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Perfluoroalkyl Acids in Maternal Serum and Indices of Fetal Growth: The Aarhus Birth Cohort

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Background: Previous studies indicated an association between intrauterine exposure to perfluorooctane sulfonate (PFOS) or perfluorooctanoate (PFOA) and lower birth weight. However, these perfluoroalkyl acids (PFAAs) have to some extent been substituted by other compounds on which little is known.

Objectives: We investigated the association between specific PFAAs and birth weight, birth length, and head circumference at birth.

Methods: We studied 1,507 mothers and their children from the Aarhus Birth Cohort (2008–2013). Nulliparous women were included during pregnancy, and serum levels of 16 PFAAs were measured between 9 and 20 completed gestational weeks (96% within 13 weeks). For compounds with quantifiable values in > 50% of samples (7 compounds), we report the associations with birth weight, birth length, and head circumference at birth determined by multivariable linear regression.

Results: Estimated mean birth weights were lower among women with serum perfluorohexane sulfonate, perfluoroheptane sulfonate, and PFOS concentrations above the lowest exposure quartile, but we found no consistent monotonic dose–response patterns. These associations were stronger when the population was restricted to term births (n = 1,426). For PFOS, the birth weight estimates for the highest versus lowest quartile were –50 g (95% CI: –123, 23 g) in all births and –62 g (95% CI: –126, 3 g) in term births. For the other PFAAs, the direction of the associations was inconsistent, and no overall association with birth weight was apparent. No PFAAs were associated with birth length or head circumference at birth.

Conclusions: Overall, we did not find strong or consistent associations between PFAAs and birth weight or other indices of fetal growth, though estimated mean birth weights were lower among those with exposures above the lowest quartile for some compounds.

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Introduction

Perfluoroalkyl acids (PFAAs) are human-made chemicals found in various products, for example, food items and packaging, pots and pans, and textiles such as carpets, furniture, shoes, and clothing (Kantiani et al. 2010). Specific PFAAs [perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA)] have been voluntarily phased out or regulated in some parts of the world (Environment Canada 2010; European Parliament 2006; UNEP 2009; U.S. EPA 2000, 2006), and these compounds have to some extent been replaced by novel, similar compounds.

PFAAs accumulate in the human body (Butenhoff et al. 2006) and are persistent in the environment. Some have been shown to cross the placenta (Fei et al. 2007; Inoue et al. 2004; Kim et al. 2011; Midasch et al. 2007), and it has been hypothesized that they may affect fetal growth and development, possibly due to interaction with the peroxisome proliferator-activated receptor alpha (Abbott 2009), estrogen biosynthesis or interaction with receptors *in vitro* (Benninghoff et al. 2011; Du et al. 2013; Henry and Fair 2011; Kjeldsen and Bonefeld-Jørgensen 2013), thyroid hormone signaling (Du et al. 2013; Wang et al. 2013; Thibodeaux et al. 2003; Lau et al. 2003; Long et al. 2013; Inoue et al. 2004; Kim et al. 2011), or lipid metabolism (Apelberg et al. 2007; Thibodeaux et al. 2003). It is also plausible that exposures could affect the mother's appetite and food intake, or have direct effects on placental growth and/or function.

In animals, several studies have found lower birth weight with exposure to PFOS (Luebker et al. 2005; Thibodeaux et al. 2003), PFOA (Koustas et al. 2014), and perfluoroundecanoic acid (PFUnA) (Takahashi et al. 2014). However, exposure levels were higher than average environmental exposures in humans. Epidemiological studies have investigated the association between exposure to PFOS and PFOA and birth weight or related outcomes (Apelberg et al. 2007; Arbuckle et al. 2013; Chen et al. 2012; Darrow et al. 2013; Fei et al. 2007; Hamm et al. 2010; Inoue et al. 2004; Kishi et al. 2015; Lee et al. 2013; Maisonet et al. 2012; Monroy et al. 2008; Robledo et al. 2015; Stein et al. 2009; Washino et al. 2009; Whitworth et al. 2012b; Wu et al. 2012). Even though most studies indicated an association with lower birth weight, in particular for PFOA, many studies had limited power and thus low precision due to small sample sizes (Bach et al. 2015). Few small studies (all with < 500 participants) investigated other PFAAs such as perfluorononanoic acid [PFNA (Arbuckle et al. 2013; Chen et al. 2012; Monroy et al. 2008; Robledo et al. 2015)], PFUnA (Chen et al. 2012), perfluorohexane sulfonate [PFHxS (Arbuckle et al. 2013; Hamm et al. 2010; Lee et al. 2013; Maisonet et al. 2012; Monroy et al. 2008)], perfluorodecanoic acid [PFDA (Robledo et al. 2015)], and perfluorooctane sulfonamide (Robledo et al. 2015) and found no consistent associations. To our knowledge, the present study is the largest to address PFAAs other than PFOS and PFOA to date. We aimed to examine the association between maternal serum levels of several PFAAs and birth weight, birth length, and head circumference at birth in a large sample of pregnant women exposed to present (2008–2013) population levels of PFAAs. Additionally, we aimed to investigate the association between PFAAs and gestational age at birth and preterm birth.

Methods

The Aarhus Birth Cohort and Biobank

Annually, approximately 4,500 women give birth at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark. The ongoing Aarhus Birth Cohort

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(ABC) was established in 1989 and contains self-administered questionnaire data from pregnant women who plan to give birth at the hospital. Most women complete the questionnaire at approximately 12 weeks of gestation. The cohort also contains information about birth outcomes collected by clinical staff (attending midwives) immediately after delivery using a structured birth registration form. Trained research midwives validated birth data until January 2013, and after this date the authors reviewed the registry records. So far, the cohort contains information on > 100,000 women (Larsen et al. 2013).

A biobank was added to the cohort in 2008 and contains blood samples from pregnant women, their partners, and umbilical cord material (Mortensen et al. 2013). Most maternal blood samples were obtained at approximately gestational week 12. All samples were processed within 2 hr and stored at –80°C until further analysis. All participants provided written informed consent accepting that blood samples are stored in a biobank, that the questionnaire data are stored electronically, and that all information can be used for future research approved by the proper authorities (Mortensen et al. 2013). Currently, the biobank contains blood samples from > 10,000 women.

Selection of Participants

For this study, women in the cohort were eligible if they donated a blood sample between 9 and 20 completed gestational weeks, gave birth to a live-born, singleton neonate, and were nulliparous. From the women who fulfilled these criteria (n = 2,853) we randomly sampled 1,533 women recruited during 2008–2013 (220–290 participants annually). Of these women, 1,507 (98%) had complete data on exposure, birth weight, and covariates and were included in the final study population. Regarding birth length, 1,499 (98%) participants were included, and for head circumference, 1,494 (97%) participants were included in the analyses. Approval was obtained from the Danish Data Protection Agency (reference 2012-41-1288), and the data collection was accepted by the Danish National Committee on Health Research Ethics (reference M-20110054).

Exposure Assessment

We measured the levels of 16 PFAAs in maternal serum and included compounds where at least 50% of the samples were above the lower limit of quantification (LOQ) (Table 1). PFAA analysis was performed at the Department of Environmental Science, Aarhus University, by use of high performance liquid chromatography–tandem mass spectrometry after solid phase extraction (Liew et al. 2014).

Outcomes

The outcomes available in the cohort included birth weight (continuous and z-score), birth length, and head circumference at birth. z-Scores were calculated by standardization of birth weight for gestational age according to the most recent (1996) Scandinavian fetal reference (Marsál et al. 1996). Furthermore, we studied the gestational age at birth and the odds for preterm birth (birth before 37 weeks and 0 days of gestation). Gestational age at birth was determined by first trimester ultrasound measurements. We identified no implausible values of gestational age at birth (< 24 weeks or > 45 weeks). We identified birth weight and gestational age mismatches (Alexander et al. 1996), and participants with implausible combinations (n = 5) were excluded from the analyses of birth weight along with six participants with missing birth weight.

Statistical Analysis

We performed multivariable linear regression with robust standard errors (Huber–White sandwich estimator) to estimate the association between individual PFAAs and continuous birth weight and birth weight z-scores, birth length, head circumference at birth, and gestational age at birth. The association between levels of PFAAs and preterm birth was analyzed by logistic regression. We substituted PFAA values below the LOQ with the LOQ divided by the square root of 2. Levels of PFAAs were divided into quartiles with the lowest category used as reference. Moreover, we assessed the associations between continuous exposure measures and the above-mentioned outcomes. The continuous exposure measures were rescaled to assess the change in outcomes with a 0.1-ng/mL increase in PFAA levels because most of the compounds had median values < 1 ng/mL. To enhance comparability of individual PFAAs within our study, we also modeled estimates per interquartile range of exposure. In addition, PFAA levels were modeled by the use of restricted cubic splines with prespecified knots according to the quartile boundaries for each PFAA.

We identified covariates to include in the analyses by directed acyclic graphs (DAGs) (see Figures S1 and S2). The analyses were adjusted for maternal age (continuous), maternal prepregnancy body mass index [BMI (continuous)], and maternal level of education (four categories). Furthermore we conditioned on parity by restricting to nulliparous women. Information on maternal age and parity was available in the birth registration form, and information on BMI and maternal level of education was extracted from the questionnaire. There were no missing values for maternal age. Few values were missing for BMI (n = 11) and level of education (n = 4).

In a secondary analysis, we included gestational age (continuous) in the birth weight model in addition to the other covariates. We did this to compare our findings with the existing literature, even though we are aware of the caveats of adjustment for a potential intermediate (Wilcox et al. 2011). These considerations apply to birth weight z-scores as well. We also restricted the analyses to children born at term (≥ 37 weeks of gestation). Due to previous reports on sex differences concerning the investigated association (Andersen et al. 2010; Maisonet et al. 2012; Robledo et al. 2015; Washino et al. 2009), we performed the analyses of birth weight separate for each sex, as well as pooled. We examined the importance of the gestational age at blood draw by restriction to participants who gave a blood sample within 13 completed gestational weeks [n = 1,440 (96%)]. STATA statistical software version 12 (StataCorp, College Station, TX, USA) was used for all the statistical analyses.

Results

For seven of the measured PFAAs, more than 50% of the samples had concentrations above the lower limit of quantification [PFHxS, perfluoroheptane sulfonate (PFHpS), PFOS, PFOA, PFNA, PFDA, and

Table 1. Perfluoroalkyl acid abbreviations, limits of quantification (LOQ), levels above the LOQ, and exposure distributions for included compounds measured in 1,507 serum samples from the Aarhus Birth Cohort, 2008–2013.

Full name of PFAA	Abbreviation	LOQ	% above LOQ	Median (IQR)	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Perfluorohexane sulfonate	PFHxS	0.08	99.9	0.5 (0.4–0.6)	< LOQ–0.36	0.37–0.47	0.48–0.63	0.64–6.82
Perfluoroheptane sulfonate	PFHpS	0.11	76	0.2 (0.1–0.2)	< LOQ–0.11	0.12–0.16	0.17–0.21	0.22–1.16
Perfluorooctane sulfonate	PFOS	0.28	99.9	8.3 (6.0–10.8)	< LOQ–6.02	6.03–8.29	8.30–10.80	10.81–36.10
Perfluorooctanoic acid	PFOA	0.20	99.9	2.0 (1.5–2.6)	< LOQ–1.53	1.54–2.02	2.03–2.64	2.65–15.10
Perfluorononanoic acid	PFNA	0.27	99	0.8 (0.6–1.0)	< LOQ–0.60	0.61–0.75	0.76–0.97	0.98–4.69
Perfluorodecanoic acid	PFDA	0.09	99	0.3 (0.2–0.4)	< LOQ–0.24	0.25–0.31	0.32–0.42	0.43–2.87
Perfluoroundecanoic acid	PFUnA	0.15	87	0.3 (0.2–0.4)	< LOQ–0.20	0.21–0.29	0.30–0.44	0.44–2.47

Abbreviations: IQR, Interquartile range; PFAA, perfluoroalkyl acid.
All concentrations are in nanograms per milliliter.

PFUnA]. LOQ, levels above the LOQ, and distributions of the included PFAAs are listed in Table 1, and corresponding information regarding the excluded compounds is listed in Table S1. Pearson's correlations for the seven included PFAAs are shown in Table S2. The two PFAAs with the highest correlation were PFNA and PFDA (Pearson's correlation = 0.85), and the lowest correlation was found for PFUnA and PFHxS (Pearson's correlation = 0.14).

Women with exposure levels in the higher quartiles were slightly older than those with exposure levels in the lower quartiles—the median ages were 29 years in the lowest quartiles and 30–31 years in the highest (Table 2). Maternal prepregnancy BMI did not differ according to exposure levels. For women with the three higher levels of education, there was not much difference between exposure distributions, but for the group of women with the lowest educational level, 38–50% of women had exposure levels in the lowest PFAA quartiles.

For three perfluoroalkane sulfonic acids (PFHxS, PFHpS, and PFOS) estimated mean birth weights were lower for all quartiles above the first quartile (Table 3). Only PFHxS showed some indication of a monotonic dose–response relationship with birth weight. Further adjustment for gestational age did not change the results in any consistent direction, but the associations for PFHxS, PFHps, and PFOS were stronger in term births (n = 1,426). Continuous exposure measures of these compounds were not consistently associated with lower estimated mean birth weights.

No obvious association was found between PFOA, PFNA, PFDA, and PFUnA and birth weight (Table 3) regardless of whether exposures were modeled as continuous or categorical variables. For individual compounds the direction of the estimates was not consistent in each quartile, and no dose–response relationships were evident.

Restricted cubic splines of the associations between PFAAs and birth weight are presented in Figure S3. In general these did not identify any clear thresholds nor did they indicate monotonic dose–response patterns.

The associations between PFAA exposure and birth weight did not differ substantially between boys and girls for most compounds (Table 4). For PFNA and PFDA, estimated mean birth weights were lower for girls than for boys for quartiles above the first quartile, but in girls there was no monotonic dose–response pattern, and some of the apparent sex differences were attributable to higher estimated mean birth weight in boys with exposures above the lowest quartile.

Estimates for the association between PFAA exposures and birth length and head circumference at birth were all close to zero (see Table S3). There was no obvious association between PFAA exposure and gestational age at birth or preterm birth (see Table S4). The levels of PFAAs were similar in samples taken before and after 13 gestational weeks (data not shown), and the exclusion of 67 participants with a blood sample drawn after 13 completed gestational weeks did not change the results (data not shown).

Discussion

Overall, we found weak and inconsistent associations between PFAA exposures and birth weight, birth length, and head circumference at birth. Independent of offspring sex, estimated mean birth weights were lower in quartiles above the lowest quartile of three perfluoroalkane sulfonic acids, without clear monotonic dose–response patterns, whereas PFNA and PFDA tended to be associated with lower birth weight in girls only. However, the sex-specific estimates were less precise than the estimates from the complete population.

Quite a few studies have investigated the association between PFAAs and infant size at birth. PFAAs were measured in plasma or serum from maternal blood before conception, during pregnancy, or at birth, or in umbilical cord blood; and exposures were modeled as different continuous or categorical variables, which have made comparison of the results cumbersome. Also, the studies controlled for different factors (Bach et al. 2015). Nine studies investigated the association between PFOA and birth weight (Apelberg et al. 2007; Chen et al. 2012; Darrow et al. 2013; Fei et al. 2007; Hamm et al. 2010; Kishi et al. 2015; Maisonet et al. 2012; Robledo et al. 2015; Washino et al. 2009), and all found lower estimated mean birth weights with increasing exposure levels even though the magnitude and precision of the estimates varied substantially. Seven of 10 studies found tendencies towards lower birth weight with higher PFOS levels (Apelberg et al. 2007; Chen et al. 2012; Darrow et al. 2013; Fei et al. 2007; Hamm et al. 2010;

Table 2. Maternal characteristics according to early pregnancy levels of perfluoroalkyl acids in 1,507 mothers from the Aarhus Birth Cohort, 2008–2013.

PFAA	Age (years) [median (IQR)]	Prepregnancy BMI (kg/m^2) [median (IQR)]	Education (%)			
			1 (n = 42)	2 (n = 439)	3 (n = 580)	4 (n = 446)
PFHxS						
Q1	29 (27–31)	22 (20–25)	50	27	27	19
Q2	29 (27–31)	22 (21–25)	19	24	26	25
Q3	30 (27–32)	22 (21–25)	21	27	23	25
Q4	31 (29–33)	22 (20–25)	10	23	24	31
PFHpS						
Q1	29 (27–32)	22 (20–24)	48	23	26	24
Q2	29 (27–32)	22 (20–24)	14	28	25	26
Q3	29 (27–32)	22 (20–25)	21	24	26	22
Q4	30 (28–33)	22 (21–25)	17	24	22	28
PFOS						
Q1	29 (27–32)	22 (20–25)	45	25	27	22
Q2	29 (27–32)	22 (20–25)	19	25	25	24
Q3	29 (27–32)	22 (20–24)	22	27	23	29
Q4	30 (28–32)	22 (21–25)	14	23	25	25
PFOA						
Q1	29 (27–32)	22 (21–26)	43	23	27	23
Q2	29 (27–32)	22 (20–24)	28	25	26	26
Q3	29 (27–31)	22 (20–25)	10	27	23	25
Q4	30 (28–32)	22 (21–25)	19	25	24	26
PFNA						
Q1	29 (27–32)	22 (20–25)	48	26	25	21
Q2	30 (28–32)	22 (21–25)	17	26	25	27
Q3	30 (27–32)	22 (20–24)	10	24	24	27
Q4	30 (28–32)	22 (21–25)	26	24	26	24
PFDA						
Q1	29 (27–32)	22 (20–25)	38	27	27	20
Q2	29 (27–31)	22 (21–25)	19	25	26	24
Q3	30 (27–33)	22 (20–25)	10	25	23	29
Q4	30 (28–32)	22 (20–24)	33	23	24	28
PFUnA						
Q1	29 (27–32)	22 (21–26)	48	30	27	18
Q2	29 (27–32)	22 (20–25)	19	25	26	22
Q3	30 (27–32)	22 (20–25)	17	23	23	31
Q4	30 (28–32)	22 (20–24)	17	22	24	29

Abbreviations: IQR, interquartile range; PFAA, perfluoroalkyl acid; Q, quartile. For specific PFAA abbreviations see Table 1. Definitions of highest completed maternal education: 1. Municipal primary and lower secondary school; 2. upper secondary school, or 1–2 years of vocational training; 3. additional 3–4 years of education, e.g., Bachelor's degree; 4. > 4 additional years of education, e.g., Master's degree.

Inoue et al. 2004; Kishi et al. 2015; Maisonet et al. 2012; Robledo et al. 2015; Washino et al. 2009). Compared with some previous studies, we report lower serum levels of PFOS (Darrow et al. 2013; Fei et al. 2007; Lee et al. 2013; Maisonet et al. 2012; Monroy et al. 2008) and PFOA (Darrow et al. 2013; Fei et al. 2007; Maisonet et al. 2012; Wu et al. 2012). For instance, the mean level of PFOA was 5.6 ng/mL in a previous Danish study (1996–2002) by Fei et al. (2007) compared with 2.2 ng/mL in the present study. In the study by Fei et al. (2007), the mean level of PFOS was 35.3 ng/mL compared with 8.9 ng/mL in the present study. This may be attributable to a decreasing exposure trend over time. If a threshold value of exposure exists, this may partly explain the lack of an association between PFOA and birth weight, birth length, and head circumference at birth in the present study. It is possible that regulatory measures might have decreased exposure sources sufficiently, perhaps to an extent that PFOA does not pose a potential threat to perinatal health. Thus, the results of the present study are largely reassuring. However, in accordance with other studies, the present results suggest an association between PFOS and lower birth weight. Other compounds, such as PFHxS and PFHpS, were also associated with lower birth weight. If an association between PFAAs and birth weight is mediated by changes in the sex hormone homeostasis, this may explain the somewhat different associations that we found according to offspring sex for PFNA and PFDA, but

Table 3. Maternal levels of perfluoroalkyl acids and birth weight in 1,507 children from the Aarhus Birth Cohort, 2008–2013.

	Birth weight (g)					Birth weight *z*-score	
PFAA/exposure scale	Mean ± SD	Crude	Adjusted[a] (95% CI)	Adjusted[b] (95% CI)	Restricted[c] (95% CI)	Crude	Adjusted[a] (95% CI)
PFHxS							
Q1	3,460 ± 556	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,452 ± 460	–9	–15 (–87, 57)	–11 (–67, 44)	–41 (–105, 24)	0.00	–0.01 (–0.15, 0.12)
Q3	3,436 ± 504	–24	–25 (–100, 50)	–21 (–79, 37)	–34 (–101, 32)	–0.04	–0.03 (–0.17, 0.11)
Q4	3,424 ± 511	–37	–29 (–106, 47)	–49 (–109, 11)	–49 (–118, 19)	–0.13	–0.11 (–0.25, 0.03)
Per IQR (0.3 ng/mL)		–9	–7 (–28, 14)	–13 (–30, 3)	–11 (–32, 9)	–0.04	–0.03 (–0.07, 0.01)
Per 0.1 ng/mL		–3	–2 (–10, 5)	–5 (–11, 1)	–4 (–12, 3)	–0.01	–0.01 (–0.03, 0.00)
PFHpS							
Q1	3,473 ± 509	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,418 ± 540	–56	–52 (–126, 21)	–20 (–75, 35)	–46 (–109, 17)	–0.05	–0.04 (–0.17, 0.10)
Q3	3,446 ± 478	–27	–34 (–105, 36)	–50 (–107, 6)	–56 (–118, 7)	–0.10	–0.11 (–0.24, 0.02)
Q4	3,436 ± 504	–38	–42 (–115, 31)	–43 (–100, 14)	–63 (–129, 2)	–0.10	–0.10 (–0.23, 0.04)
Per IQR (0.1 ng/mL)		–8	–12 (–40, 17)	–17 (–40, 6)	–23 (–50, 4)	–0.03	–0.04 (–0.09, 0.02)
Per 0.1 ng/mL		–7	–11 (–37, 16)	–15 (–36, 5)	–21 (–45, 3)	–0.03	–0.04 (–0.09, 0.02)
PFOS							
Q1	3,481 ± 520	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,397 ± 518	–84	–86 (–159, –13)	–66 (–122, –11)	–93 (–157, –29)	–0.15	–0.15 (–0.29, –0.02)
Q3	3,461 ± 486	–20	–21 (–91, 48)	–30 (–86, 26)	–50 (–113, 13)	–0.07	–0.06 (–0.19, 0.07)
Q4	3,431 ± 510	–50	–50 (–123, 23)	–58 (–105, 8)	–62 (–126, 3)	–0.11	–0.11 (–0.25, 0.02)
Per IQR (4.8 ng/mL)		–1	–2 (–30, 26)	–8 (–30, 14)	–14 (–40, 11)	–0.02	–0.02 (–0.07, 0.04)
Per 0.1 ng/mL		0	0 (–1, 1)	0 (–1.0)	0 (–1, 0)	0.00	0.00 (0.00, 0.00)
PFOA							
Q1	3,441 ± 536	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,419 ± 522	–22	–1 (–75, 74)	3 (–54, 59)	–36 (–101, 30)	–0.04	0.009 (–0.13, 0.14)
Q3	3,458 ± 488	17	28 (–45, 102)	15 (–42, 72)	–7 (–73, 58)	0.01	0.04 (–0.09, 0.17)
Q4	3,455 ± 488	13	26 (–47, 98)	9 (–47, 64)	4 (–59, 67)	–0.005	0.03 (–0.10, 0.16)
Per IQR (1.1 ng/mL)		19	21 (–1, 44)	7 (–10, 23)	13 (–6, 33)	0.01	0.02 (–0.02, 0.06)
Per 0.1 ng/mL		2	2 (–1, 4)	1 (–1, 2)	1 (–1, 3)	0.00	0.00 (0.00, 0.00)
PFNA							
Q1	3,458 ± 544	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,452 ± 496	–6	–12 (–85, 61)	–20 (–77, 37)	–26 (–92, 40)	–0.02	–0.03 (–0.17, 0.10)
Q3	3,391 ± 501	–67	–63 (–137, 11)	–43 (–100, 14)	–72 (–137, –6)	–0.10	–0.08 (–0.22, 0.05)
Q4	3,471 ± 490	14	11 (–62, 84)	3 (–54, 61)	10 (–55, 75)	0.03	0.02 (–0.11, 0.16)
Per IQR (0.4 ng/mL)		16	15 (–7, 38)	8 (–9, 25)	11 (–9, 31)	0.02	0.02 (–0.02, 0.06)
Per 0.1 ng/mL		4	4 (–2, 10)	2 (–2, 7)	3 (–2, 9)	0.01	0.01 (0.00, 0.02)
PFDA							
Q1	3,461 ± 554	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,432 ± 492	–29	–34 (–107, 39)	–45 (–103, 13)	–55 (–120, 11)	–0.09	–0.10 (–0.24, 0.04)
Q3	3,411 ± 506	–50	–44 (–119, 31)	–55(–113, 2)	–52 (–117, 13)	–0.15	–0.13 (–0.26, 0.01)
Q4	3,468 ± 480	7	17 (–56, 90)	2 (–55, 59)	4 (–60, 69)	–0.01	0.02 (–0.12, 0.15)
Per IQR (0.2 ng/mL)		11	15 (–6, 37)	9 (–7, 24)	13 (–6, 31)	0.01	0.02 (–0.01, 0.06)
Per 0.1 ng/mL		6	9 (–3, 21)	5 (–4, 13)	7 (–3, 17)	0.01	0.01 (–0.01, 0.03)
PFUnA							
Q1	3,449 ± 532	Reference	Reference	Reference	Reference	Reference	Reference
Q2	3,439 ± 510	–10	3 (–71, 76)	–3 (–61, 55)	4 (–60, 69)	–0.04	–0.007 (–0.15, 0.13)
Q3	3,459 ± 513	10	29 (–46, 105)	17 (–42, 76)	24 (–43, 91)	–0.02	0.03 (–0.11, 0.18)
Q4	3,425 ± 480	–24	8 (–65, 81)	–13 (–72, 45)	–15 (–81, 51)	–0.11	–0.03 (–0.17, 0.11)
Per IQR (0.2 ng/mL)		–9	0 (–21, 21)	–5 (–22, 11)	–8 (–27, 11)	–0.03	–0.01 (–0.05, 0.03)
Per 0.1 ng/mL		–4	0 (–8, 9)	–2 (–9, 5)	–3 (–11, 5)	–0.01	0.00 (–0.02, 0.01)

Abbreviations: IQR, interquartile range; Q, quartile. For PFAA abbreviations see Table 1.
[a]Adjusted for maternal age, prepregnancy BMI and educational level. [b]Additionally adjusted for gestational age (continuous). [c]Adjusted as model A and restricted to term births (> 37 gestational weeks and 0 days). Adjustment for gestational age among infants born at term did not changes the results (data not shown).

these differences may also be attributable to statistical imprecision. Compounds other than PFOS and PFOA have been studied to a lesser extent, are currently not regulated, and thus need further investigation.

We studied women who were nulliparous at inclusion, gave birth to a live-born child, provided blood samples, and completed a questionnaire. This may influence the validity and generalizability of our results. Selection bias due to nonresponse may not be very likely since participants were unaware of individual exposure levels (at any time) as well as the outcomes at the time of inclusion. However, it cannot be ruled out that the selection of study participants may have been associated with both exposure levels and the outcomes.

A few studies investigated the association between PFAAs and fecundability (Buck Louis et al. 2013; Fei et al. 2009; Jørgensen et al. 2014; Vélez et al. 2015; Vestergaard et al. 2012; Whitworth et al. 2012a), miscarriage (Darrow et al. 2014; Jensen et al. 2015; Savitz et al. 2012a; Stein et al. 2009), and stillbirth (Savitz et al. 2012a, 2012b) and found inconsistent results. Survival until birth may be less likely to occur among smaller fetuses, and if PFAA exposure is also associated with a decreased chance of live birth, restriction of the study population to live births only may have introduced selection bias which potentially attenuated a possible association between PFAAs and lower birth weight (Liew et al. 2015). However, the magnitude of a possible bias is largely unknown, and the bias relies on the strong assumption of very strong associations between PFAA exposure and a decreased chance of live birth. Adjustment for common causes of low birth weight and fetal survival, such as maternal age, BMI, and educational level, would have reduced a possible live birth bias (Liew et al. 2015).

Accurate exposure assessment and the use of multiple exposure scales (continuous, categorical, splines) were strengths of our study. We chose to use the same continuous exposure scales for all compounds even though an increase of 0.1 ng/mL was a large increase for compounds with low average concentrations and a small increase for compounds with higher average concentrations such as PFOS and PFOA. To ease comparability for the different PFAAs within our study, we also used continuous exposures divided by the interquartile range. We demanded strict laboratory procedures from sampling to the final analysis. Limited time was allowed from blood sampling to processing and freezing, state-of-the-art laboratory equipment was used, and the high performance chromatography–tandem mass spectrometry setup was controlled using internal and external validation and controls. Objectively measured exposures such as PFAA levels are unlikely to be prone to differential measurement error. Because levels of PFAAs decrease throughout pregnancy (Glynn et al. 2012), we only included women who gave a blood sample before 20 completed gestational weeks.

Trained health care professionals systematically assessed the outcomes as part of routine data collection concerning all births at the hospital. Measurement error concerning birth weight, particularly differential measurement error, is unlikely to be of importance. However, birth length and head circumference at birth may be more prone to measurement error, and this might partly explain our close-to-null results for these outcomes.

We were able to control for the potential confounders we considered to be most important (see Figures S1 and S2), including maternal prepregnancy BMI, age, educational level, and parity (by restriction to first-time mothers). Maternal prepregnancy BMI and

Table 4. Sex-stratified associations between levels of perfluoroalkyl acids and birth weight in 764 boys and 743 girls from the Aarhus Birth Cohort, 2008–2013.

	Birth weight in boys		Birth weight in girls		Sex-exposure interaction[b]
PFAA/exposure scale	Crude	Adjusted[a] (95% CI)	Crude	Adjusted[a] (95% CI)	Adjusted[a] (95% CI)
PFHxS					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	–14	–21 (–124, 82)	5	6 (–93, 106)	27 (–115, 170)
Q3	–31	–19 (–127, 89)	–19	–21 (–123, 80)	–3 (–151, 145)
Q4	–13	–16 (–125, 93)	–56	–34 (–141, 73)	–17 (–170, 135)
Per IQR (0.3 ng/mL)	–14	–14 (–51, 22)	–5	–1 (–25, 22)	13 (–30, 56)
Per 0.1 ng/mL	–5	–5 (–19, 8)	–2	0 (–9, 8)	5 (–11, 21)
PFHpS					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	–82	–69 (–178, 40)	–36	–39 (–138, 60)	30 (–117, 177)
Q3	0	0 (–102, 101)	–48	–60 (–153, 37)	–58 (–197, 82)
Q4	–15	–16 (–123, 92)	–76	–78 (–176, 20)	–63 (–208, 83)
Per IQR (0.1 ng/mL)	5	4 (–35, 43)	–27	–30 (–72, 12)	–34 (–91, 23)
Per 0.1 ng/mL	5	4 (–32, 39)	–25	–27 (–65, 11)	–31 (–83, 21)
PFOS					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	–132	–129 (–239, –19)	–37	–44 (–140, 52)	85 (–61, 231)
Q3	16	9 (–93, 110)	–56	–55 (–148, 38)	–63 (–201, 75)
Q4	–40	–37 (–141, 67)	–73	–71 (–174, 31)	–34 (–180, 112)
Per IQR (4.8 ng/mL)	25	26 (–13, 65)	–32	–32 (–71, 7)	–58 (–114, –3)
Per 0.1 ng/mL	1	1 (0, 1)	–1	–1 (–1, 0)	–1 (–2, –1)
PFOA					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	–35	–17 (–126, 93)	–11	6 (–95, 107)	23 (–126, 172)
Q3	36	54 (–54, 163)	–11	–2 (–100, 95)	–56 (–202, 89)
Q4	11	21 (–84, 126)	11	22 (–79, 124)	1 (–144, 147)
Per IQR (1.1 ng/mL)	27	31 (4, 59)	1	4 (–34, 42)	–27 (–74, 20)
Per 0.1 ng/mL	2	3 (0, 5)	0	0 (–3, 4)	–2 (–7, 2)
PFNA					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	63	62 (–48, 172)	–89	–97 (–193, –2)	–160 (–305, –14)
Q3	20	19 (–94, 133)	–131	–123 (–218, –29)	–143 (–291, 5)
Q4	50	46 (–64, 155)	–39	–35 (–133, 63)	–81 (–228, 66)
Per IQR (0.4 ng/mL)	28	27 (–5, 59)	–5	–4 (–38, 31)	–31 (–78, 16)
Per 0.1 ng/mL	8	7 (–2, 16)	–1	–1 (–11, 8)	–9 (–22, 5)
PFDA					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	11	13 (–98, 124)	–65	–70 (–167, 26)	–84 (–230, 63)
Q3	30	38 (–73, 148)	–136	–127 (–228, –26)	–165 (–314, –15)
Q4	74	84 (–25, 192)	–73	–58 (–156, 39)	–142 (–287, 4)
Per IQR (0.2 ng/mL)	18	21 (–7, 49)	–6	0 (–36, 37)	–20 (–166, 25)
Per 0.1 ng/mL	10	12 (–4, 27)	–3	0 (–20, 21)	–11 (–37, 14)
PFUnA					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	–17	–12 (–124, 99)	–14	0 (–97, 97)	13 (–135, 161)
Q3	7	25 (–86, 136)	2	24 (–79, 127)	–1 (–152, 150)
Q4	–19	13 (–101, 127)	–41	–11 (–102, 81)	–24 (–169, 122)
Per IQR (0.2 ng/mL)	–8	1 (–33, 35)	–13	–5 (–31, 22)	–6 (–49, 37)
Per 0.1 ng/mL	–3	1 (–14, 15)	–5	–2 (–13, 9)	–2 (–20, 15)

Abbreviations: IQR, interquartile range; Q, quartile. For PFAA abbreviations, see Table 1.
[a]Adjusted for maternal age, prepregnancy BMI, and educational level. [b]Differences in birth weight between sexes are based on girls compared with boys—negative estimates refer to lower birth weight estimates for girls compared with boys.

education were self-reported and may thus be recorded with some error. It is debatable whether the slightly stronger association for PFHxS, PFHpS, and PFOS after adjustment for gestational age, restriction to term births, or modeling of *z*-scores may be attributable to collider stratification bias (if gestational age is a mediator of the association between PFAAs and birth weight, and any factors we did not account for affected both gestational age and birth weight, conditioning on gestational age may have induced a spurious association between PFAAs and birth weight).

Physiological phenomena in pregnancy, including changes in the maternal glomerular filtration rate (GFR) and plasma volume expansion, may be potentially important confounders if exposures are assessed in late pregnancy or at birth (Loccisano et al. 2013; Morken et al. 2014). These phenomena are of much larger magnitude in late than in early pregnancy, and the fact that we measured PFAA levels early is likely to have reduced potential confounding by these factors, which we did not collect information on. In previous studies measuring PFAAs in late pregnancy, or at birth, confounding by changes in GFR and plasma volume expansion may potentially explain the associations demonstrated between higher levels of PFAAs and lower birth weight. However, in a recent review of the literature, we found no systematic differences in the magnitude and direction of the association between PFAAs and the estimated mean birth weight differences according to the timing of exposure assessment (Bach et al. 2015). Because the causal window of exposure is largely unknown, the optimal timing of exposure assessment is unsettled. We consider early measurements to be preferable in order to limit the impact of physiological changes during pregnancy that may influence the measured exposures.

Levels of PFAA compounds are correlated (see Table S2), and different PFAAs are likely derived from similar exposure sources. Biologically, it is possible that different PFAAs share health effects.

Conclusions

We found no strong associations between PFAA exposures and birth weight, birth length, or head circumference at birth. In particular, we failed to replicate the association between PFOA and lower birth weight previously shown primarily in populations with higher exposures that were not restricted to nulliparous women. The estimated mean birth weights were lower in quartiles above the reference for PFOS, PFHxS, and PFHpS for all infants and for PFNA and PFDA in girls only. Most of the compounds we investigated have not been studied much, and more studies are warranted.

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