to 0.47 (Supplemental Table 5). Associations between prenatal OH-PAH and IQ averaged across three periods of pregnancy are shown in Fig. 4. 2-hydroxynapthalene (β = −1.28 [95%CI: −2.53, −0.03]) and sum of hydroxynapthalenes (β = −1.56 [95%CI: −2.87, −0.26]) were associated with lower IQ in fully adjusted models (Fig. 4). Associations of prenatal OH-PAH exposure and IQ stratified by pregnancy period with and without mutual adjustment for exposure in the other periods are shown in Supplemental Figures 6 and 7, respectively. In period-specific analyses, we observed an association between early pregnancy 2-hydroxynaphthalene and lower IQ that persisted with full (β = −1.14 [95%CI: −2.00, −0.28]) and extended (β = −1.15 [95%CI: −2.01, −0.29]) adjustment for covariates (Supplemental Figure 6) but was not statistically significant after adjustment for OH-PAHs in the other two pregnancy periods (Supplemental Figure 7).

In additional secondary analyses we explored effect modification by child sex and pre-pregnancy BMI on pregnancy-averaged and early pregnancy associations of 2-hydroxynapthalene and IQ. While none of the tests for interaction were significant, patterns suggest interesting areas for future research in larger samples. We observed inverse associations between pregnancy-averaged 2-hydroxynapthalene and IQ in males (β_{males} = −1.59 [95% CI: −3.11, −0.06]) but not females ($\beta_{females}$ = −0.97 [95% CI: −2.84,0.89] ($p_{interaction}$ = 0.60). The pattern was similar for early pregnancy 2-hydroxynapthalene exposure, with lower IQ in males (β_{males} = −1.50 [95% CI: −2.55,−0.45]), but no association in females ($\beta_{females}$ = −0.68 [95% CI:−1.85,0.48]) and no significant interaction ($p_{interaction}$ = 0.24). Analyses of effect modification by pre-pregnancy BMI showed inverse associations between pregnancy-averaged 2-hydroxynapthalene and IQ in normal weight and underweight women (β_{normal}= −2.06 [95% CI:−3.73,−0.38]), with no evidence of associations in overweight or obese women (β_{obese} = −0.30 [95% CI: −1.98, 1.37]) and without evidence of interaction ($p_{interaction}$ = 0.12). Associations were similar for early pregnancy 2-hydroxynapthalene and IQ (β_{normal} = −1.67, [95% CI: −2.98, −0.35]; (β_{obese} = −0.75, [95% CI: −1.71, 0.21]) *pinteraction* = 0.21).

4. Discussion

To the best of our knowledge, this is the largest prospective study to date of prenatal PAH exposure and preschool and early school-aged cognition and the first to examine associations using exposure measures across three windows of pregnancy. For our primary

analyses, we examined associations of mid-pregnancy OH-PAH and IQ using a multi-center pooled cohort, taking advantage of a relatively large and diverse sample spanning several regions of the U.S. In this pooled sample, we did not observe evidence of associations between individual OH-PAH metabolites nor OH-PAH mixtures with child IQ. Moreover, we did not observe evidence of effect modification by child sex or maternal obesity, with the exception of potential sex-specific associations of 2-hydroxynapthalene, which was associated with lower IQ in boys but not girls.

In secondary analyses, we leveraged the availability of multiple OH-PAH measures across pregnancy in the smaller cohort, TIDES, to address two specific gaps in the existing literature: 1) potential measurement error resulting from single time point OH-PAH assessment, and 2) examination of sensitive periods during pregnancy. OH-PAH metabolites in a spot urine sample reflect exposure only in the hours prior to urine collection, due to the short half-lives of OH-PAHs(Li et al., 2012). While it is standard for epidemiological studies to include a single measure of prenatal PAH exposure (Edwards et al., 2010; Perera et al., 2009), this approach is likely vulnerable to measurement error and may bias measured associations toward the null(Cathey et al., 2018). To address this limitation, we calculated pregnancy-average exposures using measures in early, mid and late pregnancy in a subset of our study sample with multiple OH-PAH measures available. These pregnancy-average OH-PAH metabolites should better approximate exposure across pregnancy. We observed that pregnancy-average 2-hydroxynapthalene as well as the sum of naphthalene mono-hydroxylated metabolites were both associated with lower IQ. If these reflect true adverse impacts of PAHs upon fetal neurodevelopment, it may be that such associations are more easily detectable by averaging multiple measures of PAHs across pregnancy than using a single pregnancy assessment. In addition, we used the multiple measures of OH-PAHs available in TIDES to explore evidence for sensitive windows of exposure. These analyses indicated that adverse associations between IQ and OH-PAH metabolites were most evident for early pregnancy exposures, in particular for 2-hydroxynapthalene. This suggests that early pregnancy may be a period of greater sensitivity, which is consistent with evidence for some other chemical exposures(Zhu et al., 2020). However, our study was not specifically designed to test sensitive periods of PAH exposure during pregnancy, which would require a larger sample size sufficiently powered to enable formal testing of differences across timing of exposure (Sánchez et al., 2011); thus, these preliminary findings need to be replicated in other study populations.

Epidemiological evidence of adverse associations between PAHs and child cognitive development has been somewhat inconsistent. In a New York City cohort of non-smoking Black and Dominican-American mothers, prenatal PAH exposure measured in personal air in the third trimester of pregnancy was associated with developmental delay in their children at age 3(Perera et al., 2006) and reduced IQ at age 5(Perera et al., 2009). In a second cohort of mother–child dyads in Krakow, prenatal PAH exposure measured by personal air in the second or third trimester of pregnancy was associated with lower nonverbal reasoning skills at age 5(Edwards et al., 2010). In contrast, a third prospective cohort of mother–child dyads in Chongqing, China showed no association between prenatal PAHs measured in DNA adducts and IQ at age 5, and associations of PAH with IQ only in the presence of interaction with environmental tobacco smoke(Perera et al., 2012). Likewise, a cross-sectional study

using data from the National Health and Nutrition Examination Survey found no evidence of associations between urinary PAH metabolites and the need for educational assistance in middle childhood, though their PAH measures were contemporaneous with their outcome rather than a reflection of the *in utero* environment(Abid et al., 2014).

There are several possible explanations for heterogeneity in the literature, including variability in magnitude of exposure between populations. For example, the ambient air PAH concentrations measured in the Krakow cohort were very high relative to measurements from other urban settings in Europe(Binková et al., 1995) and Canada (Nethery et al., 2012), and more than five times that observed in the New York cohort(Jedrychowski et al., 2005). Differences in the method used to measure PAHs (e.g., urine, cord blood, personal air), furthermore, preclude direct comparison of PAH concentrations across cohorts. The PAH metabolites captured in our urinary measures were limited to low molecular weight PAHs, which reflect both dietary and air pollution sources (Agency for Toxic Substances and Disease Registry (ATSDR), 1995). High molecular weight PAHs are largely excreted in feces (Ramesh et al., 2004), not urine, and nearly all of the high molecular weight PAHs measured in our study were excluded from analyses due to a large proportion of samples being below the limit of detection. The urinary OH-PAH metabolites concentrations measured in this study were similar to other studies of pregnant women and women participating in NHANES(Woodruff et al., 2011). The largely null findings of mid-pregnancy PAH in our full cohort could be explained by relatively low PAH exposures. The composition of prenatal PAH mixtures also varies across study regions and may lead to inconsistency across studies. For example, in the Chongqing cohort, the major source of PAH was a coal-fired power plant that operated the winter before child participants were born, which may have led to a substantially different profile of PAH exposure(Perera et al., 2012). In comparison, a major source of airborne PAHs in New York City is thought to be vehicular traffic, which may be more similar to the sources and thus the composition of PAH mixtures encountered in our cohort(Perera et al., 2009).

Between-study heterogeneity in results could also stem from differences in methodological approach. We observed that several individual OH-PAH metabolites were negatively associated with IQ in the full cohort analysis but only in the model with minimal covariate adjustment, and our associations were greatly attenuated with full covariate adjustment. The New York and Krakow studies(Edwards et al., 2010; Perera et al., 2009) utilized less robust adjustment models, including using maternal education alone as a proxy for socioeconomic status, while we controlled for multiple domains and levels of socioeconomic status. We considered whether the results of prior studies were affected by residual confounding; to explore this, we conducted additional sensitivity analyses utilizing similar covariate adjustment as in the New York and Krakow studies. Even with this less robust adjustment, we saw no evidence of associations between prenatal OH-PAH metabolites and IQ in our dataset, which suggests that covariate adjustment cannot entirely explain the discrepancies between studies.

Effect modification may also contribute to the inconsistency in findings across studies. Based on possible mechanisms for neurotoxicity of prenatal PAH, we hypothesized that associations may vary by participant characteristics, including infant sex and maternal

obesity. In both our full cohort and TIDES-only analyses, 2-hydroxynapthalene was associated with lower IQ in boys but not girls. This is notable as studies in animals and humans suggest that the neurodevelopmental consequences from environmental toxicant exposure differ between males and females(Gade et al., 2021). PAHs in particular are linked to neuroinflammation, (Saunders et al., 2006; Deanna D Wormley et al., 2004) which trigger sex-specific responses in the fetus,(McCarthy et al., 2017) and are theorized to underlie differences in the frequency and severity of neurodevelopmental disorders between sexes(McCarthy et al., 2017). PAHs also accumulate in fatty tissue (Pastor-Belda et al., 2019), potentially exposing fetuses of overweight or obese women to a greater burden of PAH exposure even at similar environmental exposures (Vizcaino et al., 2014). We saw no evidence for differences in associations by maternal obesity in the full cohort analyses. In our TIDES-only analyses we observed inverse associations with IQ for 2-hydroxynapthalene in normal and underweight women and not overweight or obese women, but without statistical evidence for effect modification. Given the mixed results and exploratory nature of some of these analyses, future studies that are well-powered to detect effect modification and with larger variation in exposure are needed to characterize the populations most vulnerable to PAH exposure.

Despite primarily null findings in this analysis and others, a growing body of toxicological evidence provides biological plausibility for neurotoxic effects of prenatal PAH exposure. A number of pathophysiological mechanisms have been proposed for how PAHs harm the developing brain. PAHs are transferred across the placenta, easily cross the blood–brain barrier, and are accumulated and metabolized in the brain(Rouet et al., 1981). PAH exposure is associated with endocrine disruption(Takeda et al., 2004) and alterations to global methylation, implying epigenetic modification (Herbstman et al., 2012), with subsequent effects on neurodevelopment. Toxicological studies also point to oxidative stress, suggesting that PAH metabolism increases intracellular reactive oxygen species and inhibits the brain antioxidant scavenging system(Saunders et al., 2006), as well as initiating p38MAP kinase pathways and activation of inflammatory microglial cells and bystander neuronal death(Dutta et al., 2010). Other suggested mechanisms include downregulation of developmental ionotropic glutamate receptor sub-unit expression, which is critical for synaptic formation and the maintenance of synaptic plasticity mechanisms during cortical and hippocampal development(D. D. Wormley et al., 2004; Deanna D Wormley et al., 2004).

There are important limitations to our study. Our primary analyses leveraged the large sample size of a multi-cohort sample but relied on a single measure of prenatal PAH exposure. As discussed above, this is an important limitation because urinary OH-PAH metabolites reflect exposure in approximately the prior 12 h(Jongeneelen et al., 1990) and have exhibited moderate to high intraindividual variability in some (Cathey et al., 2018) but not all(Dobraca et al., 2018) prior analyses of urinary PAHs measured repeatedly. Notably, we were able to reduce the measurement error associated with using a single timepoint in our analysis using our subsample of TIDES participants with three measures across pregnancy. However these three spot urinary PAH measures reflect exposure over a relatively short window of time and as a result limited our ability to further investigate window-specific effects. Second, we were interested in both the associations of individual PAH compounds as well as their potential effects as a mixture; we therefore had a large

number of prospectively defined analyses, increasing the opportunity for chance findings. A third possible limitation in our study sample is the pooling of two cohorts that have different demographics, average age at outcome assessment, and measures of IQ. Our "leave one site out" sensitivity analyses supported robustness of the study results to cohort and site inclusion or exclusion. Although the SB-5 and WISC-V IQ measures were standardized to age and estimates were adjusted for age at assessment, the children administered the WISC-V were older on average than those given the SB-5, which may have contributed to the differences in IQ scores, and we cannot exclude the possibility of residual confounding by child age. Fourth, all of our PAH measures were subject to left-censoring due to batch-specific LOD, which could be a source of bias in measured associations.(Hewett and Ganser, 2007). Our method of imputing PAH measures using the value of $\mathrm{LOD}/\sqrt{2}$ is a limitation as it centers all imputed values on a single value without variability as opposed to a true distribution of low exposures. It is reassuring that our results were not sensitive to using likelihood-based CLMI in place of the primary approach of substituting the value of $\mathrm{LOD}/\sqrt{2}$, but this is still a limitation since CLMI assumes a common distribution of PAHs across batches, which was not observed in our data (Supplemental Table 2). Finally, because we excluded children of mothers who smoked during pregnancy, our results are only generalizable to a non-smoking population.

In summary, this study represents the largest and most robustly adjusted epidemiological analysis of prenatal PAH exposure and childhood cognition, including examination of multiple measurements of PAH across time in a subsample. In our primary analysis of mid-pregnancy PAH exposure in the overall, multi-cohort sample, we observed no associations. However, in secondary analyses in the TIDES cohort, we found that average exposure across pregnancy and early pregnancy exposure to 2-hydroxynapthalene were each associated with lower IQ. Better-powered studies assessing multiple prenatal PAH measures as well as early pregnancy exposures to PAH are needed to confirm these findings and advance our understanding of PAH impacts on child neurodevelopment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data utilized for this study are not publicly available but de-identified data may be available on request, subject to approval by the internal review board and under a formal data use agreement. Contact the corresponding author for more information.

Abbreviations:

1nap	1-hydroxynaphthalene
2nap	2-hydroxynaphthalene
2phen	2-hydroxyphenanthrene
3phen	3-hydroxyphenanthrene
19-phen	1/9-hydroxyphenanthrene
239fluo	2/3/9-hydroxyfluorene
1pyr	1-hydroxypyrene
nap sum	sum of hydroxynaphthalenes
phen sum	sum of hydroxyphenanthrenes
95% CI	95% Confidence Interval
BMI	Body mass index
CLMI	Censored Likelihood Multiple Imputation
LOD	Limit of Detection
IQ	Intellectual Quotient
OH-PAH	Hydroxy-Polycyclic Aromatic Hydrocarbon
PAH	Polycyclic Aromatic Hydrocarbon
WISC-V	Wechsler Intelligence Scale for Children Fifth Edition
WQS	Weighted Quantile Sum Regression

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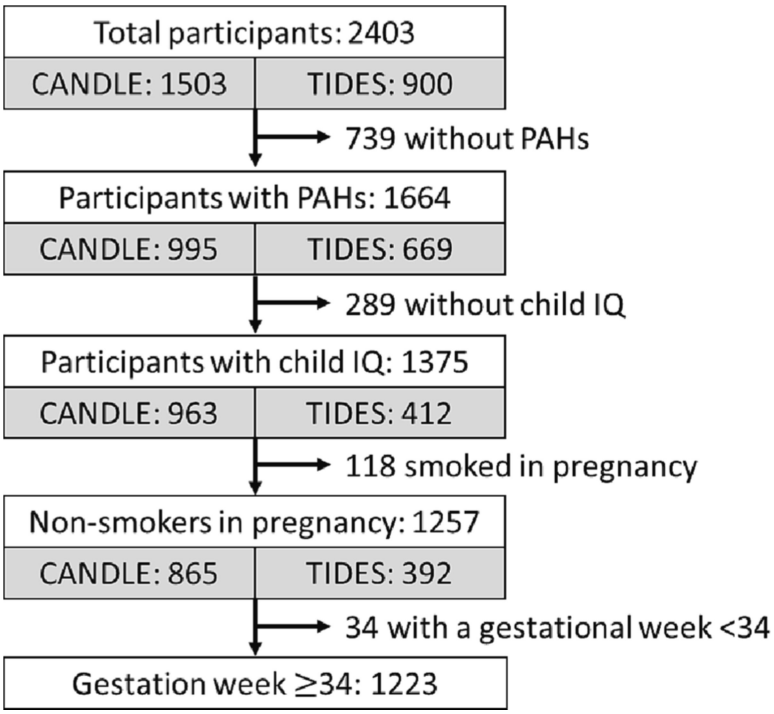

Fig. 1.
Study sample construction from constituent cohorts.

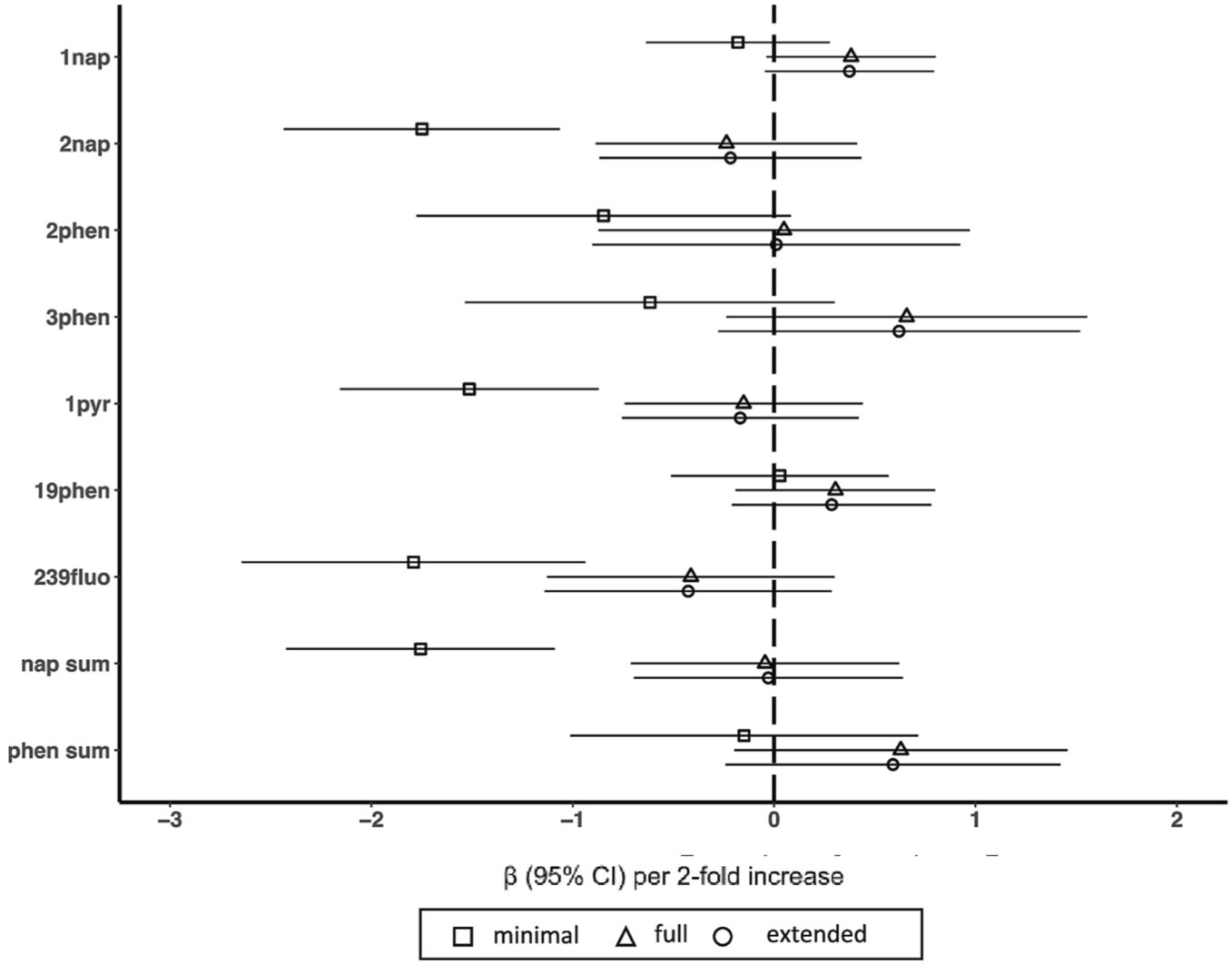

Fig. 2.

Associations between individual polycyclic aromatic hydrocarbons and early childhood IQ. Models represent effect estimates (symbols) and 95% confidence intervals (bars) from linear regressions. The *minimal adjustment model* includes study site (categorical, 5 categories), child sex (binary), child age (continuous), batch (categorical), specific gravity (continuous), and an interaction between specific gravity and cohort to account for urinary dilution in each cohort's OH-PAH measures. The *fully adjustment model* includes terms in the minimal adjustment model plus maternal education (categorical, 4 categories), maternal IQ (continuous), maternal age (continuous), marital status (binary, married or living as married vs. not), birth order (binary, first born vs. not), prenatal urinary cotinine (continuous), secondhand smoke exposure (binary, any vs. none), breastfeeding practice (binary, none vs. any), an interaction between household income and household count, child race, and each of the education and economics domains of the Child Opportunity Index (continuous). The *extended adjustment model* includes terms in the full adjustment model plus gestational age (continuous) and birthweight (continuous). All estimates represent effect per 2-fold increase in log OH-PAH. **Abbreviations: 1nap = 1-**

hydroxynaphthalene, 2nap = 2-hydroxynaphthalene, 2phen = 2-hydroxyphenanthrene, 3phen = 3-hydroxyphenanthrene, 19-phen = 1/9-hydroxyphenanthrene, 239fluo = 2/3/9-hydroxyfluorene, 1pyr = 1-hydroxypyrene, nap sum = sum of hydroxynaphthalenes, phen sum = sum of hydroxyphenanthrenes, 95% CI = 95% Confidence Interval.

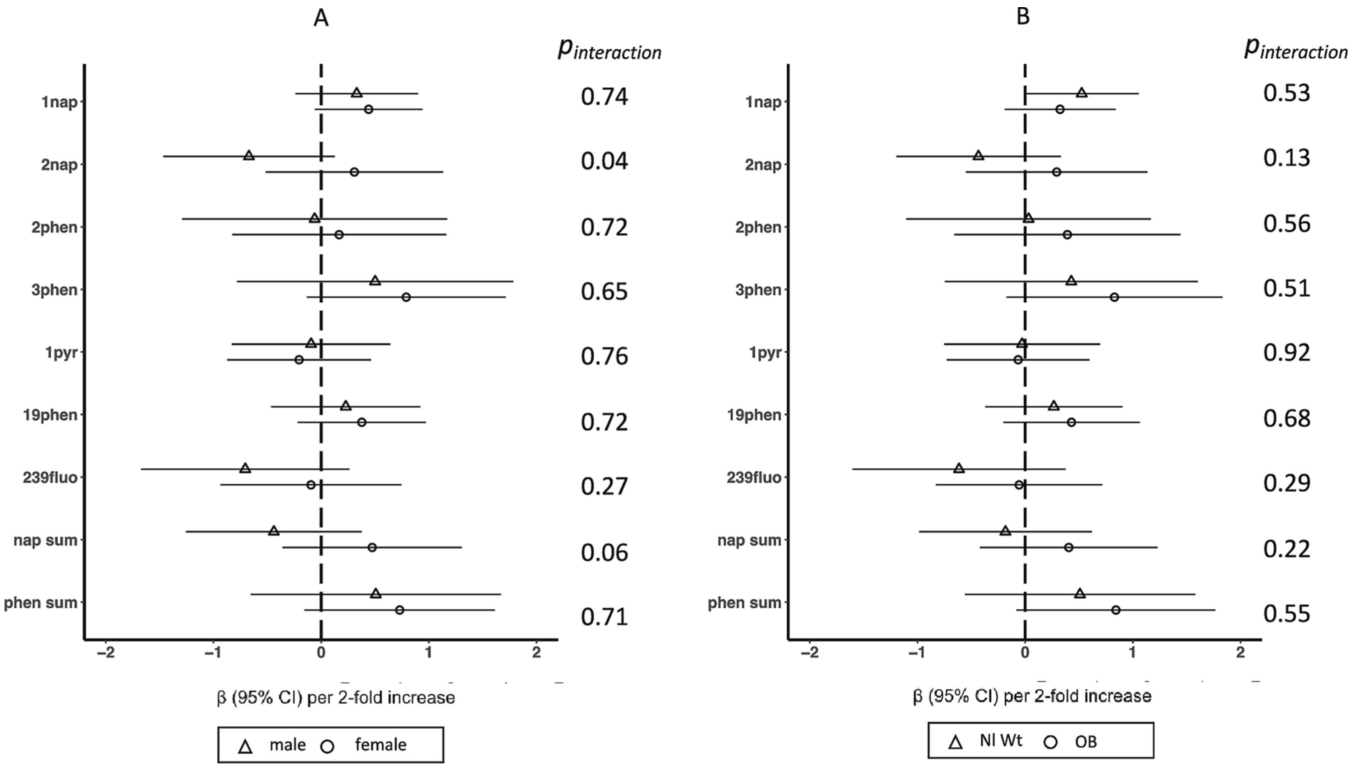

Fig. 3.

Associations between individual polycyclic aromatic hydrocarbons and early childhood IQ, stratified by A) child sex and B) pre-pregnancy body mass index. Models represent effect estimates (symbols) and 95% confidence intervals (bars) from linear regressions. The *full adjustment model* includes study site (categorical, 5 categories), child sex (binary), child age (continuous), batch (categorical), specific gravity (continuous), and an interaction between specific gravity and cohort, maternal education (categorical, 4 categories), maternal IQ (continuous), maternal age (continuous), marital status (binary, married or living as married vs. not), birth order (binary, first born vs. not), prenatal urinary cotinine (continuous), secondhand smoke exposure (binary, any vs. none), breastfeeding practice (binary, none vs. any), an interaction between household income and household count, child race, and each of the education and economics domains of the Child Opportunity Index (continuous). All estimates represent effect per 2-fold increase in log OH-PAH. Abbreviations: 1nap = 1-hydroxynaphthalene, 2nap = 2-hydroxynaphthalene, 2phen = 2-hydroxyphenanthrene, 3phen = 3-hydroxyphenanthrene, 19-phen = 1/9-hydroxyphenanthrene, 239fluo = 2/3/9-hydroxyfluorene, 1pyr = 1-hydroxypyrene, nap sum = sum of hydroxynaphthalenes, phen sum = sum of hydroxyphenanthrenes, 95% CI = 95% Confidence Interval, Nl Wt = Normal weight, OB = Obese.

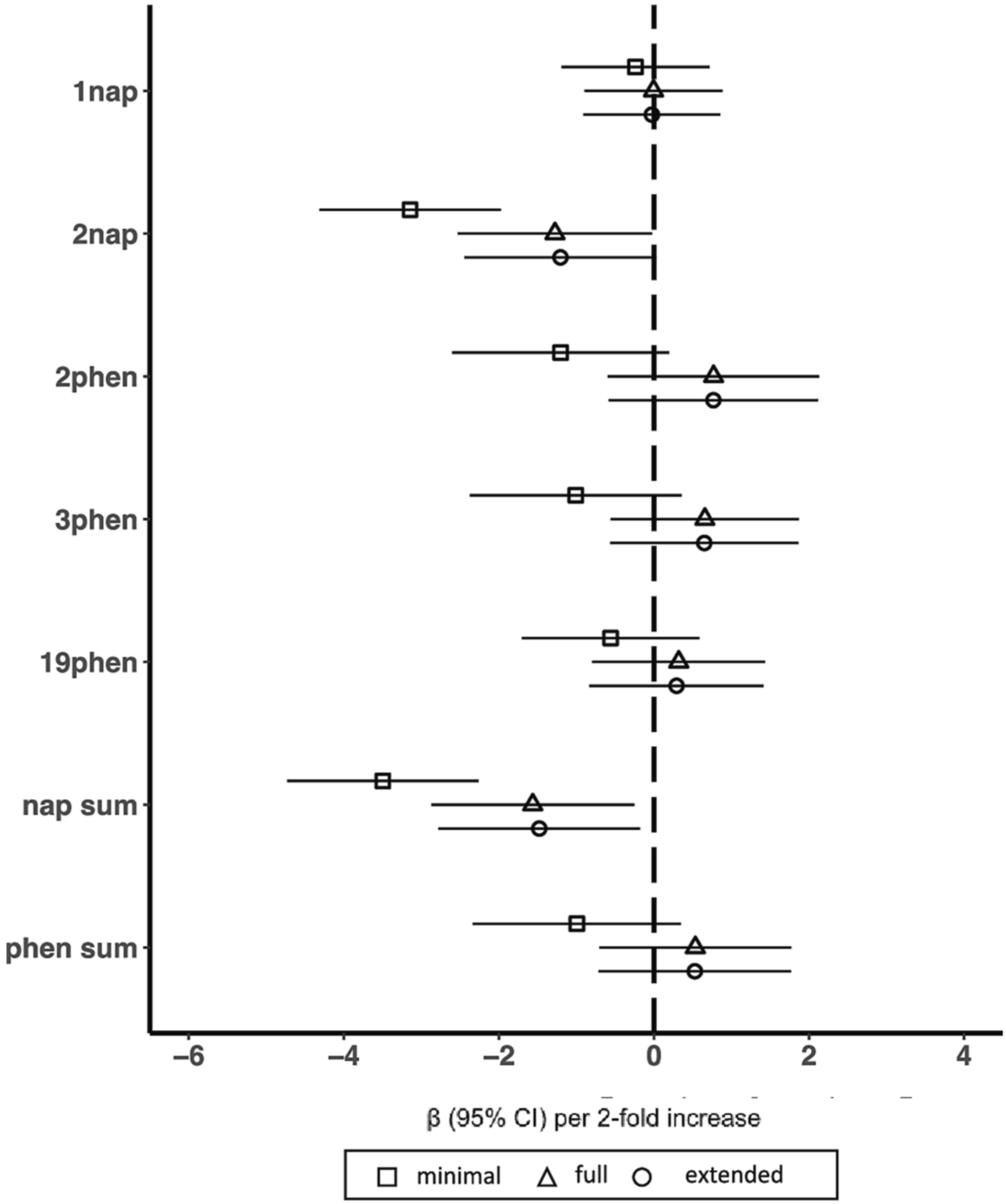

Fig. 4.

Associations of polycyclic aromatic hydrocarbons averaged across trimesters of pregnancy and early childhood IQ in the TIDES cohort. Models represent effect estimates (symbols) and 95% confidence intervals (bars) from linear regressions. The *minimal adjustment model* includes study site (categorical, 5 categories), child sex (binary), child age (continuous), batch (categorical), specific gravity (continuous), and an interaction between specific gravity and cohort to account for urinary dilution in each cohort's OH-PAH measures. The *fully adjustment model* includes terms in the minimal adjustment model plus maternal education

(categorical, 4 categories), maternal IQ (continuous), maternal age (continuous), marital status (binary, married or living as married vs. not), birth order (binary, first born vs. not), prenatal urinary cotinine (continuous), secondhand smoke exposure (binary, any vs. none), breastfeeding practice (binary, none vs. any), an interaction between household income and household count, child race, and each of the education and economics domains of the Child Opportunity Index (continuous). The *extended adjustment model* includes terms in the full adjustment model plus gestational age (continuous) and birthweight (continuous). All estimates represent effect per 2-fold increase in log OH-PAH. Abbreviations: 1nap = 1-hydroxynaphthalene, 2nap = 2-hydroxynaphthalene, 2phen = 2-hydroxyphenanthrene, 3phen = 3-hydroxyphenanthrene, 19-phen = 1/9-hydroxyphenanthrene, nap sum = sum of hydroxynaphthalenes, phen sum = sum of hydroxyphenanthrenes, 95% CI = 95% Confidence Interval.

Table 1

Demographic characteristics of the study sample.

Characteristic	Total (N = 1223)	Cohort	
		CANDLE (N = 838)	TIDES (N = 385)
Child age			
Mean (SD)	4.96 (±1.04)	4.32 (±0.48)	6.33 (±0.34)
Child sex			
Female	641 (52 %)	430 (51 %)	211 (55 %)
Male	582 (48 %)	408 (49 %)	174 (45 %)
Child race			
White	500 (42 %)	242 (29 %)	258 (69 %)
Black	572 (48 %)	527 (64 %)	45 (12 %)
Other	128 (11 %)	58 (7 %)	70 (19 %)
Birth order			
First born	541 (45 %)	339 (40 %)	202 (54 %)
Gestational week			
Mean (SD)	39.2 (±1.42)	39.1 (±1.30)	39.4 (±1.63)
Breastfeeding			
Ever breastfed	929 (76 %)	574 (68 %)	355 (93 %)
Postnatal secondhand smoking exposure			
Yes	214 (18 %)	206 (25 %)	8 (2 %)
Maternal age at delivery (year)			
Mean (SD)	28.5 (±5.95)	27.0 (±5.60)	31.7 (±5.33)
Region-, inflation-adjusted household income, $			
Mean (SD)	62,200 (±50,100)	42,400 (±29,300)	105,000 (±58,300)
Household counts			
2–3	271 (23 %)	186 (22 %)	85 (23 %)
4	497 (41 %)	313 (38 %)	184 (50 %)
5	257 (21 %)	193 (23 %)	64 (17 %)
>=6	173 (14 %)	140 (17 %)	33 (9 %)
Maternal education			
Less than high school	91 (7 %)	73 (9 %)	18 (5 %)
High school/GED	438 (36 %)	378 (45 %)	60 (16 %)
College/technical school	408 (33 %)	272 (32 %)	136 (36 %)
Graduate or Professional degree	281 (23 %)	114 (14 %)	167 (44 %)
Marital status			
Married/living as married	829 (68 %)	495 (59 %)	334 (87 %)
Single/living as single	393 (32 %)	342 (41 %)	51 (13 %)
Pre-pregnancy weight status			
Under/normal weight	535 (44 %)	326 (39 %)	209 (56 %)
Overweight/obese Maternal IQ	675 (56 %)	509 (61 %)	166 (44 %)
Mean (SD)	101 (±17.4)	96.6 (±16.4)	111 (±15.5)

Characteristic	Total (N = 1223)	Cohort	
		CANDLE (N = 838)	TIDES (N = 385)
2nd trimester urinary cotinine (ng/mL)			
Mean (SD)	2.85 (±12.2)	3.35 (±13.0)	1.77 (±10.2)
2nd trimester urinary specific gravity			
Mean (SD)	1.02 (±0.00749)	1.02 (±0.00706)	1.01 (±0.00795)
Child Opportunity Educational Index (Prenatal)			
Mean (SD)	−0.0242 (±0.0740)	−0.0442 (±0.0660)	0.0190 (±0.0718)
Child Opportunity Economics Index (Prenatal)			
Mean (SD)	−0.0513 (±0.265)	−0.106 (±0.264)	0.0660 (±0.227)
Recruitment site			
Memphis	838 (69 %)	838 (100 %)	–
San Francisco	96 (8 %)	–	96 (25 %)
Minneapolis	110 (9 %)	–	110 (29 %)
Rochester	91 (7 %)	–	91 (24 %)
Seattle	88 (7 %)	–	88 (23 %)
Child IQ at age 4–6 visit			
Mean (SD)	102.9 (±15.6)	101.2 (15.1)	106.6 (16.2)

Missing: child race (n = 23), birth order (n = 10), breastfeeding (n = 3), postnatal secondhand smoke exposure (n = 36), maternal age at delivery (n = 18), household income (n = 62), household count (n = 25), maternal education (n = 5), maternal IQ (n = 9), specific gravity (n = 3), Child Opportunity Educational Index (n = 24), Child Opportunity Economics Index (n = 24).

Table 2

Estimated effects and metabolite weights of OH-PAH matrix and early childhood IQ from WQS regression, by direction.

Direction	Estimate	SE	p-value	95% CI		Permutation p-value
Positive	0.39	0.20	0.05	−0.01	0.79	0.15
Negative	−0.18	0.24	0.45	−0.64	0.28	
Weight	**Direction**					
	Positive	**Negative**				
3phen	0.459	2nap	0.467			
19phen	0.282	1pyr	0.358			
1nap	0.227	239fluo	0.119			
239fluo	0.018	2phen	0.045			
1pyr	0.008	1nap	0.010			
2nap	0.006	19phen	0.002			
2phen	0.001	3phen	<0.001			

Models represent effect estimates and 95% confidence intervals from Weighted Quantile Sum Regression, adjusted for study site (categorical, 5 categories), child sex (binary), child age (continuous), batch (categorical), specific gravity (continuous), and an interaction between specific gravity and cohort to account for urinary dilution in each cohort's PAH measures, maternal education (categorical, 4 categories), maternal IQ (continuous), maternal age (continuous), marital status (binary, married or living as married vs. not), birth order (binary, first born vs. not), prenatal urinary cotinine (continuous), secondhand smoke exposure (binary, any vs. none), breastfeeding practice (binary, none vs. any), an interaction between household income and household count, child race, and each of the education and economics domains of the Child Opportunity Index (continuous).

Abbreviations: 1nap = 1-hydroxynaphthalene, 2nap = 2-hydroxynaphthalene, 2phen = 2-hydroxyphenanthrene, 3phen = 3-hydroxyphenanthrene, 19-phen = 1/9-hydroxyphenanthrene, 239fluo = 2/3/9-hydroxyfluorene, 1pyr = 1-hydroxypyrene, OH-PAH = Hydroxy-Polycyclic Aromatic Hydrocarbon, WQS = Weighted Quantile Sum.