HHS Public Access

Author manuscript

Chemosphere. Author manuscript; available in PMC 2020 September 20.

Published in final edited form as:

Chemosphere. 2015 August ; 133: 31–40. doi:10.1016/j.chemosphere.2015.03.015.

Maternal and Paternal Serum Concentrations of Perfluoroalkyl and Polyfluoroalkyl Substances and the Secondary Sex Ratio

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Abstract

Select persistent environmental chemicals have been associated with a reduction in the secondary sex ratio (SSR), or the ratio of male to female live births. We evaluated preconception maternal, paternal, and couple serum concentrations of perfluoroalkyl and polyfluoroalkyl substances (PFASs) in relation to the SSR, given the absence of previous investigation. Two hundred thirty-three couples from Michigan and Texas were enrolled prior to conception and prospectively followed through delivery of a singleton birth, 2005–2009. Maternal and paternal serum concentrations (ng/mL) were measured at baseline for seven PFASs. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for a male birth, after adjusting for potential confounders. When maternal and paternal PFAS concentrations were modeled jointly, five of the seven PFASs, including the two most prominent PFASs, perfluorooctane sulfonic acid and perfluorooctanoic acid, were not significantly associated with the SSR. However, paternal *N*-methyl-perfluorooctane sulfonamidoacetic acid (MeFOSAA) and perfluorononanoic acid (2nd vs 1st tertile, OR, 0.43, 95% CI, 0.21–0.88) were significantly associated with an excess of female births. Meanwhile, a dose-response relation was observed only for paternal MeFOSAA (2nd vs 1st tertile, OR, 0.53, 95% CI, 0.26–1.10; 3rd vs 1st tertile, OR, 0.34, 95% CI, 0.13–0.89). This study suggests a possible dose-response relation between a less prevalent PFAS and a reversal in the SSR, though the underlying mechanisms remain unknown and the findings await corroboration to eliminate other explanations including chance.

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Keywords

endocrine disruptors; fertility; maternal exposure; paternal exposure; perfluoroalkyl and polyfluoroalkyl substances; sex ratio

1. Introduction

While the primary sex ratio is the ratio of males to females at the time of conception, the secondary sex ratio (SSR) is the ratio of males to females at the time of birth. Given the challenges in measuring the primary sex ratio, investigators rely on the SSR to monitor population health and fertility, undeterred by debate on its usefulness (Davis et al., 1998; James, 2008a). Commonly restricted to singleton births, the SSR is calculated as the number of male live births divided by female live births, although its denominator can be all live births to indicate the percentage of male live births as well (Buck Louis and Platt, 2011). Except in countries where sex-selective abortion or infanticide misrepresents the SSR, the SSR is expected to range from 1.05 to 1.07 in the United States and worldwide, indicative of a slight excess of males (Central Intelligence Agency; Mathews and Hamilton, 2005). Variations in the SSR are associated with parental ages at the population level (Jacobsen et al., 1999; Mathews and Hamilton, 2005), and also purported to be influenced by a variety of endogenous and exogenous factors, including the timing of conception within the ovulatory cycle (James, 2008b), length of follicular phase (Weinberg et al., 1995), endocrine and immunological effects (James, 2008a; Ober, 1992), race/ethnicity (Davis et al., 2007; Mathews and Hamilton, 2005), birth order of the child (Biggar et al., 1999; Mathews and Hamilton, 2005), stress caused by war and natural disasters (Fukuda et al., 1998; Zorn et al., 2002), and possibly other lifestyle or environmental factors (Terrell et al., 2011).

In recent decades, declining trends in the SSR have been reported, notably in industrial countries such as the United States, Canada, the United Kingdom, the Netherlands, Germany, Denmark, Finland, and Japan (Davis et al., 2007; Grech et al., 2003; Mathews and Hamilton, 2005). It has been suggested that exposures to endocrine disrupting chemicals may have been contributed to the recent trends in the SSR. To date, more than 100 studies have been conducted to search for environmental or occupational toxicants perturbing sex selection and sex-selective survival in humans (Terrell et al., 2011). A comprehensive review article examined maternal and paternal exposures to polychlorinated biphenyls (PCBs), dioxins including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), metals including lead and methylmercury, dibromochloropropane (DBCP) and other pesticides, non-ionizing and ionizing radiation, boron, and g-forces, and identified select paternal PCBs as being associated with an increased SSR, whereas paternal dioxins were associated with a decreased SSR. Little evidence was observed for maternal exposures to any toxicants and the SSR (Terrell et al., 2011). On the other hand, in a systematic review of 15 studies on PCBs in relation to the SSR, Nieminen et al. (2013) found no strong or moderate indication that parental exposures to PCBs alter the SSR. Meanwhile, Taylor et al. (2007) reported increase in the odds of a male birth in relation to maternal exposures to estrogenic PCBs but not anti-estrogen PCBs. Although not statistically significant, their findings suggest varying effects of PCB congeners on the SSR depending upon their purported hormonal activity.

Despite the ubiquitous nature of perfluoroalkyl and polyfluoroalkyl substances (PFASs) for human populations given their use in textiles, carpets, upholstery, surfactants, and paper and packing protectants (Giesy and Kannan, 2002), we are unaware of any research focusing on the relation of PFASs to the SSR. Due to their bio-accumulative tendency, perfluorooctane sulfonic acid (PFOS) and select perfluorocarboxylic acids including perfluorooctanoic acid (PFOA) are known as prominent PFASs detected in human serum with varying concentrations and distributions of the chemicals among populations (Kannan et al., 2004; Kato et al., 2011). The data gap on the SSR contrasts with a growing body of evidence for potential human reproductive and developmental toxicity of PFASs, albeit not conclusive or consistent (Buck Louis et al., 2013; Fei et al., 2009; Joensen et al., 2013; Raymer et al., 2012; Toft et al., 2012; Whitworth et al., 2012). To our knowledge, a recent study first evaluated the association between sperm Y:X chromosome ratio and serum levels of PFOS and PFOA in men from Greenland, Poland, and Ukraine (Kvist et al., 2012). Among the three populations, a positive linear trend between sperm Y:X chromosome ratio and serum PFOS concentration was observed; however, when analyzing the populations separately, a negative linear trend was observed in the Inuit population. The lack of any associations between sperm Y:X chromosome ratio and serum PFOA concentration was also noted. As stated by the authors, their findings may reflect regional differences in serum PFOS and PFOA concentrations and their effects on male fertility (Kvist et al., 2012). Although not directly assessed in terms of the SSR, perfluoroundecanoic acid levels were lower in cord blood of male infants than female infants in a Taiwanese birth cohort (Lien et al., 2013). With increasing speculation that the SSR is parentally and not just paternally mediated (James, 2008a), we sought to evaluate the association between maternal, paternal, and couple serum PFAS concentrations and the SSR.

2. Materials and methods

2.1. Study population

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study is a prospective cohort study designed to assess reproductive and developmental toxicity during sensitive windows of human reproduction and development as previously described (Buck Louis et al., 2011). Briefly, this prospective cohort design includes the preconception enrollment of couples from Michigan and Texas between 2005 and 2009. Couples who were discontinuing contraception with the intention of having a baby were followed until pregnant or 12 months of attempting pregnancy. Given the absence of established population-based sampling frameworks for identifying couples planning pregnancy, a commercially available marketing database in Michigan and the fish/hunting license registry in Texas were used to recruit study participants. The inclusion criteria were as follows: a) couples who are married or in a committed relationship; b) female partners 18–40 years old and male partners ≥ 18 years old; c) self-reported menstrual cycle length between 21 and 42 days; d) no contraceptive injections in the past 12 months; e) no surgical or non-surgical sterilization history; and f) couples who had the ability to communicate in English or Spanish. Of the 501 couples who were enrolled in the LIFE study, 237 couples had a live birth during the follow-up period. Among them, couples who had a multiple birth (n=2) or couples who had missing values for both maternal and paternal PFAS levels (n=2) were excluded from the eligible

population. As a result, a total of 233 couples who had a singleton birth during the follow-up period were included in the final dataset.

2.2 Data collection

Baseline data were collected in the couples' home following a pregnancy test to ensure the female partner was not already pregnant. Approximately 20 mL of blood was obtained from each partner of the couple for quantification of a variety of environmental chemicals including PFASs following completion of a baseline interview. Couples who had a live birth were asked to complete a standardized birth announcement that captured information on date of birth, sex of the infant, birth size, and delivery mode.

This study was performed in adherence with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Boards at all collaborating institutions. All study participants provided written informed consent before any data or biospecimen collection.

2.3. Laboratory assessment

Toxicological analysis was conducted by the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) according to established protocols for measuring persistent environmental chemicals in human serum. Both maternal and paternal serum concentrations were measured at baseline using online solid phase extraction high performance liquid chromatography-tandem mass spectrometry with isotope dilution quantification for the following 7 PFASs: PFOS, PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorooctane sulfonamide (FOSA), *N*-ethyl-perfluorooctane sulfonamidoacetic acid (EtFOSAA), and *N*-methylperfluorooctane sulfonamidoacetic acid (MeFOSAA) according to published standard operating procedures, inclusive of ongoing quality assurance and control procedures (Calafat et al., 2007; Kuklenyik, 2004). PFASs in 1 mL of serum were quantified and recorded in nanograms per milliliter (ng/mL). The limits of detection (LODs) ranged from 0.1 to 0.2 ng/mL. While concentrations below the LOD were not substituted to prevent introducing bias (Richardson and Ciampi, 2003; Schisterman et al., 2006), all machine-read values for chemical concentrations were utilized for analysis.

2.4. Statistical analysis

In the descriptive phase of analysis, distributions were summarized as means (± standard deviations [SDs]) for continuous variables and categorically for other variables. Differences in maternal, paternal, and couple characteristics at baseline by infant sex were assessed using the nonparametric Wilcoxon test for continuous variables and chi-square test or Fisher's exact test for categorized variables. We estimated geometric means (GMs) and 95% confidence intervals (CIs) for serum PFAS concentrations by select characteristics (i.e., infant sex, maternal parity, and household income) and assessed significance using the nonparametric Wilcoxon test. Serum PFAS concentrations were log-transformed and standardized by their SDs to aid in the interpretation of results. Serum PFAS concentrations were also categorized into tertiles for analysis with the exception of FOSA and Et-FOSA-AcOH. FOSA and Et-FOSA-AcOH were dichotomized as < LOD or ≥ LOD for analysis.

In the analytic phase, we used logistic regression models to estimate odds ratios (ORs) and 95% CIs for infant sex (male birth versus female birth). Separate models were run for maternal and paternal serum PFAS concentrations. We adjusted *a priori* for age (years; continuous), research site (Michigan and Texas), household income (< $70,000 and ≥ $70,000), and maternal parity (nulliparous and parous). Given the absence of any detected multicollinearity between maternal and paternal PFAS concentrations (all condition indices < 30 [Lesaffre and Marx, 1993; Segerstedt and Nyquist, 1992]; data not shown), we modeled both partner's concentrations in the same model in relation to the ORs for a male birth. Additionally, we conducted sensitivity analysis excluding maternal parity, given its uncertain relationship with PFASs (Buck Louis et al., 2012). Two-sided significance levels (p-value < 0.05) were used to assess significance without correcting for multiple comparisons, given the exploratory design of this study. All statistical analyses were performed by SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

Of 233 live births, 115 (49.4 %) were boys and 118 (50.6 %) were girls. The overall SSR was 0.97 (95% CI, 0.75–1.26), indicative of a slight excess of females. Baseline maternal, paternal, and couple characteristics by infant sex are shown in Table 1. The mean ages (± SD) of mothers and fathers were 29.7 (± 3.7) years and 31.5 (± 4.6) years, respectively. Non-Hispanic white and college-educated couples comprised the majority of the study participants. Approximately half of the mothers (46.3%) were nulliparous. None of the baseline characteristics differed significantly by infant sex (Table 1).

Table 2 presents the distributions (in tertiles) of maternal and paternal serum PFAS concentrations by infant sex; no significant differences were observed. While the GMs (95% CIs) of maternal and paternal serum PFAS concentrations differed by infant sex, maternal parity, and household income, no significant differences were observed for infant sex (See Supplemental Table 1). In general, paternal serum PFOS, PFOA, PFNA, and PFDA concentrations were higher than maternal concentrations.

The ORs (95% CIs) for a male birth by log-transformed maternal, paternal, and couple serum PFAS concentrations are presented in Table 3. When the effects of maternal or paternal serum PFASs on the SSR were evaluated separately, no significant associations were observed between serum PFAS concentrations and a male birth. When couple serum PFAS concentrations were modeled jointly, the ORs for a male birth ranged from 0.64 to 0.66 per one SD increase in the log-transformed paternal serum MeFOSAA concentrations across the three different models (Table 3).

When the tertiles of couple serum PFAS concentrations were used in the models, the findings for paternal MeFOSAA and a male birth were suggestive of a possible dose-response relation, as reflected by a 47% reduction in the odds of a male birth observed for men in the second versus first tertile (adjusted OR, 0.53; 95% CI, 0.26–1.10), increasing to a 66% reduction for men in the third versus first tertile (adjusted OR, 0.34; 95% CI, 0.13–0.89) (Table 4). Additionally, the odds of a male birth were significantly reduced among

fathers in the second PFNA tertile versus fathers in the first tertile across all models (ORs, range 0.43–0.50).

4. Discussion

This prospective study with preconception enrollment of couples demonstrated that less prevalent PFASs (i.e., paternal MeFOSAA and PFNA) were significantly associated with an excess of female births. Conversely, more prevalent PFASs, such as PFOS and PFOA, were not significantly associated with the SSR. Use of a couple-based design enabled us to detect an association between paternal PFAS concentrations and a female excess of live births. Had we enrolled only females, this observation would have missed. Of particular note is that, although not statistically significant, the ORs for a male birth were elevated for maternal MeFOSAA (ORs, range 1.29–1.32 per one SD increase in the log-transformed maternal serum MeFOSAA concentrations across all models), suggestive of possible varying patterns for the SSR in relation to parental exposures (Table 3). This speculation is strengthened by a possible dose-response relation noted for maternal MeFOSAA and a male birth (the second versus first tertile, adjusted OR, 1.73 [95% CI, 0.81–3.69]; the third versus first tertile, adjusted OR, 1.88 [95% CI, 0.76–4.65]), though again not significant (Table 4).

To our knowledge, Kvist et al. (2012) first reported that paternal exposure to PFASs may be related to a lower proportion of Y-bearing sperm in the father's semen, which in turn may be related to an excess of female births. However, evidence has indicated that the predominance of either sons or daughters in households may not be directly explained by an altered ratio of X- and Y-bearing sperm in the ejaculate (Irving et al., 1999). One of the implications of our study includes the fact that the reproductive effects of both maternal and paternal PFASs were assessed in relation to the SSR, as a couple-dependent fertility endpoint. As proposed previously (James, 2008a), when using the SSR for testing endocrine disruption, both maternal and paternal factors should be taken into account, considering possible opposing hormonal effects in mothers and fathers.

Albeit speculative, the positive association of paternal MeFOSAA and PFNA with an excess of female births and the null association of maternal PFASs with an excess of male or female births noted in this study seem to be comparable to previous findings on a wide range of environmental or occupational exposures. Although existing evidence has been inconsistent, there has been little evidence that paternal exposures to environmental toxicants other than PCBs are associated with a male excess in offspring. A large number of studies on other environmental toxicants, on the other hand, have indicated more female offspring born to fathers exposed to environmental toxicants (Terrell et al., 2011). Several animal studies have linked the production of male offspring to fertility. In a study in red deer, more male offspring were born to male animals with a higher percentage of morphologically normal spermatozoa, which is believed to be an important determinant of male fertility (Gomendio et al., 2006). Human studies have also shown that family size, as a possible indicator of fertility, is positively associated with the SSR, independent of possible negative associations between parental ages (Jacobsen et al., 1999; Mathews and Hamilton, 2005) or birth order (Biggar et al., 1999; Mathews and Hamilton, 2005) and the SSR (James, 2013).

While suggestions have been made for identifying genetic (e.g., the *SRY* [sex-determining region Y] gene) and environmental determinants, the precise mechanism for offspring sex determination in humans is unknown. Some prevailing hypotheses on the SSR include the hormonal hypothesis, which theorizes that parental hormone levels around the time of conception are, in part, responsible for the alteration of SSR (James, 2008a, 2008b, 2013). According to this hypothesis, high levels of testosterone (of either parent) and estrogen (of mother) may be associated with a male excess in offspring. Contrarily, high levels of parental gonadotropins, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), around the time of conception may be associated with a female excess in offspring (James, 2013). Another hypothesis is the 'over-ripeness ovopathy' concept, which postulates that the SSR is influenced by oocyte maturation and cervical mucus liquefaction (Jongbloet, 2004). Allegedly, non-optimally matured oocytes with coexisting non-optimally liquefied cervical mucus are more accessible by Y-bearing sperm, which are smaller, and in turn more desirable to navigate non-optimal cervical mucus, than X-bearing sperm. The preferential fertilization of non-optimally matured oocytes by Y-bearing sperm may cause disproportional loss of male embryos and fetuses. As both oocyte maturation and cervical mucus liquefaction are modulated by estrogen, perturbed hormonal milieu elicited by various endogenous and exogenous factors may affect the SSR (Jongbloet, 2004).

The xenoestrogenic properties of PFASs have been revealed in several experimental studies, in which PFASs exhibited estrogenic, anti-estrogenic, and/or anti-androgenic activities in a concentration-dependent manner or in a mixture (Henry and Fair, 2013; Kjeldsen and Bonefeld-Jørgensen, 2013). The effects of PFAS on reproductive hormone levels have been demonstrated in both animal and human studies, despite inconsistent findings among these studies. In vitro and in vivo assays in zebrafish exhibited that exposure to PFOS increased estradiol, decreased testosterone, and altered endocrine-related gene expression (Du et al., 2013). The administration of 25 mg PFOA/kg/day for 14 days to male rats increased estradiol in serum, decreased testosterone in serum and testicular interstitial fluid, and ultimately developed Leydig cell adenoma (Biegel et al., 1995). However, in male cynomolgus monkeys, oral exposure to 0.75 mg/kg/day potassium PFOS for 182 days resulted in lowered serum estradiol levels but no significant change in serum testosterone levels (Seacat et al., 2002). In a study of 256 men in the United States, LH but not FSH was positively correlated with plasma PFOS and PFOA. No statistically significant associations were observed for total testosterone or estradiol (Raymer et al., 2012). However, a study of 247 healthy young Danish men showed that serum PFOS was negatively associated with total testosterone, free testosterone, free androgen index (FAI), and other hormonal ratios (i.e., testosterone/LH, free testosterone/LH, and FAI/LH) (Joensen et al., 2013).

Equivocal findings on the reproductive and developmental toxicity of PFASs have been demonstrated in recent human studies. In a study of 588 partners of pregnant women from Greenland, Poland and Ukraine, a negative association between serum PFOS concentration and sperm morphology was observed (Toft et al., 2012). However, a study of 256 American men seeking infertility treatment showed that serum PFOS and PFOA concentrations were not significantly associated with semen quality parameters including volume, sperm concentration, and sperm motility (Raymer et al., 2012). In a study of 247 men from the general Danish population, no associations between PFASs and semen quality parameters

were observed, except for perfluoroheptanoic acid being associated with progressively motile sperm (Joensen et al., 2013). A study conducted among 1240 women from the Danish National Birth Cohort showed that higher maternal plasma PFOS and PFOA concentrations measured at 4–14 weeks of pregnancy were associated with longer time-to-pregnancy (TTP) (Fei et al., 2009). A study using data from the LIFE study indicated that increased serum concentration of FOSA, a fluorochemical residual, in females was significantly associated with reduced couple fecundity, as assessed by a prolonged TTP, though serum concentrations of this fluorochemical residual were below the LOD in 90% of females (Buck Louis et al., 2013). On the other hand, a case-control study of 910 women from the Norwegian Mother and Child Cohort suggested the post-pregnancy re-accumulation of PFASs as a possible explanation of the association between PFASs and subfecundity, given that a long interpregnancy interval among parous women may increase the body burden of PFASs (Whitworth et al., 2012). In a case-cohort study of 156 cerebral palsy cases from the Danish National Birth Cohort during 1996–2002, high maternal plasma PFOS and PFOA levels in early or midpregnancy were associated with an increased risk of cerebral palsy in boys (Liew et al., 2014).

To date, the reproductive and developmental toxicity of fluorochemical residuals, such as Et-FOSAAcOH and MeFOSAA, has scarcely been reported in humans. FOSA, which can metabolize to PFOS, is not specific to any one consumer application like PFOS. However, Et-FOSA-AcOH and MeFOSAA, which can metabolize to FOSA, are markers of consumer-related exposure. While EtFOSAA is primarily detected in paper and packaging protectant applications, MeFOSAA is mainly detected in surface treatment applications such as textiles, carpets, and upholstery (Olsen et al., 2005). However, the biotransformation of fluorochemical residuals has not been well-established, although some toxicological studies proposed possible metabolic pathways and toxic mechanisms of select fluorochemical residuals (O'Brien and Wallace, 2004; O'Brien et al., 2006; Xu et al., 2004). This, in part, has led us to be unable to provide any biological explanations specific to paternal MeFOSAA, particularly considering the biotransformation of this chemical. It is important to note that chance may be an explanation for our findings, reflecting random error by multiple statistical tests performed. It is also noteworthy that serum MeFOSAA concentrations were relatively low and below the LOD (0.2 ng/mL) in 21.1% of the male partners (Table 2). However, the GMs of serum PFAS concentrations among the study participants were comparable to those for the U.S. population from the National Health and Nutrition Examination Survey, except for higher serum PFOS concentrations observed in the current study (CDC, 2014).

Important study limitations need to be considered when interpreting the findings, including the competing risk of pregnancy loss relative to live birth, and our inability to measure the primary sex ratio for all conceptions. As such, our findings only speak to the SSR. Another consideration is the impact of PFASs on semen quality and the relevancy of our preconception measure for spermatogenesis. Given the long half-life of most PFASs, particularly long-chain PFASs (Han et al., 2012; Olsen et al., 2007), it is plausible that the male partners' PFAS concentrations were relevant for the sensitive window of spermatogenesis. Although this study is strengthened by its unique features including the prospective cohort design with both partners' preconception measurements of serum PFASs

and the use of a couple-based approach when assessing a couple-dependent outcome, a relatively small sample size was used for the detection of variability in the SSR. Selection bias is a consideration if couples with higher or lower PFAS concentrations disproportionately participated in the study; however, none of the couples were aware of their concentrations at enrollment. Still, we cannot rule out other selective factors or residual confounding. Lastly, our results may not be generalizable to the general population or among couples with unplanned pregnancy, given our sampling on couples planning pregnancies.

While not inconsistent with previous data from persistent environmental chemicals and reversal of the SSR, our findings await corroboration specifically in relation to PFASs before a more meaningful interpretation can be made. Efforts to incorporate hormonal profiles or semen quality relative to the SSR would provide a more complete investigation regarding the effect of persistent environmental chemicals on sex selection and sex-selective survival in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (contracts #N01-HD-3-3355, N01-HD-3-3356, N01-HD-3-3358). J.B. was supported by the Korea-US Visiting Scientist Training Award (VSTA) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (award #VFTB057303).

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Highlights

- Several persistent chemicals have been reported to be associated with the SSR.
- The effects of serum PFAS concentrations on the SSR have not been explored.
- Paternal MeFOSAA and PFNA were significantly associated with a female excess.
- PFOS, PFOA, PFDA, FOSA, and EtFOSAA were not significantly associated with the SSR.
- These findings await corroboration given the absence of previous investigation.

Table 1.

Baseline characteristics by infant sex, Michigan and Texas, 2005–2009

Characteristic	Boy (n=115) n (%)	Girl (n=118) n (%)	*p*-value	Secondary sex ratio (boys/girls)
Maternal characteristic				
Age (year, mean ± SD)	30.0 ± 4.0	29.5 ± 3.5	0.65	0.97
Parity			0.27	
0	57 (50.0)	50 (42.7)		1.14
1+	57 (50.0)	67 (57.3)		0.85
Education			0.96	
≤ High school graduate/GED	5 (4.4)	4 (3.4)		1.25
Some college/technical school	13 (11.5)	14 (11.9)		0.93
College graduate or higher	95 (84.1)	100 (84.8)		0.95
Race/ethnicity			0.45	
Non-Hispanic white	91 (80.5)	101 (85.6)		0.90
Non-Hispanic black	2 (1.8)	1 (0.9)		2.00
Hispanic	13 (11.5)	7 (5.9)		1.86
Other	7 (6.2)	9 (7.6)		0.78
Paternal characteristic				
Age (year, mean ± SD)	32.2 ± 5.1	30.8 ± 4.0	0.24	0.97
Education			0.22	
≤ High school graduate/GED	3 (2.6)	4 (3.4)		0.75
Some college/technical school	34 (29.8)	23 (19.7)		1.48
College graduate or higher	77 (67.5)	90 (76.9)		0.86
Race/ethnicity			0.29	
Non-Hispanic white	90 (79.0)	104 (88.1)		0.87
Non-Hispanic black	3 (2.6)	2 (1.7)		1.50
Hispanic	13 (11.4)	8 (6.8)		1.63
Other	8 (7.0)	4 (3.4)		2.00
Couple characteristic				
Research site			0.41	

Characteristic	Boy (n=115) n (%)	Girl (n=118) n (%)	*p*-value	Secondary sex ratio (boys/girls)
Michigan	21 (18.3)	26 (22.0)		0.81
Texas	94 (81.7)	92 (78.0)		1.02
Household income ($)			0.32	
< 70,000	32 (27.8)	40 (33.9)		0.80
≥ 70,000	83 (72.2)	78 (66.1)		1.06

SD, standard deviation; GED, General Educational Development

Note: Excludes two couples with twin pregnancies and two couples without serum perfluoroalkyl and polyfluoroalkyl substance concentrations.

Table 2.

Distribution of maternal and paternal serum PFAS concentrations by infant sex, Michigan and Texas, 2005–2009

PFAS (ng/mL)	LOD	% < LOD	Boy n (%)	Girl n (%)	*p*-value	Secondary sex ratio (boys/girls)
Maternal serum (n=230)			*(n=114)*	*(n=116)*		
PFOS	0.2	0.0			0.29	
1st ≤ 9.9			34 (29.8)	43 (37.1)		0.79
9.9 < 2nd ≤ 16.0			38 (33.3)	41 (35.3)		0.93
3rd > 16.0			42 (36.8)	32 (27.6)		1.31
PFOA	0.1	0.4			0.21	
1st ≤ 2.6			33 (29.0)	44 (37.9)		0.75
2.6 < 2nd ≤ 4.4			46 (40.4)	35 (30.2)		1.31
3rd > 4.4			35 (30.7)	37 (31.9)		0.95
PFNA	0.1	2.2			0.93	
1st ≤ 1.0			44 (38.6)	47 (40.5)		0.94
1.0 < 2nd ≤ 1.6			34 (29.8)	35 (30.2)		0.97
3rd > 1.6			36 (31.6)	34 (29.3)		1.06
PFDA	0.2	9.1			0.93	
1st ≤ 0.3			44 (38.6)	47 (40.5)		0.94
0.3 < 2nd ≤ 0.5			36 (31.6)	37 (31.9)		0.97
3rd > 0.5			34 (29.8)	32 (27.6)		1.06
FOSA	0.1	89.6			0.96	
< LOD			102 (89.5)	104 (89.7)		0.98
≥ LOD			12 (10.5)	12 (10.3)		1.00
EtFOSAA	0.2	97.0			0.06	
< LOD			108 (94.7)	115 (99.1)		0.94
≥ LOD			6 (5.3)	1 (0.9)		6.00
MeFOSAA	0.2	25.2			0.62	
1st ≤ 0.2			48 (42.1)	52 (44.8)		0.92
0.2 < 2nd ≤ 0.4			33 (29.0)	27 (23.3)		1.22
3rd > 0.4			33 (29.0)	37 (31.9)		0.89
Paternal serum (n=227)			*(n=112)*	*(n=115)*		

PFAS (ng/mL)	LOD	% < LOD	Boy n (%)	Girl n (%)	*p*-value	Secondary sex ratio (boys/girls)
PFOS	0.2	0.4			0.89	
1st ≤ 18.0			37 (33.0)	38 (33.0)		0.97
18.0 < 2nd ≤ 28.1			37 (33.0)	41 (35.7)		0.90
3rd > 28.1			38 (33.9)	36 (31.3)		1.06
PFOA	0.1	0.4			0.22	
1st ≤ 4.3			45 (40.2)	34 (29.6)		1.32
4.3 < 2nd ≤ 6.2			32 (28.6)	42 (36.5)		0.76
3rd > 6.2			35 (31.3)	39 (33.9)		0.90
PFNA	0.1	0.4			0.19	
1st ≤ 1.2			45 (40.2)	34 (29.6)		1.32
1.2 < 2nd ≤ 2.0			34 (30.4)	46 (40.0)		0.74
3rd > 2.0			33 (29.5)	35 (30.4)		0.94
PFDA	0.2	4.0			0.70	
1st ≤ 0.4			54 (48.2)	56 (48.7)		0.96
0.4 < 2nd ≤ 0.6			34 (30.4)	30 (26.1)		1.13
3rd > 0.6			24 (21.4)	29 (25.2)		0.83
FOSA	0.1	84.1			0.65	
< LOD			93 (83.0)	98 (85.2)		0.95
≥ LOD			19 (17.0)	17 (14.8)		1.12
EtFOSAA	0.2	98.2			0.37	
< LOD			109 (97.3)	114 (99.1)		0.96
≥ LOD			3 (2.7)	1 (0.9)		3.00
MeFOSAA	0.2	21.1			0.19	
1st ≤ 0.2			53 (47.3)	41 (35.7)		1.29
0.2 < 2nd ≤ 0.5			34 (30.4)	40 (34.8)		0.85
3rd > 0.5			25 (22.3)	34 (29.6)		0.74

PFAS, perfluoroalkyl and polyfluoroalkyl substance; PFOS, perfluorooctane sulfonic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; FOSA, perfluorooctane sulfonamide; EtFOSAA, *N*-ethyl-perfluorooctane sulfonamidoacetic acid; MeFOSAA, *N*-methylperfluorooctane sulfonamidoacetic acid.

Note: Excludes two couples with twin pregnancies and five mothers or eight fathers without serum PFAS concentrations.

Table 3.

Log-transformed serum PFAS concentrations and the odds ratios for a male birth, Michigan and Texas, 2005–2009

PFAS	Unadjusted model		Adjusted model[a]		Sensitivity model[b]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Maternal serum (n=230)						
PFOS	1.23	(0.94–1.60)	1.16	(0.88–1.53)	1.19	(0.91–1.56)
PFOA	1.06	(0.82–1.37)	0.93	(0.68–1.26)	1.01	(0.76–1.34)
PFNA	1.03	(0.80–1.34)	0.94	(0.70–1.26)	0.96	(0.72–1.28)
PFDA	1.15	(0.88–1.49)	1.07	(0.81–1.42)	1.10	(0.83–1.45)
FOSA	1.01	(0.78–1.30)	1.07	(0.81–1.41)	1.05	(0.80–1.38)
EtFOSAA	1.20	(0.92–1.57)	1.22	(0.92–1.60)	1.23	(0.93–1.62)
MeFOSAA	0.95	(0.73–1.23)	0.98	(0.75–1.28)	0.97	(0.75–1.27)
Paternal serum (n=227)						
PFOS	1.06	(0.81–1.37)	1.01	(0.78–1.33)		
PFOA	0.95	(0.73–1.23)	0.94	(0.72–1.23)		
PFNA	0.99	(0.76–1.29)	0.94	(0.71–1.24)		
PFDA	1.05	(0.81–1.36)	1.02	(0.78–1.34)		
FOSA	1.11	(0.85–1.44)	1.14	(0.86–1.51)		
EtFOSAA	0.99	(0.77–1.29)	0.98	(0.75–1.29)		
MeFOSAA	0.82	(0.63–1.07)	0.80	(0.60–1.06)		
Couple serum (n=224)						
PFOS (maternal)	1.24	(0.93–1.65)	1.13	(0.83–1.54)	1.17	(0.87–1.58)
PFOS (paternal)	0.98	(0.73–1.30)	0.98	(0.73–1.33)	0.97	(0.72–1.30)
PFOA (maternal)	1.08	(0.83–1.41)	0.91	(0.66–1.26)	1.01	(0.75–1.35)
PFOA (paternal)	0.92	(0.71–1.21)	0.95	(0.72–1.26)	0.93	(0.71–1.23)
PFNA (maternal)	1.06	(0.77–1.45)	0.92	(0.65–1.31)	0.96	(0.69–1.35)
PFNA (paternal)	0.96	(0.70–1.32)	0.99	(0.71–1.38)	0.97	(0.70–1.34)
PFDA (maternal)	1.18	(0.83–1.68)	1.03	(0.71–1.49)	1.07	(0.74–1.54)
PFDA (paternal)	0.95	(0.67–1.35)	1.01	(0.71–1.46)	1.00	(0.70–1.44)
FOSA (maternal)	0.86	(0.61–1.21)	0.89	(0.62–1.28)	0.87	(0.61–1.25)
FOSA (paternal)	1.24	(0.88–1.76)	1.23	(0.86–1.76)	1.24	(0.87–1.77)

PFAS	Unadjusted model		Adjusted model[a]		Sensitivity model[b]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
EtFOSAA (maternal)	1.20	(0.90–1.61)	1.15	(0.85–1.56)	1.18	(0.87–1.59)
EtFOSAA (paternal)	0.92	(0.69–1.23)	0.94	(0.70–1.27)	0.93	(0.69–1.25)
MeFOSAA (maternal)	1.32	(0.85–2.06)	1.29	(0.82–2.03)	1.30	(0.83–2.04)
MeFOSAA (paternal)	0.65	(0.42–1.02)	0.66	(0.41–1.04)	0.64	(0.41–1.02)

PFAS, perfluoroalkyl and polyfluoroalkyl substance; OR, odds ratio; CI, confidence interval; PFOS, perfluorooctane sulfonic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; FOSA, perfluorooctane sulfonamide; EtFOSAA, *N*-ethyl-perfluorooctane sulfonamidoacetic acid; MeFOSAA, *N*-methyl-perfluorooctane sulfonamidoacetic acid.

[a]Adjusted for age, research site, household income, and maternal parity.

[b]Adjusted for above except for maternal parity.

Table 4.

Categorized serum PFAS concentrations and the odds ratios for a male birth, Michigan and Texas, 2005–2009

PFAS (ng/mL)	Unadjusted model		Adjusted model[a]		Sensitivity model[b]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Maternal serum (n=230)						
PFOS						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.23	(0.65–2.32)	1.10	(0.57–2.10)	1.17	(0.62–2.22)
3rd tertile	1.56	(0.83–2.96)	1.37	(0.70–2.66)	1.46	(0.77–2.80)
PFOA						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.69	(0.89–3.19)	1.47	(0.75–2.86)	1.58	(0.83–3.03)
3rd tertile	1.33	(0.71–2.52)	1.05	(0.51–2.16)	1.24	(0.64–2.41)
PFNA						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.04	(0.55–1.94)	0.91	(0.47–1.78)	0.96	(0.50–1.83)
3rd tertile	1.13	(0.61–2.11)	0.95	(0.48–1.87)	1.00	(0.52–1.94)
PFDA						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.04	(0.56–1.92)	0.84	(0.43–1.62)	0.90	(0.47–1.73)
3rd tertile	1.13	(0.60–2.14)	0.92	(0.46–1.81)	0.99	(0.51–1.93)
FOSA						
< LOD	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥ LOD	1.02	(0.44–2.37)	1.23	(0.50–3.06)	1.18	(0.48–2.90)
EtFOSAA						
< LOD	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥ LOD	1.28	(0.71–2.28)	1.28	(0.69–2.38)	1.33	(0.72–2.45)
MeFOSAA						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.32	(0.70–2.52)	1.41	(0.72–2.77)	1.39	(0.71–2.71)

PFAS (ng/mL)	Unadjusted model		Adjusted model[a]		Sensitivity model[b]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
3rd tertile	0.97	(0.52–1.78)	1.03	(0.55–1.94)	1.03	(0.55–1.93)
Paternal serum (n=227)						
PFOS						
1st tertile	1.00	(referent)	1.00	(referent)		
2nd tertile	0.95	(0.50–1.79)	0.96	(0.50–1.83)		
3rd tertile	1.05	(0.56–2.00)	0.91	(0.47–1.77)		
PFOA						
1st tertile	1.00	(referent)	1.00	(referent)		
2nd tertile	0.58	(0.30–1.09)	0.61	(0.32–1.17)		
3rd tertile	0.68	(0.36–1.28)	0.68	(0.35–1.30)		
PFNA						
1st tertile	1.00	(referent)	1.00	(referent)		
2nd tertile	0.56	(0.30–1.05)	0.48	(0.25–0.95)		
3rd tertile	0.71	(0.37–1.37)	0.58	(0.28–1.17)		
PFDA						
1st tertile	1.00	(referent)	1.00	(referent)		
2nd tertile	1.18	(0.63–2.18)	1.14	(0.60–2.17)		
3rd tertile	0.86	(0.44–1.66)	0.78	(0.39–1.54)		
FOSA						
< LOD	1.00	(referent)	1.00	(referent)		
≥ LOD	1.18	(0.58–2.40)	1.28	(0.60–2.72)		
EtFOSAA						
< LOD	1.00	(referent)	1.00	(referent)		
≥ LOD	0.90	(0.50–1.64)	0.88	(0.47–1.62)		
MeFOSAA						
1st tertile	1.00	(referent)	1.00	(referent)		
2nd tertile	0.66	(0.36–1.21)	0.65	(0.34–1.23)		
3rd tertile	0.57	(0.29–1.10)	0.54	(0.27–1.08)		
Couple serum (n=224)						

PFAS (ng/mL)	Unadjusted model		Adjusted model[a]		Sensitivity model[b]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
PFOS (maternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.28	(0.67–2.45)	1.08	(0.55–2.12)	1.16	(0.60–2.26)
3rd tertile	1.56	(0.78–3.12)	1.22	(0.58–2.57)	1.35	(0.66–2.74)
PFOS (paternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	0.92	(0.48–1.75)	0.94	(0.49–1.80)	0.95	(0.50–1.82)
3rd tertile	0.94	(0.47–1.87)	0.85	(0.42–1.75)	0.84	(0.42–1.70)
PFOA (maternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.72	(0.89–3.32)	1.56	(0.78–3.12)	1.66	(0.85–3.27)
3rd tertile	1.46	(0.75–2.85)	1.12	(0.52–2.43)	1.34	(0.67–2.70)
PFOA (paternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	0.55	(0.29–1.06)	0.63	(0.32–1.23)	0.61	(0.31–1.18)
3rd tertile	0.59	(0.30–1.14)	0.61	(0.30–1.21)	0.60	(0.30–1.18)
PFNA (maternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.23	(0.62–2.42)	0.96	(0.46–2.00)	1.01	(0.50–2.05)
3rd tertile	1.54	(0.74–3.18)	1.21	(0.55–2.66)	1.28	(0.60–2.74)
PFNA (paternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	0.50	(0.26–0.99)*	0.43	(0.21–0.88)*	0.44	(0.22–0.90)*
3rd tertile	0.58	(0.27–1.22)	0.52	(0.23–1.14)	0.52	(0.23–1.13)
PFDA (maternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	0.99	(0.52–1.91)	0.75	(0.37–1.51)	0.83	(0.41–1.65)
3rd tertile	1.22	(0.60–2.48)	0.86	(0.40–1.86)	0.97	(0.46–2.06)
PFDA (paternal)						

PFAS (ng/mL)	Unadjusted model		Adjusted model[a]		Sensitivity model[b]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.14	(0.60–2.16)	1.19	(0.61–2.32)	1.13	(0.58–2.20)
3rd tertile	0.82	(0.40–1.71)	0.89	(0.41–1.89)	0.83	(0.39–1.75)
FOSA (maternal)						
< LOD	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥ LOD	0.74	(0.26–2.05)	0.81	(0.27–2.39)	0.78	(0.27–2.29)
FOSA (paternal)						
< LOD	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥ LOD	1.45	(0.60–3.49)	1.46	(0.59–3.60)	1.45	(0.59–3.58)
EtFOSAA (maternal)						
< LOD	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥ LOD	1.28	(0.67–2.44)	1.09	(0.54–2.17)	1.16	(0.59–2.30)
EtFOSAA (paternal)						
< LOD	1.00	(referent)	1.00	(referent)	1.00	(referent)
≥ LOD	0.80	(0.41–1.55)	0.87	(0.44–1.71)	0.83	(0.42–1.64)
MeFOSAA (maternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	1.73	(0.84–3.58)	1.73	(0.81–3.69)	1.73	(0.81–3.67)
3rd tertile	1.96	(0.80–4.78)	1.88	(0.76–4.65)	1.92	(0.78–4.73)
MeFOSAA (paternal)						
1st tertile	1.00	(referent)	1.00	(referent)	1.00	(referent)
2nd tertile	0.52	(0.26–1.06)	0.53	(0.26–1.10)	0.53	(0.26–1.10)
3rd tertile	0.34	(0.13–0.87)*	0.34	(0.13–0.89)*	0.33	(0.13–0.86)*

PFAS, perfluoroalkyl and polyfluoroalkyl substance; OR, odds ratio; CI, confidence interval; PFOS, perfluorooctane sulfonic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; FOSA, perfluorooctane sulfonamide; EtFOSAA, *N*-ethyl-perfluorooctane sulfonamidoacetic acid; MeFOSAA, *N*-methyl-perfluorooctane sulfonamidoacetic acid; LOD, limit of detection.

[a]Adjusted for age, research site, household income, and maternal parity.

[b]Adjusted for above except for maternal parity.

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* p-value < 0.05