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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.

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Conflicts of interest statement

None declared.

Keywords

PFAS; Language; Communication skills; Child; Girls; ALSPAC

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 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 postdelivery (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 age at which the sample was collected. Analyses at 38 months also controlled for total CCEI score. Maternal alcohol consumption status during the first three months of pregnancy was considered as a potential confounder but not included in the final model because of lack of statistical significance. Maternal age and maternal education were selected a priori to be evaluated for effect modification with PFAS variables by testing appropriate cross-product interaction terms. To account for the original nested case-control study design, we weighted the sample to adjust for under-representation of the true number of girls without early menarche (weight for cases was 1 and for controls was 15.1). All statistical tests were 2-tailed; a p-value < 0.05 was considered statistically significant. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used to conduct all analyses.

3. Results

Table 1 presents demographic characteristics for 432 mother-daughter dyads included in our analysis. PFAS were detected in all maternal serum samples with PFOS present at the highest concentration, followed by PFOA, PFHxS, and PFNA (Table 1). Pearson correlation coefficients among the PFAS ranged from 0.69 for PFOS and PFHxS to 0.11 for PFNA and PFHxS, and coefficients between communication development outcomes at 15 and 38 months ranged from 0.34 for social development at 15 months and language development at 38 months and 0.02 for verbal comprehension at 15 months and intelligibility at 38 months (data not shown).

In the overall adjusted main effect models at 15 months of age (Table 2), positive associations were seen between PFOS, PFOA, PFHxS, and PFNA maternal concentrations and daughters' verbal comprehension, vocabulary comprehension and production, and nonverbal communication. The association between maternal PFAS concentrations and early communication development varied by maternal age at delivery. After stratification for maternal age at delivery, positive and negative associations were found by maternal age between maternal PFAS concentrations and vocabulary comprehension and production. For daughters whose mothers were < 25 years of age at the time of delivery, vocabulary score was 3.82 points (95% confidence interval (CI): −6.18, −1.47) lower for every ng/mL of PFOS, 11.39 points (95% CI: −22.76, −0.02) lower for every ng/mL of PFOA, 16.26 points (95% CI: −36.79, 4.27) lower for every ng/mL of PFHxS, and 36.29 (95% CI: −79.51, 6.92) points lower for every ng/mL of PFNA. In contrast, for daughters whose mothers were over 30 years of age, positive associations were observed between all measured PFAS and vocabulary score.

In the overall adjusted main effect models at 38 months of age (Table 3), positive and negative associations were seen between measured maternal PFAS concentrations and language, intelligibility, and communicative scores. For every ng/mL of PFOS, language score was lower by 0.29 point (95% CI: −0.54, −0.06) and intelligibility score was lower by 0.01 point (95% CI: −0.01, 0.00). In the overall adjusted main effect model, intelligibility score was associated with a 0.04 point (95% CI: −0.08, −0.01) lower score for every ng/mL of PFOA. The associations observed at 38 months between maternal PFAS concentrations and MCDI scores also varied by maternal age at delivery. In the overall adjusted main effect model, language score was associated with a 1.52 point (95% CI: −11.21, 8.16) lower score

for every ng/mL of PFNA. After stratification for maternal age at delivery, 1 ng/mL PFNA was associated with a 3.06 point (95% CI: −20.75, −14.62) lower language score among daughters of mothers aged < 25, and 14.10 point (95% CI: −27.10, −0.50) lower language score among daughters of mothers age between 25 and 30. However, among daughters with mothers aged > 30, language score was associated with a 5.62 point (95% CI: −15.20, 26.44) higher score for every ng/mL of PFNA. Overall, after stratified for maternal age at delivery, most associations between all measured PFAS and language development score were negative. Positive and negative associations were seen between measured PFAS and intelligibility and communicative scores.

4. Discussion

PFAS exposure could result in important deficits or delays in childhood cognitive development, but previous research in large cohorts lacks consistency to draw definitive conclusions. Our study examines communication indexes at two time points during early childhood that are important periods of communication development. Our study suggests that maternal serum concentrations of select PFAS are modestly associated with communication development among girls and did not show a consistent pattern of association across all measured PFAS and endpoints. Although a direct comparison cannot be made due to differences in the items, constructs, and format of the MCDI administered at the two time points, we found less apparent associations at 38 months of age when compared to findings at 15 months of age. We also observed that the association between select maternal PFAS concentrations and communication development varied by maternal age at delivery.

Several cohort studies have found differing associations between prenatal PFAS exposure and cognitive development in children. Fei and colleagues selected 1400 boy and girl children from the Danish National Birth Cohort to assess the association between prenatal PFOS and PFOA concentrations in maternal serum samples and developmental milestones in the offspring [21]. Motor (gross and fine motor functioning) and mental (cognitive functions, language, and social-personal) development of offspring at 6 and 18 months of age were measured through maternal reports. Although there appeared to be no evidence that prenatal exposure to PFOS or PFOA was associated with overall motor or mental development, the study found that offspring of women with higher serum PFOS concentrations scored lower on the language component of the assessment at 18 months [21]. Compared to serum maternal exposure concentrations in ALSPAC, mean maternal concentrations of PFOS and PFOA in plasma were higher in girls in the Danish National Birth Cohort, at 35.3 ng/mL (SD: 13.0) and 5.5 ng/mL (SD: 2.6), respectively.

Conversely, Chen and colleagues selected 239 children from the Taiwan Birth Panel to evaluate the association between prenatal exposure to PFOS and PFOA and childhood neurodevelopment at 2 years of age. The study found a negative association between PFOS concentrations in cord blood and overall neurodevelopment, which was measured based on combined scores from the cognitive, language, motor, social, and self-help domains of the Comprehensive Developmental Inventory for Infant and Toddlers [12]. However, the study found a null association between both PFOS and PFOA and the language domain of

neurodevelopment specifically. Compared to ALSPAC, mean maternal concentrations of PFOS and PFOA were lower in the cord blood samples of the Taiwan Birth Panel, at 7.4 ng/mL (SD: 2.5) and 2.6 (SD: 2.5), respectively.

In a hospital based birth cohort study (n = 514), Goudarzi and colleagues used data from the Hokkaido Study to examine associations between prenatal PFOS and PFOA concentrations and neurodevelopment at 6 and 18 months of age using the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) from the Bayley Scales of Infant Developmental Indices [30]. Although the study did not find any significant associations at 18 months of age, they found prenatal PFOA exposure to be negatively associated with MDI at 6 months of age in females after stratifying for sex. Compared to ALSPAC, median maternal serum concentrations of PFOS and PFOA were lower in the samples of the Hakkaido Study, at 5.7 ng/mL (95% CI: 4.4–7.4) and 1.2 (SD: 0.8–1.7), respectively.

Our study extends the previous literature by reporting associations between measures of language development with PFHxS and PFNA, two compounds not examined in previous studies. The concentrations of these chemicals were relatively low in comparison to PFOS and PFOA.

Additional research has examined the association between prenatal exposure to PFAS and neurodevelopment in school aged children with differing conclusions. Wang and colleagues found a negative association between prenatal PFNA exposure and verbal intelligence quotient at 8 years of age in the Taiwan Maternal and Infant Cohort Study (TMICS) (n = 120) [31]. In another study, Vuong and colleagues examined the association between prenatal PFAS exposure and executive function at 5 and 8 years of age using data from the Health Outcomes and Measures of the Environment Study (n = 256) [32]. Although no associations were found with prenatal PFOA exposure, prenatal PFHxS and PFOS exposure were found to have a negative association with executive function. Whereas, Stein and colleagues found no adverse associations between in utero PFOA exposure and neurobehavioral development in a sample of 320 children from the C8 Health Project at 6–12 years of age [33]. Due to contaminated drinking water, children from this study were highly exposure to PFOA with a median maternal concentration of 43.7 ng/mL (interquartile range: 11.7–110.8).

In the subset of the ALSPAC cohort studied here, the association between maternal PFAS exposure and early communication development at both 15 and 38 months varied by mother's age at delivery. It is possible that the influence of maternal age may be related to social factors such as differences in the amount of time spent one-on-one or in the types of activities older versus younger mothers performed with their children [34]. Several studies have reported that quantity of parent reported child-directed speech and a richer language experience is associated with language development in children, including language processing and vocabulary [35–38]. Socioeconomic status, parental knowledge of child development, and social context have been reported to influence the association between speech directed to the child and the child's language development [36,38].

We observed a less apparent association at 38 months when compared to 15 months, although direct comparison cannot be made due to the item and overall format differences between the two questionnaires. It is possible that earlier in childhood, mothers are more central to children's development of language and communication skills. However, as they get older, children are exposed to a variety of individuals and experiences, including daycare, that may contribute to that development [39]. Center care has been found to have a positive influence on cognitive and language development [39]. The additional influences during a child's development could be a potential explanation for the less apparent association between maternal PFAS concentrations and communication development in the sample of mother daughter dyads at 38 months of age when compared to 15 months of age.

The mechanisms behind PFAS' effects on child development and specifically language, are not well understood. In toxicologic studies of animals, neurologic and behavioral effects of neonatal PFAS exposure have been documented, suggesting that exposure to PFAS during critical windows of development can affect brain development [20,40,41]. In mice, in addition to behavior changes, such as disruption of habituation, neonatal exposure to PFOS and PFOA altered the susceptibility of the cholinergic system, potentially priming the brain for cognitive deficits later in life, and led to altered amounts of proteins essential for brain development (e.g. CAMKII, GAP-43, synaptophysis and tau) [20,40]. Similar effects were also seen in mice after neonatal exposure to PFHxS [41]. Additionally, PFAS may affect neurodevelopment through alteration of myelination [42]. In humans, EDCs can alter the epigenetics of development and the development of parts of the brain, such as the cerebral cortex, possibly leading to deficits in cognitive development [43].

There are potential limitations to the current analyses. Due to PFAS' long half-lives, a one-time serum sample was used as an indicator of exposure concentrations throughout pregnancy [11]. Models were adjusted to control for gestational age at sample collection to account for potential differences in PFAS exposure levels during pregnancy. Moreover, analyzing data from a population originally selected for an ancillary study may introduce bias. However, as previously reported, sample characteristics of mother-daughter dyads in the ancillary study were similar to those dyads enrolled in the overall cohort, and linear regression models were weighted to account for this sampling scheme (23). Additionally, due to the original objectives of the case-control study that provided PFAS concentrations, the current study was limited to communication development among girls, and did not address any potential associations among PFAS and neurodevelopment in boys. Similar to previous investigations, the results did not show a consistent pattern of association either across all PFAS measured or across all endpoints [12,21]. The clinical relevance of the effect sizes of maternal PFAS concentrations on the daughter's MCDI scores is unknown, however, low MCDI scores in early childhood could be indicative of developmental delays [25]. Lastly, this study is limited by sample size and the possibility that the findings may be explained by chance is an important consideration.

There are several strengths to the current analyses. The ALSPAC dataset includes numerous covariates collected under tightly regulated conditions for both mothers and offspring in the study. Our study was able to examine development of communication skills at two different time points in early childhood, a period close to the onset of vocabulary acquisition and a

period of increased mastery of vocabulary and communication skills. The PFAS were analyzed using well-characterized methodologies performed by laboratories at the National Center of Environmental Health at the CDC [28]. The same methods were used for analysis of samples from the 2003–2004 NHANES sample population [3]. Studying health effects of PFAS, specifically on neurodevelopment, is an important topic that warrants additional research, including PFAS' effects at later time points in childhood, and in boys.

In conclusion, maternal serum concentrations to select PFAS were both positively and negatively associated with early communication development among girls, although associations were less apparent at 38 months of age compared to 15 months of age. The effect between maternal PFAS exposure and communication development varied by maternal age at delivery. There was an inconsistent pattern of association across all measured PFAS and endpoints.

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References

1. Health UDo, Services H. Draft Toxicological Profile For Perfluoroalkyls. Agency for Toxic Substances and Disease Registry; Atlanta: 2009.
2. Apelberg BJ, Witter FR, Herbstman JB, Calafat AM, Halden RU, Needham LL, et al. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. Environ. Health Perspect. 2007:1670–1676. [PubMed: 18008002]
3. Calafat AM, Wong L-Y, Kuklenyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the US population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ. Health Perspect. 2007:1596–1602. [PubMed: 18007991]
4. von Ehrenstein OS, Fenton SE, Kato K, Kuklenyik Z, Calafat AM, Hines EP. Polyfluoroalkyl chemicals in the serum and milk of breastfeeding women. Reprod. Toxicol. 2009; 27(3):239–245. [PubMed: 19429402]
5. Paul AG, Jones KC, Sweetman AJ. A first global production, emission, and environmental inventory for perfluorooctane sulfonate. Environ. Sci. Technol. 2008; 43(2):386–392.
6. Xie S, Lu Y, Wang T, Liu S, Jones K, Sweetman A. Estimation of PFOS emission from domestic sources in the eastern coastal region of China. Environ. Int. 2013; 59:336–343. [PubMed: 23892226]
7. Xie S, Wang T, Liu S, Jones KC, Sweetman AJ, Lu Y. Industrial source identification and emission estimation of perfluorooctane sulfonate in China. Environ. Int. 2013; 52:1–8. [PubMed: 23266910]
8. Lau C, Butenhoff JL, Rogers JM. The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicol. Appl. Pharmacol. 2004; 198(2):231–241. [PubMed: 15236955]
9. Harbison, RD., Bourgeois, MM., Johnson, GT. Hamilton and Hardy's Industrial Toxicology. John Wiley & Sons; 2015.
10. Wang Z, Cousins IT, Scheringer M, Hungerbühler K. Fluorinated alternatives to long-chain perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkane sulfonic acids (PFSAs) and their potential precursors. Environ. Int. 2013; 60:242–248. [PubMed: 24660230]

11. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ. Health Perspect. 2007:1298–1305. [PubMed: 17805419]
12. Chen M-H, Ha E-H, Liao H-F, Jeng S-F, Su Y-N, Wen T-W, et al. Perfluorinated compound levels in cord blood and neurodevelopment at 2 years of age. Epidemiology. 2013; 24(6):800–808. [PubMed: 24036611]
13. Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in US children 12–15 years of age. Environ. Health Perspect. 2010; 118(12):1762. [PubMed: 20551004]
14. Ribas-Fito N, Sala M, Kogevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. J. Epidemiol. Community Health. 2001; 55(8):537–546. [PubMed: 11449010]
15. Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, van der Paauw CG, Tuinstra LGT, et al. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum. Dev. 1995; 41(2):111–127. [PubMed: 7601016]
16. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, et al. Endocrine disruptors and childhood social impairment. Neurotoxicology. 2011; 32(2):261–267. [PubMed: 21182865]
17. Birnbaum LS. Developmental effects of dioxins and related endocrine disrupting chemicals. Toxicol. Lett. 1995; 82:743–750. [PubMed: 8597137]
18. Newbold RR. Developmental exposure to endocrine-disrupting chemicals programs for reproductive tract alterations and obesity later in life. Am. J. Clin. Nutr. 2011; 94(6 Suppl):1939S–1942S. [PubMed: 22089436]
19. Inoue K, Okada F, Ito R, Kato S, Sasaki S, Nakajima S, et al. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. Environ. Health Perspect. 2004:1204–1207. [PubMed: 15289168]
20. Johansson N, Eriksson P, Viberg H. Neonatal exposure to PFOS and PFOA in mice results in changes in proteins which are important for neuronal growth and synaptogenesis in the developing brain. Toxicol. Sci. 2009; 108(2):412–418. [PubMed: 19211617]
21. Fei C, McLaughlin JK, Lipworth L, Olsen J. Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy. Environ. Health Perspect. 2008; 116(10):1391–1395. [PubMed: 18941583]
22. Roth N, Wilks M. Neurodevelopmental and neurobehavioural effects of polybrominated and perfluorinated chemicals: a systematic review of the epidemiological literature using a quality assessment scheme. Toxicol. Lett. 2014; 230(2):271–281. [PubMed: 24583043]
23. Maisonet M, Terrell ML, McGeehin MA, Christensen KY, Holmes A, Calafat AM, et al. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. Environ. Health Perspect. 2012; 120(10):1432–1437. [PubMed: 22935244]
24. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Smith GD, et al. Cohort profile: the Avon Longitudinal Study of Parents and hildren: ALSPAC mothers cohort. Int. J. Epidemiol. 2013; 42(1):97–110. [PubMed: 22507742]
25. Heilmann J, Weismer SE, Evans J, Hollar C. Utility of the MacArthur—Bates Communicative Development Inventory in identifying language abilities of late-talking and typically developing toddlers. Am. J. Speech Lang. Pathol. 2005; 14(1):40–51. [PubMed: 15966111]
26. Luyster R, Lopez K, Lord C. Characterizing communicative development in children referred for autism spectrum disorders using the MacArthur-Bates Communicative Development Inventory (CDI). J. Child Lang. 2007; 34(03):623–654. [PubMed: 17822142]
27. Luyster R, Qiu S, Lopez K, Lord C. Predicting outcomes of children referred for autism using the MacArthur–Bates Communicative Development Inventory. J. Speech Lang. Hear. Res. 2007; 50(3):667–681. [PubMed: 17538108]
28. Kuklenyik Z, Needham LL, Calafat AM. Measurement of 18 perfluorinated organic acids and amides in human serum using on-line solid-phase extraction. Anal. Chem. 2005; 77(18):6085–6091. [PubMed: 16159145]

29. Kleinbaum, DG., Kupper, LL., Morgenstern, H. Epidemiologic Research: Principles and Quantitative Methods. John Wiley & Sons; 1982.
30. Goudarzi H, Nakajima S, Ikeno T, Sasaki S, Kobayashi S, Miyashita C, et al. Prenatal exposure to perfluorinated chemicals and neurodevelopment in early infancy: the Hokkaido Study. Sci. Total Environ. 2016; 541:1002–1010. [PubMed: 26473702]
31. Wang Y, Rogan WJ, Chen H-Y, Chen P-C, Su P-H, Chen H-Y, et al. Prenatal exposure to perfluroalkyl substances and children's IQ: the Taiwan maternal and infant cohort study. Int. J. Hyg. Environ. Health. 2015; 218(7):639–644. [PubMed: 26205657]
32. Vuong AM, Yolton K, Webster GM, Sjödin A, Calafat AM, Braun JM, et al. Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children. Environ. Res. 2016; 147:556–564. [PubMed: 26832761]
33. Stein, CR., Savitz, DA., Bellinger, DC. Epidemiology. Vol. 24. Cambridge, Mass: 2013. Perfluorooctanoate (PFOA) and neuropsychological outcomes in children; p. 590
34. Coon H, Fulker DW, DeFries J, Plomin R. Home environment and cognitive ability of 7-year-old children in the Colorado Adoption Project: genetic and environmental etiologies. Dev. Psychol. 1990; 26(3):459.
35. Weisleder A, Fernald A. Talking to children matters early language experience strengthens processing and builds vocabulary. Psychol. Sci. 2013; 24(11):2143–2152. [PubMed: 24022649]
36. Rowe ML. Child-directed speech: relation to socioeconomic status, knowledge of child development and child vocabulary skill. J. Child Lang. 2008; 35(01):185–205. [PubMed: 18300434]
37. Rowe ML. A longitudinal investigation of the role of quantity and quality of child-directed speech in vocabulary development. Child Dev. 2012; 83(5):1762–1774. [PubMed: 22716950]
38. Ramírez-Esparza N, García-Sierra A, Kuhl PK. Look who's talking: speech style and social context in language input to infants are linked to concurrent and future speech development. Dev. Sci. 2014; 17(6):880–891. [PubMed: 24702819]
39. Health NIoC, Network HDECCR. The relation of child care to cognitive and language development. Child Dev. 2000:960–980. [PubMed: 11016559]
40. Johansson N, Fredriksson A, Eriksson P. Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice. Neurotoxicology. 2008; 29(1):160–169. [PubMed: 18063051]
41. Viberg H, Lee I, Eriksson P. Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. Toxicology. 2013; 304:185–191. [PubMed: 23287389]
42. Fernandez M, Paradisi M, D'Intino G, Del Vecchio G, Sivilia S, Giardino L, et al. A single prenatal exposure to the endocrine disruptor 2, 3, 7, 8-tetrachlorodibenzop- dioxin alters developmental myelination and remyelination potential in the rat brain. J. Neurochem. 2010; 115(4):897–909. [PubMed: 20807317]
43. Fudvoye J, Bourguignon J-P, Parent A-S. Endocrine-disrupting chemicals and human growth and maturation: a focus on early critical windows of exposure. Vitam. Horm. 2014; 94:1–25. [PubMed: 24388185]

Table 1

Sample characteristics for mothers and daughters enrolled in ALSPAC[a] with maternal serum PFAS[b] concentrations and ALSPAC-adapted MCDI[c] sub-scores at 15 or 38 months of age (n = 432).

	N	Median	IQR[d]
Maternal PFAS exposure			
Perfluorooctane sulfonate (PFOS) (ng/mL)	432	19.8	15.0, 24.95
Perfluorooctanoate (PFOA) (ng/mL)	432	3.7	2.8, 4.8
Perfluorohexane sulfonate (PFHxS) (ng/mL)	432	1.6	1.2, 2.2
Perfluorononanoate (PFNA) (ng/mL)	432	0.5	0.4, 0.7
Adapted MCDI scores at 15 months			
Nonverbal communication score	419	15.0	13.0, 17.0
Verbal comprehension score	419	10.0	8.0, 12.0
Vocabulary comprehension and production score	419	87.0	62.0, 124.0
Social development score	420	18.0	14.5, 22.0
Adapted MCDI scores at 38 months			
Language score	400	314.0	298.5, 322.0
Intelligibility score	404	6.0	6.0,6.0
Communicative ability score	403	5.0	4.0, 6.0
Covariates			
Maternal CCEI[e] score at 8 months	405	8.0	5.0, 13.0
Gestational age at sample collection, weeks	432	15.0	10.0, 28.0
	N	%	
Maternal education			
Less than O level	83	19.21	
O level	138	31.94	
Greater than O level	196	45.37	
Missing	15	3.47	
Maternal age at delivery			
< 25 years	88	20.37	
25–29 years	163	37.73	
≥ 29 years	181	41.9	
Maternal alcohol consumption[f]			
Yes	223	51.62	
No	192	44.44	
Missing	17	3.94	
Maternal smoking status[f]			
Yes	98	22.69	
No	319	73.84	
Missing	15	3.47	
Parity			
0	205	47.45	

	N	Median	IQR[d]
1+	208	48.15	
Missing	19	4.4	

[a] Avon Longitudinal Study of Parents and Children.

[b] Perfluoroalkyl substances.

[c] MacArthur Communicative Development Inventories.

[d] Interquartile range.

[e] Crown-Crisp Experiential Index.

[f] During first three months of pregnancy.

Table 2

Regression coefficients (β) for the association between maternal PFAS serum concentration (ng/mL) and communication development scores in daughters at 15 months of age overall and by mother's age at delivery (< 25 years of age, 25–30 years of age, > 30 years of age).

	Verbal Comprehension		Vocabulary Comprehension and Production		Nonverbal Communication		Social Developmental	
	β	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
PFOS								
Overall[a]	0.03	(0.01, 0.05)*	0.02	(−0.39, 0.44)	0.02	(−0.01, 0.05)	0.02	(−0.03, 0.08)
< 25[b]	0.01	(−0.07, 0.10)	−3.82	(−6.18, 1.47)*	0.03	(−0.10, 0.17)	−0.09	(−0.34, 0.16)
25–30[b]	0.02	(−0.01, 0.05)	−0.10	(−0.64, 0.45)	0.04	(−0.01, 0.08)	0.01	(−0.07, 0.09)
> 30[b]	0.04	(0.01, 0.08)*	0.52	(−0.02, 1.07)	0.02	(−0.02, 0.07)	0.05	(−0.02, 0.12)
PFOA								
Overall[a]	0.24	(0.12, 0.36)	0.29	(−2.07, 2.64)	0.10	(−0.07, 0.27)	−0.06	(−0.36, 0.23)
< 25[b]	0.20	(−0.18, 0.58)	−11.39	(−22.76, −0.02)*	0.15	(−0.47, 0.77)	−0.53	(−1.69, 0.62)
25–30[b]	0.15	(−0.01, 0.31)	0.38	(−2.63, 3.39)	0.12	(−0.13, 0.37)	−0.06	(−0.51, 0.39)
> 30[b]	0.35	(0.15, 0.55)*	2.27	(−0.98, 5.52)	0.15	(−0.11, 0.42)	0.06	(−0.37, 0.48)
PFHxS								
Overall[a]	0.03	(0.00, 0.07)	0.35	(−0.32, 1.03)	0.02	(−0.03, 0.07)	0.05	(−0.04, 0.13)
< 25[b]	0.06	(−0.62, 0.73)	−16.26	(−36.79, 4.27)	0.29	(−0.82, 1.39)	1.02	(−1.03, 3.07)
25–30[b]	0.04	(0.00, 0.08)*	0.55	(−0.21, 1.32)	0.09	(0.03, 0.16)*	0.09	(−0.02, 0.21)
> 30[b]	0.01	(−0.06, 0.07)	0.17	(−0.87, 1.21)	−0.06	(−0.15, 0.02)	−0.02	(−0.15, 0.12)
PFNA								
Overall[a]	1.06	(0.31, 1.80)*	9.21	(−5.28, 23.70)	0.50	(−0.55, 1.56)	1.71	(−0.10, 3.51)
< 25[b]	0.68	(−0.74, 2.10)	−36.29	(−79.51, 6.92)	1.72	(−0.56, 4.01)	3.18	(−1.11, 7.47)
25–30[b]	0.05	(−1.17, 1.26)	−13.75	(−36.17, 8.68)	−1.69	(−3.55, 0.16)	−2.50	(−5.86, 0.85)
> 30[b]	1.77	(0.58, 2.96)*	31.32	(12.52, 50.11)*	1.76	(0.23, 3.30)	4.06	(1.63, 6.49)*

[a]Main effect model without interaction terms. Adjusted for parity, maternal age, maternal education, maternal smoking status, and gestational age at sample collection (n = 391).

[b]Stratified by mother's age at delivery. Model adjusted for parity, maternal education, maternal smoking status, and gestational age at sample collection (< 25 years of age: n =72; 25–30 years of age: n =151;> 30 years of age: n = 168).

* $p < 0.05$.

Table 3

Regression coefficients (β) for the association between maternal PFAS serum concentration (ng/mL) and communication development scores in daughters at 38 months of age overall and by mother's age at delivery (< 25 years of age, 25–30 years of age, > 30 years of age).

	Language		Intelligibility		Communicative	
	β	95% CI	β	95% CI	β	95% CI
PFOS						
Overall[a]	−0.29	(−0.54, −0.05)*	−0.01	(−0.01, 0.00)*	0.00	(−0.01, 0.01)
< 25[b]	−0.80	(−1.74, 0.14)	0.02	(0.01, 0.03)*	0.03	(−0.02, 0.08)
25–30[b]	−0.28	(−0.72, 0.16)	0.00	(−0.02, 0.01)	−0.01	(−0.02, 0.01)
> 30[b]	−0.30	(−0.62, 0.01)	−0.01	(−0.02, 0.00)*	0.00	(−0.02, 0.01)
PFOA						
Overall[a]	−0.83	(−2.21, 0.54)	−0.04	(−0.08, −0.01)*	−0.02	(−0.08, 0.04)
< 25[b]	−0.85	(−5.60, 3.90)	0.05	(−0.01, 0.10)	0.29	(0.03, 0.54)*
25–30[b]	−0.18	(−2.48, 2.12)	−0.03	(−0.10, 0.04)	−0.05	(−0.14, 0.05)
> 30[b]	−1.52	(−3.37, 0.33)	−0.06	(−0.11, −0.01)*	−0.03	(−0.11, 0.04)
PFHxS						
Overall[a]	0.17	(−0.26, 0.61)	0.00	(−0.01, 0.01)	−0.01	(−0.03, 0.01)
< 25[b]	−0.87	(−6.28, 4.54)	−0.05	(−0.11, 0.02)	−0.05	(−0.35, 0.26)
25–30[b]	0.23	(−0.41, 0.86)	0.01	(−0.01, 0.03)	−0.02	(−0.05, 0.00)
> 30[b]	−0.20	(−0.84, 0.45)	−0.01	(−0.02, 0.01)	0.01	(−0.02, 0.03)
PFNA						
Overall [a]	−1.52	(−11.21, 8.16)	0.02	(−0.23, 0.27)	0.39	(−0.01, 0.79)
< 25[b]	−3.06	(−20.75, 14.62)	0.23	(0.02, 0.44)*	1.32	(0.39, 2.25)*
25–30[b]	−14.10	(−27.71, −0.50)*	0.01	(−0.39, 0.40)	0.54	(−0.01, 1.08)
> 30[b]	5.62	(−15.20, 26.44)	−0.12	(−0.68, 0.44)	−0.51	(−1.34, 0.31)

[a]Main effect model without interaction terms. Adjusted for parity, maternal age, maternal education, maternal smoking status, gestational age at sample collection, and total maternal CCEI (n = 353).

[b]Stratified by mother's age at delivery. Model adjusted for parity, maternal education, maternal smoking, gestational age at sample collection, and total maternal CCEI (< 25 years of age: n = 65; 25–30 years of age: n = 130; > 30 years of age: n = 158).

* $p < 0.05$.