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Changes in markers of liver function in relation to changes in perfluoroalkyl substances - A longitudinal study

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ABSTRACT

Background: While it is known that perfluoroalkyl substances (PFASs) induce liver toxicity in experimental studies, the evidence of an association in humans is inconsistent.
Objective: The main aim of the present study was to examine the association of PFAS concentrations and markers of liver function using panel data.
Methods: We investigated 1002 individuals from Sweden (50% women) at ages 70, 75 and 80 in 2001–2014. Eight PFASs were measured in plasma using isotope dilution ultra-performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS). Bilirubin and hepatic enzymes alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT) were determined in serum using an immunoassay methodology. Mixed-effects linear regression models were used to examine the relationship between the changes in markers of liver function and changes in PFAS levels.
Results: The changes in majority of PFAS concentrations were positively associated with the changes in activity of ALT, ALP, and GGT and inversely associated with the changes in circulating bilirubin after adjustment for gender and the time-updated covariates LDL- and HDL-cholesterol, serum triglycerides, BMI, statin use, smoking, fasting glucose levels and correction for multiple testing. For example, changes in perfluorononanoic acid (PFNA) were associated with the changes liver function markers $\beta_{BILIRUBIN} = -1.56$, 95% confidence interval (CI) -1.93 to -1.19, $\beta_{ALT} = 0.04$, 95% CI 0.03–0.06, and $\beta_{ALP} = 0.11$, 95% CI 0.06–0.15.
Conclusion: Our longitudinal assessment established associations between changes in markers of liver function and changes in plasma PFAS concentrations. These findings suggest a relationship between low-dose background PFAS exposure and altered liver function in the general population.

1. Introduction

Perfluoroalkyl substances (PFASs) is a generic term representing a large group of man-made chemicals widely used in various industrial formulations and consumer products, such as for example, repellents in textiles and apparel, paper coatings, and in fire-fighting foams. Nearly every individual worldwide is exposed to PFASs (OECD, 2015). The main route of exposure occurs via ingestion of contaminated food and breastmilk, drinking water, and inhalation of air or dust in the home environment (Wang et al., 2017). Following exposure, PFASs are distributed by the circulatory system where the highest concentrations are measured in the liver (Bogdanska et al., 2011; Kärrman et al., 2010). Because of its central role in xenobiotic metabolism, the liver is considered to be the main target organ of short- and long-term exposure to many PFASs (Lau et al., 2007). Previous experimental studies of rodents and non-human primates showed that PFAS exposure was associated with liver toxicity (Butenhoff et al., 2002; Kudo et al., 2006). Although the biological mechanisms of PFAS-induced liver toxicity are not fully understood, activation of the peroxisome proliferator-activated receptors (PPARs) have been suggested to be among the key pathways, particularly in rodents (Wolf et al., 2012). Experimental studies also suggest that PFASs may preferentially influence PPARs, suggesting that longer-chain (> eight carbons) perfluoroalkyl carboxylic acids are stronger activators of PPARs and thus likely to be more important when

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compared to their short-chain analogues (Rosenmai et al., 2018; Wolf et al., 2012). Generally, information on the relationship between PFAS exposure and liver function markers in humans is inconsistent and mainly comes from studies of occupationally exposed populations focusing exclusively on PFASs consisting of eight-carbon backbone (C8), such as perfluorooctanoic acid (PFOA) and perfluorooctanoic sulfonic acid (PFOS) (Costa et al., 2009; Mundt et al., 2007; Sakr et al., 2007b). In the general population, only a few cross-sectional studies have been performed (Gallo et al., 2012; Lin et al., 2010; Yamaguchi et al., 2013) and convincing evidence remains generally limited (Khalil et al., 2015; Steenland et al., 2010).

Cross-sectional studies are often hampered with issues related to reverse causation. In that perspective, longitudinal studies are generally preferred. Therefore, the main objective of this study was to longitudinally examine the relationships between changes in eight PFASs and changes in four biomarkers of liver function, assessed three times over ten years in an elderly general population. The hypothesis tested was that the changes in liver function markers were related to the changes in PFASs over the same time period.

2. Materials and methods

2.1. Study population and sample collection

The study population was randomly selected from the general population register of Uppsala, Sweden. Letters of invitation were sent between April 2001 and June 2004 and within two months of each of the participants' 70th birthday. The target sample was 2025 participants out of which 1016 participated. Two longitudinal follow-ups were performed. The first re-investigation was performed when the participants turned 75 years (2006–2009) and the second reinvestigation was performed when the participants turned 80 years (2011–2014). The study participants went through a complete medical investigation where more than seventeen different measurements were performed ranging from cardiovascular function to self-reported history of diseases and medication. In addition, life-style information, such as exercise, smoking, alcohol intake, education, social network was also collected. More information on the study population is described by Lind et al. (2005). Blood serum and plasma were collected in the morning (8 am) after an overnight fast. After the blood plasma samples were collected (1–2 mL vials), the vials were placed in freezers (−70 °C) until used for analysis. The study was approved by the Ethics Committee of the University of Uppsala and the participants gave written informed consent.

2.2. Analysis of markers of liver function

In all participants' serum concentrations of total bilirubin (μmol/l) and catalytic activity of serum enzymes (μkat/l) aspartate transaminase (ALT), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT) were measured using routine laboratory methods, the enzyme assays being measured at 25 °C with an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA) and reported using SI units. The method coefficient of variation (CV) for the methods used to measure markers of liver function ranged from 0.7% to 2.5%. Further details on the measurements for markers of liver function are provided by Carlsson et al. (2010).

2.3. Analysis of PFASs

The sample preparation and instrumental analysis methods used in this study were previously developed and validated in terms of recovery, accuracy and precision (Salihovic et al., 2013). Target PFASs included perfluoroheptanoic acid (PFHpA), PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorohexane sulfonic acid (PFHxS), linear isomer of PFOS, and perfluorooctane sulfonamide (PFOSA). PFASs were extracted from 150 μL of plasma or serum using protein precipitation and filtered through an Ostro (Waters Corporation, Milford, USA) 96 well-plate. The samples were then analyzed with an Acquity UPLC coupled to a Quattro Premier XE tandem mass spectrometry (MS/MS) system (Waters Corporation, Milford, USA) operating in negative electrospray ionization. The PFAS concentrations were quantified via isotope dilution. Quality assurance and quality control measures implemented throughout the analyses including: a matrix matched calibration curve, NIST SRM 1957 reference material, method blanks, quality control (QC) reference plasma, instrument blanks and performance standards have been previously published (Stubleski et al., 2016). Overall, the method accuracy for PFASs at all three investigations was found to conform well with NIST SRM 1957 reference values. Method precision and repeatability for PFASs was acceptable for both NIST 1957 SRM, ranging from 2% to 24%, and for QC reference plasma, ranging from 2% to 29%. The method detection limits (MDLs) for all three investigations ranged from 0.01–0.18 ng mL^{-1} depending on the analyte. PFAS concentrations are expressed in ng/ml blood plasma.

2.4. Covariates

Covariates that were used in the statistical analyses were selected on the basis of previous epidemiological and experimental research. Sex was included because we have previously identified sex-related differences in plasma PFAS concentrations (Salihovic et al., 2015; Stubleski et al., 2016) and liver function markers (Bohnen et al., 1991; Tietz et al., 1992). It has been previously shown that PFASs interact with PPARs in the liver and induce changes in lipid metabolism in the liver (Bjork et al., 2011; Bjork and Wallace, 2009). From this perspective, we selected the available confounders that are known to be associated with fatty liver disease, such as low density lipoprotein- (LDL) and high density lipoprotein (HDL) cholesterol (mmol/l), serum triglycerides (mmol/l), body mass index (BMI), and fasting glucose levels (mmol/l). We also included statin use (self-reported, %) because it has been previously shown that statins play a major role in lipid metabolism in the liver. Smoking (active smoker, %) was also included in the model since it experimentally has been shown to increase fat infiltration in the liver (Azzalini et al., 2010).

2.5. Statistical analysis

Plasma concentrations of PFASs were skewed towards high levels, but were normally distributed following ln-transformation. We calculated correlation coefficients among the different PFASs analogues. For the main analysis, the change in liver function variables over 10 years (three measurements) were evaluated by mixed random effect models with the liver function variable as dependent variable, and time as the independent variable and sex as confounder (age same in all subjects). Thereafter, the relationships between changes over 10 years in the levels of the eight PFASs and the changes over 10 years in four markers of liver function were examined. Also for this purpose mixed random effect models were used, but here each PFAS was used as an independent variable. In this case, the independent variable was split into a between-individual component, which is the first observation for the individual, and a within-individual component, which is the difference between the measurements at future time points and the first measurement. Thus, the between-individual component is related to the mean of the three measurements of liver function, while the between-individual component, as a single term, relates the change in each PFAS to the change in each liver function marker. The theory and assumptions behind this model as well as the detailed formula is given in page 420 by Fitzmaurice et al. (2012). The general formula is; $Y_{ij} = Z_i beta_0 - X_{i1} beta_C + (X_{ij} - X_{i1}) beta_{L+} e_{ij}$, where Y is the liver function marker, X is the PFAS, i is the individual, j the time, $beta_C$ is

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