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Early life exposure to per- and polyfluoroalkyl substances and mid-childhood lipid and alanine aminotransferase levels

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ABSTRACT

Background: Growing evidence suggests that exposure to per- and polyfluoroalkyl substances (PFASs) may disrupt lipid homeostasis and liver function, but data in children are limited.
Objective: We examined the association of prenatal and mid-childhood PFAS exposure with lipids and alanine aminotransferase (ALT) levels in children.
Methods: We studied 682 mother-child pairs from a Boston-area pre-birth cohort. We quantified PFASs in maternal plasma collected in pregnancy (median 9.7 weeks gestation, 1999–2002) and in child plasma collected in mid-childhood (median age 7.7 years, 2007–2010). In mid-childhood we also measured fasting total (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and ALT. We then derived low-density lipoprotein cholesterol (LDL-C) from TC, HDL-C, and TG using the Friedewald formula.
Results: Median (interquartile range, IQR) perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorodecanoate (PFDeA) concentrations in child plasma were 6.2 (5.5), 4.3 (3.0), and 0.3 (0.3) ng/mL, respectively. Among girls, higher child PFOS, PFOA, and PFDeA concentrations were associated with detrimental changes in the lipid profile, including higher TC and/or LDL-C [e.g., β per IQR increment in PFOS = 4.0 mg/dL (95% CI: 0.3, 7.8) for TC and 2.6 mg/dL (−0.5, 5.8) for LDL-C]. However, among both boys and girls, higher plasma concentrations of these child PFASs were also associated with higher HDL-C, which predicts better cardiovascular health, and slightly lower ALT, which may indicate better liver function. Prenatal PFAS concentrations were also modestly associated with improved childhood lipid and ALT levels.
Conclusions: Our data suggest that prenatal and mid-childhood PFAS exposure may be associated with modest, but somewhat conflicting changes in the lipid profile and ALT levels in children.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; EtFOSAA, 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate; GAM, generalized additive models; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LOD, limit of detection; MeFOSAA, 2-(*N*-methyl-perfluorooctane sulfonamido) acetate; *n*-PFOA, *n*-perfluorooctanoate; *n*-PFOS, *n*-perfluorooctane sulfonate; NAFLD, nonalcoholic fatty liver disease; PFAS, per- and polyfluoroalkyl substances; PFDeA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFOSA, perfluorooctane sulfonamide; PPAR, peroxisome proliferator-activated receptor; TC, total cholesterol; TG, triglycerides; *Sb*-PFOA, branched perfluorooctanoates; *Sm*-PFOS, perfluoromethylheptane sulfonates; *Sm2*-PFOS, perfluorodimethylhexane sulfonates

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1. Introduction

Per- and polyfluoroalkyl substances (PFASs) – synthetic compounds used in a wide range of industrial and consumer products, including stain-resistant coatings for upholstery and fabrics, pesticide additives, coatings for food packaging, and fire-retardant foams (Lindstrom et al., 2011) – have structural homology with fatty acids (Fletcher et al., 2013) and may have endocrine-disrupting properties (Braun, 2017). Evidence suggests that PFAS exposure may contribute to lipid- and liver enzyme-related metabolic disturbances (Steenland et al., 2010) through activation of the peroxisome proliferator-activated receptors (PPAR) alpha (α) (Wolf et al., 2008) and gamma (γ) (Vanden Heuvel et al., 2006), and/or altered expression of lipid transport- and metabolism-related genes (Fletcher et al., 2013).

Most animal studies have shown that PFAS exposure can induce beneficial changes in circulating lipids, including lower total cholesterol (TC) and triglycerides (TG) (Kennedy et al., 2004; Lau et al., 2007; White et al., 2011). Human studies have reported conflicting associations of PFASs with lipids, with cross-sectional studies in adults and children reporting associations of higher PFASs concentrations with detrimental [i.e., higher circulating TC, low-density lipoprotein cholesterol (LDL-C), and TG] (Costa et al., 2009; Eriksen et al., 2013; Fitz-Simon et al., 2013; Geiger et al., 2014; Nelson et al., 2010; Sakr et al., 2007a; Sakr et al., 2007b; Starling et al., 2014; Steenland et al., 2009; Zeng et al., 2015) and beneficial changes in lipid profile [i.e., higher high-density lipoprotein cholesterol (HDL-C)] (Chateau-Degat et al., 2010; Starling et al., 2014). One of two published studies that explored associations of prenatal PFASs with mid-childhood lipids observed non-linear associations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) (two of the most prevalent and commonly studied PFASs) with serum lipids (TC and LDL-C): at low PFAS concentrations (lower tertile), PFAS-related associations with lipids were beneficial and at high PFAS concentrations (middle and upper tertiles), PFAS-related associations with lipids were detrimental (Maisonet et al., 2015). The other study observed beneficial associations of prenatal perfluorohexane sulfonate (PFHxS) plasma concentrations with TG z-scores measured in early childhood (Manzano-Salgado et al., 2017). These studies did not examine the association between postnatal PFAS exposure and childhood lipids.

Recent cross-sectional and cohort studies in adults have investigated the association between PFASs and liver enzymes – markers of hepatocellular dysfunction – with inconsistent results (Alexander and Olsen, 2007; Costa et al., 2009; Darrow et al., 2016; Emmett et al., 2006; Gallo et al., 2012; Gleason et al., 2015; Lin et al., 2009; Sakr et al., 2007a; Sakr et al., 2007b). For example, PFAS concentrations have been positively associated with alanine aminotransferase (ALT) levels in some population-based (Darrow et al., 2016; Gallo et al., 2012; Gleason et al., 2015) and occupational studies (Alexander and Olsen, 2007; Lin et al., 2009; Sakr et al., 2007a), but not in others (Costa et al., 2009; Sakr et al., 2007b). To our knowledge, no study has examined the association of prenatal or postnatal PFAS exposure with liver enzymes in children.

Project Viva is a prospective pre-birth cohort designed to study the extent to which events during early development affect health outcomes over the lifespan. In previous analyses of PFASs in Project Viva, we observed modest associations with increased adiposity and risk of obesity in girls, but not boys, in mid-childhood (Mora et al., 2017). However, we found no adverse effects of early-life PFAS exposure on leptin, adiponectin, or homeostatic assessment of insulin resistance (HOMA-IR) in mid-childhood; in fact, children with higher plasma concentrations of some PFASs had lower insulin resistance (Fleisch et al., 2017). In light of these findings, and given that animal data have shown that early-life exposure to PFASs may disrupt lipid metabolism and induce hepatotoxic effects (Kennedy et al., 2004; Lau et al., 2007; White et al., 2011), we evaluated the extent to which PFAS concentrations in prenatal and mid-childhood plasma were associated with childhood lipids and ALT in Project Viva.

2. Methods

2.1. Study population

Pregnant women were enrolled in Project Viva from 1999 to 2002 during their first prenatal visit to Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in Eastern Massachusetts (Oken et al., 2015). Of 2128 live singleton offspring, 1776 (84%) children had PFAS concentrations measured in maternal non-fasting plasma collected in early pregnancy [median (range) 9.7 (4.8–21.4) weeks gestation, n = 1645] or in child fasting plasma collected in mid-childhood [median age (range) 7.7 (6.7–11.0) years, n = 653]. Of these 1776 children, 682 (38%) had lipids or ALT measured in fasting mid-childhood plasma samples (same samples used to measure PFAS; see Fig. A.1).

Institutional Review Boards of participating sites approved all study protocols. All mothers provided written informed consent at each study visit and children provided verbal assent at the mid-childhood visit. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research.

2.2. Prenatal and child PFAS measurements

Maternal and child plasma samples were shipped to the Division of Laboratory Sciences at the CDC and analyzed for concentrations of eight PFAS analytes: PFOS, PFOA, PFHxS, perfluorononanoate (PFNA), 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate (Et-PFOSA-AcOH; also known as EtFOSAA), 2-(*N*-methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH; also known as MeFOSAA), perfluorodecanoate (PFDeA), and perfluorooctane sulfonamide (PFOSA; also known as FOSA). Child plasma samples were also analyzed for concentrations of linear and branched isomers of PFOS and PFOA (we did not measure linear and branched isomers in our maternal samples because they were analyzed earlier): *n*-perfluorooctane sulfonate (*n*-PFOS), perfluoromethylheptane sulfonates (*Sm*-PFOS), perfluorodimethylhexane sulfonates (*Sm2*-PFOS), *n*-perfluorooctanoate (*n*-PFOA), and branched perfluorooctanoates (*Sb*-PFOA). All samples were analyzed using online solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spectrometry, as previously described (Fleisch et al., 2017; Harris et al., 2017; Sagiv et al., 2015). Limits of detection (LOD) were 0.1 ng/mL for all PFASs except for PFOS concentrations in prenatal plasma (0.2 ng/mL). Values below the LOD were replaced with LOD divided by the square root of 2.

2.3. Lipids and ALT levels in mid-childhood

We measured fasting TC, HDL-C, TG, and ALT using enzymatic assays, in the same plasma samples used for quantification of mid-childhood PFASs. We then calculated LDL-C using the Friedewald formula: TC-(HDL-C)-(TG × 0.2) (Friedewald et al., 1972). We also calculated the ratio of TC to HDL-C, an indicator of the detrimental portion of the lipid profile (Millan et al., 2009).

2.4. Potential confounders and predictors of lipids and ALT levels

We collected information on maternal age, marital status,