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Prenatal concentrations of Perfluoroalkyl substances and early communication development in British girls

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ABSTRACT

Perfluoroalkyl substances (PFAS), found in many household products and classed as endocrine disrupting chemicals, can be transferred through the placenta and are associated with multiple developmental deficits in offspring. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), we investigated the association between intrauterine exposure to PFAS and early communication development in 432 mother-daughter dyads at 15 and 38 months of age. Concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) were measured in maternal serum collected during pregnancy. Early communication development was measured with the ALSPAC-adapted MacArthur Communicative Development Inventories for Infants and Toddlers. The infant questionnaire measured verbal comprehension, vocabulary comprehension and production, nonverbal communication, and social development. The toddler questionnaire measured language, intelligibility, and communicative subscores. Multivariable linear regression was used to examine associations between each PFAS exposure and each communication sub-scale score. The association between maternal PFAS concentrations and early communication development at 15 and 38 months of age varied by maternal age at delivery. In daughters of younger mothers (< 25 years of age), every 1 ng/mL of PFOS was associated with a 3.82 point (95% confidence interval (CI): −6.18, −1.47) lower vocabulary score at 15 months and a 0.80 point (95% CI: −1.74, 0.14) lower language score at 38 months. Prenatal exposure to select PFAS was positively and negatively associated with communication development among girls, with inconsistent pattern of association across all measured PFAS and endpoints.

1. Introduction

Perfluoroalkyl substances (PFAS) comprise a class of man-made endocrine disrupting chemicals (EDCs) involved in the production of fluoropolymers found in many household consumer products. PFAS are used to make protective coatings on textiles, furniture, food packaging, and nonstick cookware. Exposure to PFAS is common and can occur through water, indoor dust, and air [1]. PFAS are found in circulating blood, breastmilk, cord blood and can be transferred through the penetrable placenta during pregnancy [2–4]. The most commonly studied PFAS include perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA).

The risk of potential adverse health effects from PFAS has led to an industry phase out and replacement of some of these chemicals in the U.S. and Europe; however, PFOS is still commonly manufactured in China [5–7]. PFAS are a public health concern due to their persistent nature and ability to bioaccumulate in body tissue [5,8–10]. The estimated mean serum elimination half-life for PFOS, PFOA, and PFHxS is 5.4, 3.8, and 8.5 years, respectively [11].

Evidence suggests that prenatal exposure to various EDCs may be associated with certain cognitive and behavioral problems in childhood [12–17]. A fetus can be susceptible to developmental effects of PFAS associated with disruption of estrogenic activity [18,19].

PFOS and PFOA exposure during critical windows of development can affect neurodevelopment of a pregnant mother's offspring. In mice, neonatal PFOS and PFOA exposure causes altered levels of essential proteins needed for brain development, specifically affecting the

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hippocampus, which is primarily responsible for memory and learning [20]. In humans, the association between prenatal PFAS exposure and early cognitive development is unclear. A cross sectional analysis of data from the U.S. National Health and Nutrition Examination Survey (NHANES) has demonstrated that higher exposure to PFAS is associated with an increased odds of attention deficit/hyperactivity disorder (ADHD) in children 12–15 years of age [13]. However, two previous reports from the Taiwan Birth Panel Study and the Danish National Birth Cohort, have found inconsistent associations between prenatal PFOS and PFOA exposure and neurodevelopment. Specifically, using mother-reported structured questionnaires for children at 6 and 18 months of age, the Danish National Birth Cohort did not find a significant association between prenatal PFOS or PFOA exposure and neurodevelopment [21]. In contrast, using Comprehensive Development Inventory for Infants and Toddlers at 2 years of age, the Taiwan Birth Panel Study concluded that prenatal exposure to PFOS and PFOA may be negatively associated with neurodevelopment in children [12]. Additional research using longitudinal biomarker and cognitive function data to evaluate the association between early life exposure to PFAS and cognitive development in young children is warranted [22].

The current study aimed to investigate whether maternal concentrations of PFOS, PFOA, PFHxS, and PFNA during pregnancy was associated with deficits in development of communication skills at 15 and 38 months of age in British girls using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). We also examined whether the association between maternal PFAS exposure and communication development varied by maternal age at delivery or maternal education. Data used for this study was originally selected for a nested case-control study examining environmental effects on menarche [23].

2. Methods

2.1. Study Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth cohort that recruited pregnant women with expected delivery dates between April 1991 and December 1992 in three health districts of the former Avon region, Great Britain. The study enrolled 14,541 pregnant women and 14,062 children at birth. Recruitment methods have been described previously [24]. During pregnancy, mothers provided blood samples and participated in clinical assessments and questionnaires. Offspring have been followed since birth through completion of clinical assessments and questionnaires designed to assess environmental and genetic factors affecting health and development. The study website contains additional details for all available data through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

The present study used data from 448 mother-daughter dyads originally identified to participate in a nested case-control study to assess associations between prenatal EDC exposure and timing of menarche [23]. Cases and controls were chosen among all girls within the ALSPAC cohort who returned at least two puberty questionnaires between the ages of 8 and 13 years. Cases were defined as girls who attained menarche before 11.5 years and controls were defined as a random sample of girls who attained menarche at or after 11.5 years of age. Among the 448 mother-daughter dyads, 432 had measured maternal gestational blood concentrations for all studied PFAS and completed either the ALSPAC-adapted MacArthur Communicative Development Inventories (MCDI) for Infants at 15 months, the ALSPAC-adapted MCDI for Toddlers at 38 months, or both. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee, the Local Research Ethics Committees, and the Centers for Disease Control and Prevention (CDC) Institutional Review Board. Mothers provided written informed consent for participation in the study.

2.2. Data collection

An adaptation of the MCDI was used to assess early communication development at 15 and 38 months. The ALSPAC adaptation of the MCDI includes a selection of questions from the original MCDI and was modified to include words used in England. The MCDI is a parent reported questionnaire originally developed for clinicians to assess early language, non-verbal, and social development in children. The MCDI can be used to identify children with low language skills, and can potentially be useful in the assessment of children with autism spectrum disorders (ASD) [25,26]. Previous research has demonstrated that the MCDI assessment administered at 2 and 3 years of age can be used to predict developmental delays later in childhood [27].

At both time points, the MCDI questionnaire was completed by the mother and was returned via mail. At 15 months, the infant questionnaire generated 4 derived communication sub-scores (range of score): verbal comprehension (0 − 12), vocabulary comprehension and production (0–268), nonverbal communication (0 − 20), and social development (0 − 32). At 38 months, the toddler questionnaire generated 3 sub-scores (range of score): language (8–326), intelligibility (0–6), and communicative (4–12). The language sub-score at 38 months combines vocabulary, plurals, past tense, and word combination scores. Each increment of the score corresponds to a specific question or degree of communication development relating to the sub category. A higher sub-score indicates greater communication development.

Covariates were collected from medical records and questionnaires. Potential effect modifiers included maternal age at delivery (in years) and maternal education (< O level, O level, > O level). Potential confounders included parity (none, 1 or more); maternal smoking status during the first three months of pregnancy (any, none); maternal alcohol use during the first three months of pregnancy (any, none); adaptation of the Crown-Crisp Experiential Index (CCEI), an indicator of maternal anxiety, depression, and somaticism at 8 months post-delivery (continuous); and gestational age when the serum sample was collected (in weeks).

2.3. Laboratory Analysis

Concentrations of PFOS, PFOA, PFHxS, and PFNA were measured from maternal serum samples collected during pregnancy at a median gestational age of 15 weeks. Maternal serum concentrations were used as a proxy for fetal exposure. Blood samples were transferred under controlled conditions to the National Center for Environmental Health of the Centers for Disease Control and Prevention in the United States for analysis. A previous study has described methods used to measure analytes in the serum samples [28]. Limits of detection were 0.2 ng/mL for PFOS, 0.1 ng/mL for PFOA, 0.1 ng/mL for PFHxS, and 0.08 ng/mL for PFNA. Quality control measures to ensure calibration were implemented using standards, reagent blanks, and study samples. Precision of measurements for the analytes, as relative standard deviation, ranged from 8 to 13%.

2.4. Statistical analysis

To investigate the association between maternal PFAS concentrations and each early communication sub-score, stratum-weighted linear regression models were developed with the communication measures and PFAS concentrations as continuous variables. Crude associations between PFAS analytes and early communication development scores were first examined using univariate regression analysis. A set of potential confounding variables was selected a priori for consideration in multivariable regression models. The final model was achieved through backwards elimination of insignificant variables in a hierarchical manner [29]. The following variables were controlled for in the final model: parity, maternal age, maternal education, maternal smoking status during the first three months of pregnancy, and gestational