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Persistent organic pollutants measured in maternal serum and offspring neurodevelopmental outcomes — A prospective study with long-term follow-up

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ABSTRACT

Fetal exposure to persistent organic pollutants (POPs) has been linked to adverse neurodevelopment, but few studies have had follow-up beyond childhood.
The purpose of this study was to examine the association of maternal serum concentrations of two perfluoroalkyl acids (perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)), polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (p,p′-DDE) and hexachlorobenzene (HCB) with offspring behavioural and affective disorders and scholastic achievement in a prebirth cohort study with 20 years of follow up.
Between 1988 and 1989 pregnant women (n = 965) were recruited for the prebirth Danish Fetal Origins 1988 (DaFO88) Cohort in Aarhus, Denmark. Perfluoroalkyl acids, PCBs, p,p′-DDE, and HCB were quantified in serum from week 30 of gestation (n = 876 for perfluoroalkyl acids/872 for PCBs, p,p′-DDE, HCB). Offspring were followed up through national registries until 2011. We evaluated associations between maternal serum concentrations of these POPs and offspring neurodevelopmental outcomes, defined as: first admission diagnosis or prescription of medication until age >20 for (1) ADHD; (2) depression; and (3) scholastic achievement defined as mean grade on a standardized written examination given in the 9th grade (final exams of compulsory school in Denmark).
Maternal concentrations of organochlorine substances and perfluoroalkyl acids were higher than present day levels. During the follow-up period there were 27 (3.1%) cases of ADHD and 104 (11.9%) cases of depression; the mean scholastic achievement was 6.7 (SD 2.3). Overall we found no association for maternal levels of any of the measured pollutants with offspring behavioural and affective disorders or with scholastic achievement.
Our analyses based on biomarkers from a cohort of over 800 pregnant women with long-term close to complete follow-up through national registries showed little evidence of a programming effect of PFOA, PFOS, PCBs, p,p′-DDE, and HCB in relation to clinically and functionally relevant offspring neurodevelopmental outcomes.

1. Introduction

Persistent organic pollutants (POPs) are compounds that are resistant to environmental degradation and share properties that make them bioaccumulate in human and animal tissue (World Health Organization, 2010). POPs include structurally diverse groups of chemicals which differ widely in terms of rate of degradation, excretion and toxic potency. These compounds include, but are not limited to, lipophilic organochlorine compounds that were phased out of production in the late 1970s and were used either as pesticides [e.g. hexachlorobenzene (HCB) and dichlorodiphenyltrichloroethane (p,p′-DDT)] or as heat resistant oils including polychlorinated biphenyls (PCBs).

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ATC, Anatomical Therapeutic Chemical Classification System; BSID, Bayley Scales of Infant Development; BMI, body mass index; CI, confidence interval; DNPR, Danish National Patient Register; HR, hazard ratio; HCB, hexachlorobenzene; ICD, International Classification of Diseases; IQ, intelligence quotient; IQR, interquartile range; LOQ, limit of quantification; PCB, polychlorinated biphenyls; PCRR, Danish Psychiatric Central Research Register; PFAA, perfluoroalkyl acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; p,p′-DDE, dichlorodiphenyldichloroethylene; p,p′-DDT, dichlorodiphenyltrichloroethane; POP, persistent organic pollutant; RMPS, Registry of Medicinal Product Statistics; SD, standard deviation.

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Newer compounds such as perfluoroalkyl acids (PFAAs) have unique repellent properties and low surface tension and have been widely used in industrial applications until the last decade. For the organochlorine POPs the human exposure route is mainly dietary consumption of fish, meat and dairy products (World Health Organization, 2010). Human exposures to PFAAs have, on the other hand, been less well characterised although diet is thought to be the main source in background exposed populations (Halldorsson et al., 2008; Vestergren and Cousins, 2009).

Several POPs, including PCBs, are believed to be neurotoxic, influencing the synthesis and activity of neurotransmitters and the organization of the developing brain through alterations in basic cellular signalling processes and endocrine function (Seegal, 1996). Studies have also shown low environmental exposure levels of neurotoxins to be associated with increased risks of depression and panic disorder (Bouchard et al., 2009). Pregnancy and early life are believed to be particularly vulnerable ages for exposure to toxicants such as POPs, both early in pregnancy during organogenesis and later during rapid neuron development when neurons mature and form synapses (Grandjean and Landrigan, 2006). Environmental insults during such critical periods have been hypothesized to have long-lasting consequences due to alterations of the central nervous system in a manner that may cause neural and/or behavioural changes (Andersen et al., 2000). For example, there are indications from studies in rat models that early exposure to two specific PFAAs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), may be associated with delayed behavioural milestones (Luebker et al., 2005). Overall, the evidence for adverse neuropsychological effects in early infancy and childhood following developmental exposures to POPs is inconsistent for both the organochlorine POPs (El Majidi et al., 2013) and the PFAAs (Fei and Olsen, 2011).

More long-term follow-up studies are therefore needed to examine whether developmental exposures may result in latent effects that may become of functional relevance later in adult life.

The aim of this study was to examine associations between maternal exposures to PFAAs, PCBs and organochlorine pesticides and clinically relevant measures of behavioural and affective disorders and scholastic achievement as a functional indicator of cognitive development in a prospective study of 876 pregnant women with up to 22 years of offspring follow-up.

2. Methods

Data for this study derived from the Danish Fetal Origins 1988 (DaFO88) Cohort, a prebirth cohort originally formed with the aim to examine the impact of early life exposures on pregnancy outcomes. Women were recruited during a routine antenatal visit in week 30 of gestation at a midwifery practice that covered a geographically well-defined area of the city of Aarhus, Denmark in the period 1988–89. Among 1212 eligible women 965 (80%) were enrolled. A self-administered dietary questionnaire was mailed to the women 1 week before the scheduled 30th week midwife visit and a structured face-to-face interview of approximately 15 minute duration was conducted during the visit covering lifestyle, socio-economic position and health. A blood sample was also taken and processed, and serum was frozen and stored at −20° C. Information regarding delivery was extracted from hospital records and the Danish Medical Birth Registry. The DaFO88 Cohort has been described in more detail elsewhere (Olsen et al., 1995).

2.1. Exposure assessment

Using 200 μl of the archived maternal serum from week 30 of gestation, a total of six PCBs (congeners 118, 138, 153, 156, 170 and 180), p,p′-DDE, and HCB were measured by liquid–liquid extraction, silica column cleanup and gas chromatography high-resolution mass spectrometry analyses (Koponen et al., 2013). In each batch of 25 samples, two blanks and two control samples (NIST SRM 1589a) were added. Average recoveries of measured POPs in control samples were 97–106% of the certified values. The between-assay coefficient of variation was 2.1% (at 11.5 ng/ml) for p,p′-DDE, 4.0% (at 0.08 ng/ml) for HCB, 4.0% (at 0.17 ng/ml) for PCB 118, 4.2% (at 0.54 ng/ml) for PCB 138, 2.7% (at 0.94 ng/ml) for PCB 153, 6.5% (at 0.07 ng/ml) for PCB 156, 6.7% (at 0.21 ng/ml) for PCB 170, and 2.6% (at 0.52 ng/ml) for PCB 180. The limit of quantification (LOQ) for HCB was 25 pg/ml. For p,p′-DDE and the six PCBs, LOQs were between 2 and 5 pg/ml. Concentrations were above the LOQs for all compounds in all samples. The analyses were performed at the National Institute of Health and Welfare, Chemical Exposure Unit, Kuopio, Finland.

Using 150 μl of the maternal serum samples, concentrations of PFOA and PFOS were determined by column-switching, isotope dilution LC–MS/MS methodology as previously described (Haug et al., 2009a). Concentrations of PFOA and PFOS were above LOQ (0.05 ng/ml) in all samples. Quality of the analytical procedure was monitored by analysing in-house quality control samples (n = 18) as well as human serum samples from an inter laboratory comparison exercise. Coefficients of variation for PFOA and PFOS for the in-house quality control samples at 5 ng/ml were 4.2% and 2,8%, respectively and inter-laboratory comparison results were within one standard deviation of the consensus values (Haug et al., 2009a). The analyses were performed at the Department of Analytical Chemistry at the Norwegian Institute of Public Health in Oslo.

2.2. Outcome assessment

Information on outcomes was obtained by linkage to population-based registries by means of the unique Danish personal identifier (the CPR-number).

2.2.1. Behavioural and affective disorders

We used data from the Registry of Medicinal Product Statistics (RMPS) which holds information about all prescriptions filled in Danish pharmacies since January 1995 (Kildemoes et al., 2011). Furthermore, we used two registries that hold information on hospital contacts: The Danish Psychiatric Central Research Register (PCRR) which contains information on all contacts to psychiatric hospitals in Denmark since 1969 and since 1995 also contacts at psychiatric outpatient clinics (Mors et al., 2011); and The Danish National Patient Register (DNPR), which holds information on all hospitalizations in Denmark since 1977 and since 1995 since 1995 also emergency room and outpatient visits of any type (Lynge et al., 2011).

We defined an ADHD case as an offspring, who during follow-up filled at least one prescription for psychostimulant medication (Anatomical Therapeutic Chemical Classification System (ATC): N06B) as per the RMPS or was registered as an in- or outpatient contact as per the PCRR or DNPR with a diagnosis of hyperkinetic disorder (International Classification of Diseases (ICD)8: 308, ICD10: F90).

We defined a depression case correspondingly as an offspring who filled at least one prescription for antidepressant medication (ATC: N06A) or was registered as an in- or outpatient contact as per the PCRR or DNPR with a diagnosis of depression (ICD8: 2960, 2962, 2968, 2969, 2980, 3004, 3011, ICD10: F320–F329).

We did not discriminate as to whether psychiatric events were defined by use of medication and/or hospital contact. Date of ADHD/depression was defined as the date of first filled prescription for the relevant medication (after the registry was considered complete January 1995) or first hospital admission date with the relevant diagnosis, whichever came first.