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Prenatal exposure to perfluoralkyl substances (PFASs) associated with respiratory tract infections but not allergy- and asthma-related health outcomes in childhood

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ABSTRACT

Background: Prenatal exposure to perfluoralkyl substances (PFASs) has been reported to be associated with immunosuppression in early childhood, but with contradictory findings related to atopic and lung diseases.
Aim: We aimed to determine if prenatal exposure to PFASs is associated with asthma or other allergic diseases or respiratory tract infections in childhood.
Methods: Nineteen PFASs were measured in cord blood available from 641 infants in the Environment and Childhood Asthma (ECA) prospective birth cohort study. The six most abundant PFASs were perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorooctanesulfonamide (PFOSA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUnDA). Health outcomes were assessed at two and ten years of age, and included reported obstructive airways disease (wheeze by 10 years; asthma by 2 and 10 years; reduced lung function at birth; allergic rhinitis by 10 years), atopic dermatitis (AD) by 2 and 10 years, allergic sensitization by 10 years, and episodes of common respiratory tract infections (common cold by 2 years, lower respiratory tract infections (LRTI) by 10 years). The associations between exposure and health outcomes were examined using logistic and Poisson regression.
Results: The number of reported airways infections were significantly associated with cord blood concentrations of PFAS; common colds by two years with PFUnDA (β = 0.11 (0.08–0.14)) and LRTIs from 0 to 10 years of age with PFOS (β = 0.50 (0.42–0.57)), PFOA (β = 0.28 (0.22–0.35)), PFOSA (β = 0.10 (0.06–0.14)), PFNA (β = 0.09 (0.03–0.14)) and PFUnDA (β = 0.18 (0.13–0.23)) concentrations. Neither reduced lung function at birth, asthma, allergic rhinitis, AD nor allergic sensitization were significantly associated with any of the PFASs.
Conclusion: Although prenatal exposure to PFASs was not associated with atopic or lung manifestations by 10 years of age, several PFASs were associated with an increased number of respiratory tract infections in the first 10 years of life, suggesting immunosuppressive effects of PFASs.

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are synthetic fluorinated compounds widely used in different consumer products due to their water, oil and stain resistant qualities (Vestergren et al., 2009, Kotthoff et al., 2015). They are considered environmental pollutants that are ubiquitously distributed in both humans and wildlife (Houde et al., 2006; Lau et al., 2007).

For humans, the main exposure to PFAS is through food and beverages, while on an individual basis, exposure via inhalation and ingestion of indoor dust may contribute (Fromme et al., 2009; Haug et al., 2010, 2011). From food, the highest PFAS concentrations have been found in fish and shellfish (Haug et al., 2011; Denys et al., 2014). Early life exposure *occurs in utero* via placental transfer (Apelberg et al., 2007; Gutzkow et al., 2012) and through mother's milk during breastfeeding (Thomsen et al., 2010; Haug et al., 2011).

Asthma, rhinitis and atopic eczema, often coexist (Pinart et al., 2014), as allergic diseases. Asthma in children has inconsistently been associated with PFAS exposure in children, with positive associations found in a few studies (Dong et al., 2013; Humblet et al., 2014), while

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others have found no such associations (Granum et al., 2013; Smit et al., 2015). Atopic dermatitis (AD) had a negative association with perfluorotridecanoic acid (PFTrDA), and perfluoroundecanoic acid (PFUnDA) in 2 year old girls in the Hokkaido birth cohort (Okada et al., 2014), while further negative associations were found for perfluorododecanoic acid (PFDoDA) and PFTrDA for a global allergic disease outcome (symptoms of eczema, wheeze and/or rhinoconjunctivitis) (Goudarzi et al., 2016). In a Taiwanese cohort PFOA and PFOS were not significantly associated with AD at 2 years of age, although the PFASs correlated positively with total serum immunoglobulin E (IgE) (Wang et al., 2011). No associations were found between PFOS and PFOA levels and self-reported infant allergies (Okada et al., 2012).

Immunotoxic effects of prenatal PFASs have been demonstrated in vitro and in experimental animal studies (reviewed in (DeWitt et al., 2012)), suggesting that exposure to PFASs might be particularly harmful during this time of immune system development (Holsapple et al., 2004, Van Loveren and Piersma, 2004). In humans, only limited studies exist in relation to PFASs and asthma, allergic diseases, vaccine responses, and infectious diseases in childhood. Prenatal exposure to PFASs was associated with reduced immune response to childhood vaccinations in Faroese (Grandjean et al., 2012) and in Norwegian children (Granum et al., 2013), and in the Norwegian study, maternal PFAS levels were also associated with an increased number of episodes of common infectious diseases in early childhood (Granum et al., 2013). In a Danish birth cohort, PFOS and PFOA were associated with increased number of days with fever (Dalsager et al., 2016). However, no association was found between maternal PFAS serum levels and binomial (yes/no) response of childhood infections in Japanese Hokkaido birth cohort (Okada et al., 2012) nor with incidence rate of hospitalization due to infectious diseases in Danish children (Fei et al., 2010).

Our main aim was therefore to determine if prenatal exposure to PFASs measured in cord blood was associated with allergic diseases and respiratory tract infections in the first ten years of life.

2. Material and methods

2.1. Study design and health related outcomes

The present study includes data from the 0–2 and 2–10 year intervals obtained at the 2- and 10- year follow-up investigations from the prospective general population birth cohort the “Environment and Childhood Asthma” (ECA) Study in Oslo (described in detail elsewhere (Lodrup Carlsen, 2002; Bertelsen et al., 2010). Between January 1992 and March 1993, 3754 healthy newborns weighing at least 2000 g were recruited in two main hospitals in Oslo, Norway. Lung function was measured by tidal flow volume loops at birth in 802 children. A follow-up investigation was performed at 2 years in a nested case-control study of 516 of 612 identified children with recurrent physician-diagnosed bronchial obstruction (BO; (at least two separate episodes or one episode of BO lasting for at least 4 weeks)) or controls born closest in time to a case, but with no history of BO. A second follow-up investigation was performed at 10 years where 1019 out of the 1215 invited children with lung function measurements at birth and/or were included in the nested case-control study were examined (Hovland et al., 2013).

0–2 years: Questionnaires were distributed at birth and every 6 months until 2 years of age and included detailed family and personal history of allergic diseases, health-related factors, and socioeconomic and environmental factors. Also, all children had registry cards including symptoms and signs of BO, to be completed at any physician-attended episode of respiratory disease, used to aid diagnosis of recurrent BO.

Lung function was measured at birth by tidal flow volume loops as described in details elsewhere (Lodrup Carlsen et al., 1994), and is reported by the ratio of time to peak expiratory flow divided by total expiratory time (t_{PTEF}/t_E).

At 2 years of age: A parental interview and clinical investigation including skin prick test (SPT) to common inhalant and food allergens performed according to Nordic guidelines.

At 10 years of age: A clinical investigation including parental interview, SPT and blood sampling for allergic sensitisation, spirometry for lung function measures were performed.

Health outcomes used in the present study are:

i. Doctor-diagnosed asthma at 10 years (current, ever).
ii. Doctor-diagnosed wheeze (0–3, 3–10, 0–10 years).
iii. Severity of obstructive airways disease by two years of age: The Oslo Severity Score (OSS) (Devulapalli et al., 2008)) from 0 to 12, zero being no episodes of BO. The score is based on the number of episodes, persistence and hospitalization due to BO. Data are reported in three categories (0, 1–5, 6–12) where the highest category implies most severe obstructive airways disease, with zero being the reference class.
iv. Reduced lung function at birth: Lung function (t_{PTEF}/t_E) with standardized z-score, and binary variable of decreased lung function (cutoff < 0.20) (Haland et al., 2006).
v. Doctor diagnosis of atopic dermatitis (AD) at 0–2 years and at 10 years (current (last 12 months), ever) was obtained from the questionnaires.
vi. Rhinitis at 10 years (current, ever) defined as at least one of the following symptoms (without a cold): runny nose, blocked nose, or sneezing reported by the parents.
vii. Rhinoconjunctivitis at 10 y (ever) defined as rhinitis in combination with itchy/runny eyes reported by the parents.
viii. Allergic sensitization at 10 years defined as one or more positive skin prick test (SPT; ≥ 3 mm when compared to the negative control) and/or positive allergen-specific serum IgE to at least one allergen. SPT was performed according to the European standards with the following standardized allergen extracts (Soluprick, ALK-Abello, Denmark): house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farina*), pets (dog, cat, rabbit), grass, tree and mugwort pollens and moulds, as well as cow's milk, wheat, peanut and cod. Specific serum IgE was analyzed with a radioallergosorbent fluorescence immunoassay (ImmunoCAP® system, Phadia, Uppsala, Sweden) according to the instructions by the manufacturer. Specific IgE was analyzed with the same panel of allergens as for SPT and considered positive with sIgE ≥ 0.35 kU/L.
ix. Number of episodes of common cold by 2 years of age reported by the parents.
x. Number of episodes of lower respiratory tract infections (LRTI; sum of bronchitis, bronchiolitis and pneumonia) by 10 years of age reported by the parents.

Written informed consent forms were obtained from all parents. The study was approved by the Regional Medical Ethics Committee (Oslo, Norway) and the Norwegian Data Inspectorate and reported to the Norwegian Biobank Registry (Oslo, Norway).

2.2. PFAS measurements

Cord blood serum samples from 641 participants were available for PFAS measurements. Nineteen PFASs were determined using liquid chromatography-triple quadrupole mass spectrometry (LC-MS/MS) according to a previously-described method (Haug et al., 2009). The limit of quantification (LOQ) was 0.050 ng/ml for all PFAS. For quantification of PFOS, the total area of the linear and branched isomers was integrated.

Due to low concentrations and/or detection frequency for many of the 19 PFASs, statistical analyses were performed only for the following 6 PFASs: perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorooctanesulfonamide (PFOSA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and