Hormones and Behavior xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Exposure to perfluoroalkyl substances during pregnancy and child behaviour at 5 to 9 years of age

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ARTICLE INFO

Keywords:
Behaviour
Child
Child development
Cohort study
Fluorocarbons
Prenatal exposure, delayed effects

ABSTRACT

We examined associations between prenatal exposure to perfluorohexane sulfonic acid (PFHxS), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), and perfluorodecanic acid (PFDA) - and child behaviour (SDQ-total) and hyperactivity (sub-scale) at 5–9 years of age in birth cohorts from Greenland and Ukraine.

Pregnancy serum samples (N = 1023) were analysed for perfluoroalkyl substances (PFASs) and categorised into tertiles and also used as continuous exposure variables. Problem behaviour and hyperactivity were assessed, using the Strength and Difficulties Questionnaire (SDQ) and categorised as normal/borderline and abnormal. Associations were analysed using multiple logistic and linear regression.

High compared to low prenatal PFHxS exposure was associated with 1.16 (95% confidence interval (CI): 0.08; 2.25) point higher SDQ-total (more problem behaviour) in Greenland and 0.80 (CI: 0.06; 1.54) point higher SDQ-total in the combined analyses, whereas no association was present in Ukraine alone. One natural log-unit increase in prenatal PFNA exposure was associated with 0.90 (CI: 0.10; 1.71) points higher SDQ-total in Greenland and 0.72 (CI: 0.13; 1.31) points higher in the combined analysis and no association in Ukraine. Prenatal PFAS exposure was unrelated to problem behaviour (abnormal SDQ-total). In the combined analysis, odds ratio (OR) (CI) for hyperactivity was 1.8 (1.0; 3.2) for one natural log-unit increase in prenatal PFNA and 1.7 (1.0; 3.1) for one natural log-unit increase in prenatal PFDA exposure.

Findings are compatible with weak effects on child behaviour of prenatal exposure to some PFASs although spurious results are not entirely unlikely. The associations were strongest in Greenland.

1. Introduction

Perfluoroalkyl substances (PFASs) are persistent man-made chemicals with numerous industrial applications such as fire suppressants in fire extinguishers, and non-stick coatings in packaging, textiles and paper, because of their water-, dirt-, and oil-repellent properties (Calafat et al., 2007; Fromme et al., 2009). PFASs are persistent in the environment and have been detected in wildlife and humans around the world (Calafat et al., 2007; Giesy and Kannan, 2001; Kannan et al., 2004).

PFASs are known to cross the placenta, and PFAS has been found in human fetuses (Mamsen et al., 2017) raising concerns about programming effects in the developing child. Disruption of thyroid hormones by PFASs during this vulnerable period has been reported in mice and rats (Lau et al., 2003), and since thyroid hormones are essential during fetal life for normal neuro-development (Patel et al., 2011) a disruption of thyroid hormones could possibly be a potential biological mechanism by which prenatal PFAS exposure could act, although little is known.

A number of epidemiological studies have examined neuro-behavioural effects of prenatal exposure to the PFAS perfluorooctaoic acid (PFOA) and perfluorooctane sulfonate (PFOS exposure). An earlier study from our group showed an association between prenatal PFOA

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https://doi.org/10.1016/j.yhbeh.2017.11.007
Received 31 July 2017; Received in revised form 17 October 2017; Accepted 9 November 2017
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exposure and hyperactive behaviour at 5–9 years of age (Hoyer et al., 2015) and another that high prenatal PFOS exposure was associated with poor gross motor function compared to low exposure (Chen et al., 2013), other studies showed no associations between prenatal PFOA and PFOS exposure and child behaviour at various ages (Fei et al., 2008; Fei and Olsen, 2011; Forns et al., 2015; Strom et al., 2014).

In 2006 the US Environmental Protection Agency invited eight major manufacturers to voluntarily eliminate their production and use of PFOA, its precursors, and related chemicals ("Per- and Polyfluoroalkyl Substances (PFASs) under TSCA - PFOA Stewardship Program, 2006."). Furthermore, the use of PFOS has been restricted since the ratification of Annex A on Persistent Organic Pollutants in 2009 (The new POPs under the Stockholm Convention, 2009). Hence, trends in the level of PFAS exposure show lower PFOS concentrations in the US population; whereas serum concentrations of perfluorononanoic acid (PFNA) showed a significant upward trend between 1999 and 2008 and perfluorohexane sulfonic acid (PFHxS) fluctuated with downward concentrations from 1999 to 2006, and increased concentrations during 2007–2008 (Kato et al., 2011). In Norway, trends of PFHxS increased from 1979 to 2001 and did not decrease through 2007, while PFDA and PFNA increased during the intire period (Nost et al., 2014). Thus, it seems that PFOS and PFOA in part have been replaced by PFNA and PFDA (Armitage et al., 2009), and PFNA and PFDA also have longer halflives and more bioaccumulating abilities compared to shorter chained PFASs (Conder et al., 2008).

To our knowledge, only two cross-sectional studies and one case-control study have reported results on the association between the PFASs used in increasing levels over the recent years and child behaviour (Hoffman et al., 2010; Ode et al., 2014; Stein and Savitz, 2011). One study found a positive association between PFHxS and ADHD diagnosis and intake of ADHD medication (Stein and Savitz, 2011), another study found a weak positive association between PFNA and ADHD (Hoffman et al., 2010), and no associations were reported in the case-control study (Ode et al., 2014). To our knowledge, no studies have examined the relationship between perfluorodecanic acid (PFHpA) and perfluorodecanic acid (PFDA) and child behaviour. Hence, in the present follow-up study, we examine prospectively collected data on prenatal exposure to PFNA, PFHxS, PFDA, and PFHpA and their associations with child behaviour at 5–9 years of age measured using the Strength and Difficulties Questionnaire (SDQ). We hypothesize that prenatal levels of these PFASs may be associated with ADHD like behaviour (hyperactivity subscale of SDQ).

2. Materials and methods

2.1. Study population

The study population consisted of mother-child pairs from the INUENDO (Biopersistent organochlorines in diet and human fertility) birth cohort during the period from May 2002 to February 2004. A total of 1441 pregnant women from Greenland, Kharkiv (Ukraine) and Warsaw (Poland) were enrolled throughout pregnancy from antenatal health care clinics. The women delivered a blood sample at median gestational week 25 in Greenland and 23 in Ukraine at local hospitals. With few exceptions the antenatal health programs covered all pregnant women in the localities. Details on the baseline study population are available elsewhere (Toft et al., 2005).

From January 2010 through May 2012, a follow-up interview and a clinical examination was performed when the children were between 5 and 9 years old (Hoyer et al., 2014). Parents responded to questions concerning child characteristics in a face-to-face interview or by filling in a questionnaire themselves.

A total of 1023 mother–child pairs (singleton births) had available blood samples and were followed up in Greenland and Ukraine. The study population was distributed between Greenland [n = 531 (52%)] and Ukraine [n = 492 (48%)]. Further, 92 mother-child pairs were followed up in Poland. However, given a low participation rate at follow-up (< 20%) and a low number of cases in Poland, these mother-child pairs were only included in a subanalyses on the overall combined association in this study. The participation rate at follow-up was 93% in Greenland and 80% in Ukraine.

2.2. Ethics

The study was approved by local ethical committees; Ethical Committee for Human Research in Greenland (approval no. 2010–13) and the Commission on Ethics, Bioethics Kharkiv National Medical University in Ukraine (protocol number 7, October 7, 2009), and Polish Bioethical Committee (approval no. 6/2002 of 3.07.2002). All participating parents signed informed consent.

2.3. Determination of PFHxS, PFHpA, PFNA and PFDA

Plasma concentrations of PFHxS, PFHpA, PFNA, PFDA, PFOS and PFOA were analysed at The Department of Occupational and Environmental Medicine in Lund, Sweden, using liquid chromatography-tandem-mass-spectrometry (LC/MS/MS). Cotinine, a biomarker of maternal smoking, was analysed by the same method. Aliquots of 100 µl serum were added to 25 µl of water: acetonitrile (50:50) solution containing labelled internal standards. Proteins were precipitated with acetonitrile and vigorously shaking for 30 min. The samples were then centrifuged and the supernatant was analysed using a LC (UFLCXR, SHIMADZU Corporation, Kyoto, Japan) connected to a hybrid triple quadrupole linear ion trap mass spectrometer (QTRAP 5500, AB Sciex, Foster City, CA, USA). Limits of detection (LOD) determined as the concentrations corresponding to three times the standard deviation of the responses in chemical blanks were 0.06 ng/ml for PFHxS, 0.07 ng/ml for PFHpA, 0.04 ng/ml for PFOA and 0.2 ng/ml for PFNA, PFDA, and PFOS. Coefficient of variation of duplicate samples worked-up and analysed on different days were 8% for PFHxS and PFHpA, 9% for PFNA, PFDA, and PFOS, and 11% for PFOA. A detailed description of the method is presented elsewhere (Lindh et al., 2012). Samples > LOD for PFHxS: 99.8%; PFHpA: 81.5%; PFNA, PFOA and PFOA: 100% and PFDA: 91.7%. PFAS values < LOD were imputed using simple imputation. Imputed values were drawn at random from a log-normal distribution and conditional on the value being between zero and the compound-specific LOD as described elsewhere (Lenters et al., 2016).

2.4. Child behaviour

To assess child behaviour at 5–9 years of age, we used the parent version of the country-specific standardized questionnaire, SDQ. Parents were asked to assess their child's behaviour during the past six months in an interview-based questionnaire at follow-up.

The SDQ comprises 25 items on five scales: emotional symptoms, conduct problems, hyperactivity, peer problems, and pro-social behaviour (R. Goodman, 1997). The items in each scale were coded 0 "not true", 1 "somewhat true" or 2 "certainly true", and each scale had a summed score ranging from 0 to 10. In all scales, except the pro-social subscale, a high score indicated problems. A SDQ-total score was calculated by summing four of the scales - emotional, conduct, hyperactivity and peer with a range of 0 to 40. The SDQ scores were categorised as normal, borderline and abnormal scores based on published cut-off values (SDQ-total score: normal 0–13, borderline 14–16, abnormal (behavioural problems) 17–40; hyperactivity score: normal 0–5, borderline 6, abnormal 7–10) (R. Goodman, 1997).

2.5. Statistical analysis

2.5.1. Chained multiple imputation

The number of missing variables ranged from 0 to 12%. To minimize the risk of selection bias, we performed chained multiple

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