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# Prenatal exposures to perfluoroalkyl acids and serum lipids at ages 7 and 15 in females

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ABSTRACT

*Background:* In some cross-sectional epidemiologic studies the shape of the association between serum concentrations of perfluoroalkyl acids (PFAAs) and lipids suggests departures from linearity.
*Objectives:* We used statistical approaches allowing for non-linearity to determine associations of prenatal exposures of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) with lipid concentrations.
*Methods:* PFAAs were measured in serum from pregnant women collected in 1991–1992 at enrollment in the Avon Longitudinal Study of Parents and Children and lipids in serum from their daughters at ages 7 (n = 111) and 15 (n = 88). The associations of PFAAs with lipids were first explored by cubic splines, followed by piecewise linear regressions by tertiles to obtain regression coefficients (β) and their 95% confidence limits (95% CL) (in mg/dL per 1 ng/mL).
*Results:* At age 7, total cholesterol was positively associated with prenatal PFOA concentrations in the lower tertile (β = 15.01; 95% CL = 2.34, 27.69) but not with PFOA concentrations in the middle (β = −3.63; 95% CL = −17.43, 10.16) and upper (β = −1.58; 95% CL = −4.58, 1.42) tertiles. At age 15, a similar pattern was noted as well. Positive associations between LDL-C and prenatal PFOA concentration in the lower tertile were observed in daughters at ages 7 (β = 14.91; 95% CL = 3.53, 28.12) and 15 (β = 13.93; 95% CL = 0.60, 27.26). LDL-C was not associated with PFOA concentrations in the middle or upper tertile at any age. Neither HDL-C nor triglycerides was associated with prenatal PFOA exposure. Non-linear patterns of association of total cholesterol and LDL-C with prenatal PFOS were less consistently noted.
*Conclusion:* Exposure to low levels of PFOA during prenatal development may alter lipid metabolism later in life. Given the small sample size further replication of the association in large independent cohorts is important.


## 1. Introduction

Perfluoroalkyl acids (PFAAs) constitute a class of synthetic chemicals whose water and oil repellency and surfactant properties have useful applications in industrial and commercial products (Lindstrom et al., 2011). Some PFAAs are persistent, ubiquitous in the environment, and can be found in higher concentrations at higher levels in the food chain (Stockholm Convention, 2014). Human exposure to PFAAs is common (Joensen et al., 2013; Kato et al., 2011) and sources include food (Noorlander et al., 2011; Vestergren and Cousins., 2009), water (Eschauzier et al., 201\3), and dust (Knobeloch et al., 2012). Detectable concentrations of some PFAAs have been found in cord blood and amniotic fluid from pregnant women (Apelberg et al., 2007; Stein et al., 2012).

The prenatal period is a sensitive time of development during which chemical exposures can have lasting effects on bodily functions. The fetal programming hypothesis proposed by Barker (1997) suggests that adverse fetal conditions such as undernutrition or altered concentrations of growth factors or hormones during critical periods of development may permanently change the structure and functions of the body. Knowledge on the role of prenatal exposures to PFAA is still developing, but growing evidence suggests inverse associations of prenatal exposures of PFAA with fetal growth (Johnson et al., 2014) and a positive association with risk of overweight at age 20 (Halldorsson et al., 2012). To our knowledge there are no previous studies on the association between prenatal exposure to PFAAs and serum lipid concentrations later in life.

Exposure to perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) has been associated with higher serum lipid concentrations in children and adolescents (Frisbee et al., 2010; Geiger et al., 2014), adults (Eriksen et al., 2013; Nelson et al., 2010; Steenland et al., 2009), and pregnant women (Starling et al., 2014).

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Current evidence on the influence of PFAAs on serum lipid concentrations in humans originates from cross-sectional epidemiologic studies, thus causal inference is limited.

A relevant finding of two cross-sectional studies, one in adolescents and another in adults, from a community in the United States (US) with elevated PFOA exposure from contaminated drinking water was the non-linear shape of the association of PFOA with total cholesterol (TC) (Frisbee et al., 2010; Steenland et al., 2009). In both studies the exposure–response slope appeared to reach a plateau after a certain exposure threshold suggesting a pattern consistent with that of a saturation exposure–response curve. Also in these two studies, where PFOS levels were similar to those found in the US general population, positive non-linear exposure–response slopes were observed for the association of PFOS with TC. In the study of adults (Steenland et al., 2009), however, results suggest a negative exposure–response slope for the association between serum concentrations of PFOS and TC at the higher exposure levels. Results from a population-based study of Danish adults are also suggestive of a negative exposure–response trend at the highest exposure levels of PFOS exposure (Eriksen et al., 2013). Such patterns were not apparent in the other population-based epidemiologic studies reviewed.

In contrast to evidence from epidemiologic studies, results from toxicologic studies suggest hypolipidemic effects of exposures to PFOA and PFOS in mice and rats (Loveless et al., 2006; Qazi et al., 2010). Reasons for the lack of concordance between human and animal studies may include differing species or dosages. In the toxicologic studies cited above, for instance, mean serum concentrations of either PFOS or PFOA in the groups of animals with the higher dietary exposure to these substances were several orders of magnitude higher than levels of exposure detected in participants of the epidemiologic studies.

A proposed mechanism of action explaining the above mentioned associations is via activation of peroxisome proliferator-activated receptor α (PPAR-α) (Wolf et al., 2008). Higher serum TC, low density lipoprotein cholesterol (LDL-C), and triglycerides (TG) and lower high-density lipoprotein cholesterol (HDL-C) are known predictors of cardiovascular disease in humans hence the importance of elucidating the influence of PFAAs on lipid metabolism. We used statistical approaches allowing for non-linearity to explore the associations of prenatal exposures to PFOS and PFOA with lipids serum concentrations at two age points, 7 and 15 years, in females enrolled in a prospective cohort study. The analysis focuses on female participants because prenatal PFAAs exposure data in males enrolled in the ALSPAC are not yet available for analyses. This study also addresses current limitations in causal inference while searching for non-linearity.

## 2. Methods

### 2.1. Source population

The Avon Longitudinal Study of Parents and Children (ALSPAC) enrolled pregnant women from three health districts of the old administrative county of Avon, UK, with an expected delivery date between April, 1991 and December, 1992. A total of 14,541 pregnant women, approximately 72% of the eligible source population, enrolled in the cohort during the 1990–1992 recruitment campaign. The eligible study sample has been defined retrospectively, using ALSPAC recruitment records and maternity, birth and child health records (Boyd et al., 2013). Details on eligibility and recruitment methods are described in detail elsewhere (Boyd et al., 2013; Fraser et al., 2013).

### 2.2. Study population

We linked concentrations of PFAAs measured in enrolled pregnant women with their daughters' serum TC, LDL-C, HDL-C, and TG concentrations measured at age 7 and again at age 15. Maternal concentrations of PFAAs were measured in banked blood for a nested case–control study of prenatal exposures to PFAAs and menarche in daughters (Christensen et al., 2011). We only used daughters in the control group for the current study (N = 230) because these are representative of the range of ages when menarche is most commonly attained. Lipid concentrations were measured in serum samples of cohort enrollees attending the 7-years clinic visit and of those attending the 15-years clinic visit open to all members of the ALSPAC cohort. After linkage, 111 daughters had both prenatal concentrations of PFAAs and lipids data at age 7 and 88 had both prenatal concentrations of PFAAs and lipids data at age 15.

### 2.3. Covariates

We identified maternal and daughter's predictors of lipid concentration a priori and identified common causes for adjustment in regression models. The set of covariates retained for the analyses consisted of maternal age at delivery (years); maternal education (lowest: none/Certification of Secondary Education or Vocational; middle: Ordinary Level; highest: Advance Level or University Degree); and previous live births (none; 1+). All daughters in the analyses were born to mothers of white race. Data collection instruments have been described in detail elsewhere (ALSPAC, 2014).

### 2.4. Laboratory analyses

PFOS and PFOA were measured in stored maternal blood samples collected between 1991–1992 at enrollment into the study. The median gestational age when samples were obtained was 15 weeks and the interquartile range was 10–28 weeks. Blood samples were analyzed at the National Center for Environmental Health of the CDC. Analytical methods used for detection of PFAAs (Kuklenyik et al., 2005) as well as prenatal PFAAs concentrations of all daughters in the nested case–control study (Christensen et al., 2011) have been described elsewhere. Limits of detection (LOD) were 0.2 ng/mL for PFOS and 0.1 ng/mL for PFOA. Prenatal concentrations of the PFAAs measured

**Table 1**
Distribution of PFAAs concentrations (in ng/mL) in serum from pregnant mothers and of serum lipids (in mg/dL) in daughters at ages 7 and 15.

| Analyte | Age 7 (n = 111) | | | | | | Age 15 (n = 88) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Min | Median | 95th | Max | Mean | SD | Min | Median | 95th | Max |
| *In maternal serum* | | | | | | | | | | | | |
| PFOS | 22.2 | 11.4 | 7.6 | 20.5 | 38.2 | 94.5 | 22.5 | 12.8 | 7.6 | 19.4 | 44.9 | 94.5 |
| PFOA | 4.2 | 2.3 | 1.2 | 3.6 | 7.6 | 16.4 | 4.5 | 2.5 | 1.1 | 3.6 | 7.6 | 16.4 |
| *In daughters' serum* | | | | | | | | | | | | |
| TC | 174.6 | 27.6 | 112.7 | 175.5 | 225.0 | 244.1 | 153.3 | 30.1 | 92.8 | 148.8 | 205.9 | 230.9 |
| LDL-C | 90.6 | 21.8 | 32.4 | 90.5 | 124.0 | 156.0 | 86.0 | 25.0 | 33.6 | 83.0 | 130.2 | 165.4 |
| HDL-C | 60.5 | 12.6 | 30.4 | 58.9 | 80.3 | 106.1 | 52.8 | 13.1 | 26.1 | 50.9 | 74.1 | 111.9 |
| TG | 84.1[a] | – | 30.3 | 83.7 | 195.8 | 271.5 | 68.4[a] | – | 24.0 | 68.1 | 124.6 | 210.9 |

SD = standard deviation; Min = minimum; 95th = 95th percentile; Max = maximum; TC = total cholesterol; LDL-C = low density lipoprotein-cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides.
[a] Geometric means.