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Oral contraceptive use as a determinant of plasma concentrations of perfluoroalkyl substances among women in the Norwegian Mother and Child Cohort (MoBa) study

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ABSTRACT

Objective: Because oral contraceptives (OC) tends to lessen menstrual fluid loss – a route of excretion for perfluoroalkyl substances (PFASs) – we hypothesized that such use would be positively associated with PFAS concentrations.

Methods: This analysis was based on the Norwegian Mother and Child Cohort (MoBa) study. We included 1090 women from two previous substudies of women enrolled from 2003 to 2007. Characteristics of OC use were obtained at baseline: use in the past 12 months, duration and recency of use, age at first use. We examined log-transformed plasma concentrations of seven PFASs (perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), and perfluorooctane sulfonate (PFOS)). Linear regression analyses, adjusted for maternal age, menstrual cycle length, parity, and education, were used to examine whether OC use characteristics were determinants of PFAS concentrations.

Results: Except for PFDA and PFUnDA, women who used OCs in the 12 months preceding the baseline interview had 12.9–35.7% higher PFAS concentrations than never OC users. To a lesser extent, past OC use was positively associated with PFASs (estimates ranged from 7.2–32.1%). Compared with never users, using OCs for 10 or more years was associated with increased PFAS concentrations, except for PFDA and PFUnDA (estimates for other PFASs ranged from 18.9–46.2%). We observed little effect of age at first OC use.

Conclusions: This analysis shows that characteristics of OC use, and duration of use in particular, may be important considerations when investigating relationships between women's reproductive outcomes and PFASs.

1. Introduction

Perfluoroalkyl substances (PFASs) are fully-fluorinated carbon chains with a terminal functional group, and have been used in a wide variety of products (Paul et al., 2009; NIEHS, 2012; Haug et al., 2010). Several PFASs, especially perfluoroctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been detected in both animal and human populations (NIEHS, 2012). The most significant route of non-occupational PFAS exposure among humans is diet (Haug et al., 2011).

PFASs have relatively long half-lives in humans. In occupationally exposed groups, the half-life of PFOA has been estimated as 3.5 years (95% CI: 3.0–4.1) while the half-lives of PFOS and perfluorohexane

Abbreviations: MoBa, The Norwegian Mother and Child Cohort Study; PFAS, Perfluoroalkyl substance; PFDA, perfluorodecanoic acid; PFHpS, perfluoroheptane sulfonate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoic acid

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sulfonate (PFHxS) have been estimated as 4.8 years (95% CI: 4.0–5.8) and 7.3 years (95% CI: 5.8–9.2), respectively (Olsen et al., 2007). A recent study of Swedish individuals exposed to PFASs in drinking water estimated half-lives for PFOA, PFOS, and PFHxS as 2.7, 3.4, and 5.3 years, respectively (Li et al., 2017). Studies among the general population provide estimates of the half-life of PFOA around 2.3 or 2.4 years (Bartell et al., 2010; Russell et al., 2015). In humans, PFASs tend bind to proteins, particularly plasma albumin (Han et al., 2003), and are excreted by the kidney, via gastrointestinal tract (Andersen et al., 2008), fetal transfer, as well as through and menstruation and breastfeeding (Ruark et al., 2017; Brantsaeter et al., 2013). Many studies have observed higher blood concentrations of various PFASs in human males compared to females (Harada et al., 2004), and menstruation may account for up to 30% of this difference (Wong et al., 2014). Data have demonstrated significantly higher blood PFAS concentrations in post-menopausal women compared with currently menstruating women (Harada et al., 2004). Increased PFAS concentrations have also been associated with menstrual cycle irregularities and long cycle lengths (Fei et al., 2009; Lyngso et al., 2014; Zhou et al., 2016; Lum et al., 2017).

Women of reproductive age often use oral contraceptives (OCs), such as combination estrogen and progestin pills (i.e., “pill”) or progestin-only pills (i.e., “mini-pill”), which tend to lessen menstrual fluid loss (Burkman et al., 2004). It is also possible that OCs impact the glomerular filtration rate and thus, excretion of PFASs (Wang et al., 2016; Oelkers et al., 1995). However, to the best of our knowledge, the relation of PFAS concentrations with OC use has not been examined, and such information could be helpful when selecting confounders for adjustment in studies of potential health effects of PFASs. Therefore, we examined this association among women in the Norwegian Mother and Child (MoBa) Cohort Study. We hypothesized that characteristics of OC use would be positively associated with plasma PFAS concentrations.

2. Material and methods

2.1. Study subjects

The present analysis was based on a sample of women from the Norwegian Mother and Child (MoBa) Cohort Study, a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health and designed to study various exposures and health outcomes (Magnus et al., 2006; Magnus et al., 2016). From 1999 to 2008 pregnant women across Norway were recruited into MoBa during their first prenatal visit, around 17–18 weeks of gestation. The women consented to participation in 41% of pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Informed consent was obtained and each participant was administered a baseline questionnaire at the time of enrollment. A blood sample was also collected at this time (Paltiel et al., 2014). The baseline questionnaire collected information on medical history, reproductive history, including the use of hormonal contraceptives (HCs), work and lifestyle habits, and various other exposures. The current analysis is based on version v9 of the quality-assured data files.

Women from two previous MoBa substudies were included in this analysis. In the first substudy (Study A) women were selected as part of a case-base study to examine the relation between PFAS concentrations and fecundity (Whitworth et al., 2012). To be included in Study A, women must have been enrolled in MoBa from 2003 to 2004, had a live birth, submitted a baseline plasma sample at enrollment, and have information related to the time-to-pregnancy of their index pregnancy. Study A women selected at random, without regard to their fecundity (i.e., the base sample), were included in the present analysis. In the second substudy (Study B), women were selected as part of a case-base study to examine the relation between PFAS concentrations and preeclampsia (Starling et al., 2014). Women in Study B were originally enrolled in MoBa from 2003 to 2007, were nulliparous, had a live birth to a singleton infant, and had no chronic hypertension prior to pregnancy. Study B women selected at random, without regard to preeclampsia (i.e., the base sample), were included in the present analysis. Thus, the number of women eligible for the present analysis was 549 women from Study A and 541 women from Study B, for a total of 1090 women.

The establishment and data collection in MoBa has obtained a license from the Norwegian Data Inspectorate and approval from The Regional Committee for Medical Research Ethics. The current study also received approval from the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston (UTHealth).

2.2. Outcomes

PFAS levels were quantitated from the blood plasma sample provided at enrollment (around 17–18 weeks gestation) at the Norwegian Institute of Public Health (NIPH) in Oslo using high-performance liquid chromatography/tandem mass spectrometry; this method has been previously described (Haug et al., 2009). Of the thirteen PFASs measured in the MoBa study, the following seven were quantitated in at least 50% of samples and were included in the present analyses: four perfluoroalkyl carboxylic acids: PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA); and three Perfluoroalkyl sulfonates: perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), and PFOS. The limit of quantification (LOQ) for all PFASs was 0.05 ng/mL. Blinded assessment of the assay precision, measured at concentrations similar to the study population, gave a median coefficient of variation of 14.6% for the seven PFASs (Starling et al., 2014).

2.3. Exposure

During the baseline interview, which occurred at enrollment, MoBa participants were asked about their use of a variety of birth control methods in the preceding 12 months, including the following hormonal birth control methods: “hormonal IUD,” “hormone injection,” “mini pill,” (i.e., birth control pills containing progestin only) and “pill” (i.e., birth control pills containing progestin and estrogen). Women could also choose “no such methods”. An additional series of questions was asked regarding women's specific use of OCs (i.e., pill or mini pill), including use in the four months preceding the pregnancy. For the present analysis, we created variables to indicate use of either non-oral HCs (hormonal IUD or hormone injection) or OCs (pill or mini pill) in the 12 months preceding the baseline interview. Additionally, if women indicated they had used the pill or mini pill within four months of their pregnancy, they were classified as having used OCs in the past 12 months. If women indicated ‘no such methods’ used, they were categorized as not having used non-oral HCs or OCs in the past 12 months. If non-oral HC or OC use was not indicated and “no such methods” was also not indicated, women were classified as missing this information (8.4%).

As mentioned, women were asked additional questions regarding OC use (but not HC); thus, additional OC variables were created. Women were asked about their lifetime duration of OC use (less than one year, 1–3 years, 4–6 years, 7–9 years, and 10 years or more), whether they had used the pill or mini pill in the four months before the pregnancy (yes/no), and the age (years) at which they first began using the pill or mini pill. Women were categorized as never OC users if they had not used OCs in the past 12 months, had not used OCs in the four months before the pregnancy, had no lifetime duration of use, and did not provide an age at first OC use.

For analysis, we categorized women's lifetime duration of OC use as: non-users, used OCs ≤ 3 years, used OCs 4–6 years, used OCs 7–9 years, and used OCs ≥ 10 years. If women reported using both the pill and mini-pill, they were classified according to the longer duration. If

women responded that they had used OCs within the past year or provided an age at first OC use but did not provide a duration of use, they were classified as missing duration of use (10.4%). We also created a variable representing women's recency of OC use. This variable was classified as: non-users, recent users (i.e., women who had used the pill or mini pill within the 12 months preceding the baseline interview), and past users (i.e., women with a non-missing value for lifetime duration of OC use but who responded that they had not used OCs within the 12 months preceding the baseline interview). Approximately 8.4% of women were missing recency of OC use information. Among women who used OCs, the age at which they reported first using OCs was analyzed as a continuous variable; 11.5% of women were missing this information.

To examine potential interaction between recency and duration of OC use, we created a combined variable. For this variable, women were categorized into never-users and eight combined categories (each duration category combined with both recency categories: recent users with ≤ 3 years duration of use, past users with ≤ 3 years duration of use, recent users with 4–6 years duration of use, past users with 4–6 years duration of use, recent users with 7–9 years duration of use, past users with 7–9 years duration of use, recent users with ≥ 10 years duration of use, past users with ≥ 10 years duration of use). Approximately 14.5% of women were missing this information.

2.4. Covariates

Maternal age at the time of blood draw was included in the models as an a priori confounder. Additional covariates for this analysis were chosen based on their potential to impact PFAS concentrations (Brantsaeter et al., 2013). The following variables were considered for inclusion in the final model: maternal education (< high school, high school, some college, 4 + years of college), maternal income in Norwegian Kroner (NOK; 1 NOK = $0.12 US; < 150,000; 150,000–299,999; > 300,000 NOK), menstrual cycle length (days), maternal smoking status three months before pregnancy (never, former, current), parity (0, 1, or 2 + previous births), and pre-pregnancy BMI (kg/m2). A total of 10.2% women were missing covariate information (see Table 1 for proportion of women missing each variable).

In sensitivity analyses, inter-pregnancy interval, or the days between the date of birth of the most recent previous pregnancy and the estimated date of conception of the current pregnancy as well as duration of breastfeeding the most recent livebirth, were considered. Among parous women, inter-pregnancy interval was categorized by tertiles and nulliparous women were included as the referent group. Duration of breastfeeding was included as a continuous variable, with nulliparous women being assigned a value of zero. Lastly, we conducted multiple imputation using PROC MI and PROC MIANALYZE using SAS software to impute missing values of PFAS variables as well as covariates. Multiple imputation of missing PFAS values (unmeasured values < LOQ) was based on measured values of all seven PFAS compounds, conducted on the log-transformed values, and constrained such that imputed values were required to be less than the LOQ.

2.5. Statistical analyses

Plasma PFAS concentrations < LOQ were quantitated and reported when possible. Thus, there were three possibilities for PFAS concentrations: measured and ≥ the LOQ; measured < LOQ; and not measured (which were all < LOQ). The number of women with measured values < LOQ was tabulated and we report distributional data both for PFAS concentrations measured ≥ LOQ and all measured values (i.e., including values both < LOQ and ≥ LOQ). Linear regression analyses were used to estimate the association between plasma PFAS concentrations and OC use in the previous 12 months, separately for each PFAS. The distributions of the seven PFAS were skewed with a long tail to the right, and the PFAS concentrations were natural log-transformed before fitting models. Crude, age-adjusted, and fully adjusted models were used. We aimed to obtain a single set of common covariates to include in the final adjusted models for each PFAS. Thus, if, for the majority of the PFASs (i.e., at least four of the seven compounds), 1) the covariate was statistically significantly associated with the PFAS or 2) its inclusion in the age-adjusted model changed the effect estimate of the association between OC use in the previous 12 months and PFAS concentrations by ≥ 10%, it was included in the final models. Education, menstrual cycle length, and parity met these criteria and were included in the fully adjusted models. Beta coefficients and confidence intervals were re-expressed as a percent change of plasma PFAS concentration using the following formula (28):

Table 1
Distribution of selected characteristics among 1090 women from the Norwegian Mother and Child Cohort (MoBa) study, 2003–2007.

Age (years) [%]	
≤ 24	11.7
25–29	36.3
30–34	38.2
≥ 35	13.9
Missing	0.0
Parity [%]	
0	70.6
1	20.6
2 +	8.6
Missing	0.0
Smoking status at 17 weeks [%]	
Never	47.3
Former	43.8
Current	7.3
Missing	1.7
Education [%]	
< High school	6.0
High school	28.6
Some college	41.2
4 + years college	22.6
Missing	1.7
Income (NOK) [%][a]	
< 150,000	14.0
150,000–299,999	43.7
> 300,000	37.7
Missing	4.6
BMI (kg/m^2) [median (IQR)]	23.4 (21.2, 26.0)
Missing [%]	4.0
Menstrual cycle length (days) [median (IQR)]	28.0 (28.0, 30.0)
Missing [%]	3.8
Non-oral HC[a] use [%]	
Yes	3.9
No	87.7
Missing	8.4
OC[b] use [%]	
Yes	45.3
No	46.6
Missing	8.4
Recency of OC use (months) [%]	
Never-user	8.1
Recent user	45.3
Past user	38.3
Missing	8.4
Lifetime duration of OC Use [%]	
Never-user	8.1
≤ 3 years	22.6
4–6 years	22.4
7–9 years	20.6
≥ 10 years	16.9
Missing	9.5
Age at first OC use (years) [median (IQR)][c]	18.0 (17.0, 20.0)
Missing [%]	11.5

BMI: body mass index; HC: hormonal contraceptive; IQR: interquartile range; OC: oral contraceptive; NOK = Norwegian Krones (1 NOK = $0.12 US).

[a] Use of hormonal IUD or hormone injection in the 12 months preceding the baseline interview.

[b] Use of pill or mini-pill in the 12 months preceding the baseline interview.

[c] Restricted to OC users (n = 470).

$$\%Change = (e^{\beta} - 1) * 100$$

The associations between PFAS concentrations and characteristics of OC use (i.e., age at first OC use, recency of OC use, lifetime duration of OC use, and combined recency/duration variable) were also examined. Formal tests of interaction were conducted by including dummy variables for duration and recency; interaction was assessed using alpha level of 0.10. We also conducted several sensitivity analyses. First, final adjusted models were rerun after separately including inter-pregnancy interval and breastfeeding duration as covariates. Models were also rerun using the multiply imputed dataset. Next, to account for potential differences by sub-study, we conducted a sensitivity analysis including, as a covariate, a dichotomous indicator term for original sub-study (A or B). Lastly, because parity is an important confounder, we explored adjusted for a four category parity variable (0, 1, 2, or 3 + previous births). All statistical analyses were performed using SAS (v9.4, Cary, NC).

3. Results

The majority of women included in this study were 25 years or older (68.5%; Table 1). Most women were normal weight; median pre-pregnancy BMI for the study population was 23.35 kg/m^2 (Table 1). Just less than half of women (47.3%) were never-smokers. The most common educational attainment in the study population was some college education (41.2%). The proportion of nulliparous women in this study is high (70.6%) due to the inclusion criteria of women in Study B. Though nearly 9% of women reported two or more previous births, the majority of these were women with exactly two previous births; < 2% had more than two previous births (data not shown). OC use in the 12 months preceding the baseline interview was reported by 45.3% of women (Table 1). Only 3.9% of women reported using non-oral HCs in the 12 months preceding the baseline interview. For duration of OC use, women were nearly evenly split between 0 and 3 years total use (22.6%), 4–6 years total use (22.4%), 7–9 years total use (20.6%), and ≥ 10 years total use (16.9%). There were more women classified as recent OC users (45.3%) than past OC users (38.3%).

Values ≥ LOQ were obtained for all PFASs in at least 74.5% of women (Table 2). Measured values (i.e., including values both < LOQ and ≥ LOQ) were identified for all PFASs in at least 91.2% of women (PFHpS and PFDA were quantitated in the least number of participants). PFOS and PFOA were found ≥ LOQ in 100% of participants. The highest concentration was observed for PFOS with a median of 12.82 ng/mL, followed by PFOA with a median of 2.50 ng/mL. Following PFOA, in descending order, was PFHxS at 0.65 ng/mL, PFNA at 0.45 ng/mL, PFUnDA at 0.20 ng/mL, and PFHpS at 0.15 ng/mL. PFDA was found at the lowest concentrations (median = 0.11 ng/mL).

Overall, self-reported OC use in the 12 months preceding the baseline interview was associated with increased plasma PFAS concentrations for all PFASs, except PFUnDA. Crude analyses indicate a range of 1.1% (for PFDA) to 20.1% (for PFOA) increase in plasma PFAS concentrations associated with OC use, compared to women who had not used OCs in the 12 months preceding the baseline interview (Table A1). In the fully adjusted models, these estimates ranged from 3.4 (for PFDA) to 14.6% (for PFOS) (Table 3).

Compared with never OC users, both recent and past OC users had higher plasma concentrations of PFASs (Table 3). In general, recent OC use predicted stronger associations with plasma PFAS concentrations than past OC use. Except for PFDA and PFUnDA, for which little evidence of an effect of recency of OC use was observed, recent OC users had 12.9–35.7% higher concentrations of PFASs than never OC users. Past OC use was also a predictor of increased PFAS concentrations for each compound except PFDA and PFUnDA, though the magnitude of the associations were slightly attenuated compared with the effect in recent users (percent increases in PFAS concentrations ranged from 7.2–32.1%).

A clear pattern of increased PFAS concentrations associated with lifetime duration of OC use was observed, except for PFDA and PFUnDA (Table 3). For the remaining five PFASs, compared with never users, the percent increase in PFAS concentrations among women who reported using OCs for 10 or more years ranged from 18.9–46.2%. Further, a statistically significant increase in plasma PFAS concentrations was observed with increasing duration of use for each of these five PFASs (in all cases, $p < 0.05$; data not shown). Age at first OC use showed no clear relationship with PFAS concentrations.

Overall, results from Table 4 indicate little evidence of effect modification between duration and recency of OC use. Few statistically significant interactions between recency and duration were observed, and these were isolated to PFOA and PFOS. Associations between short lifetime duration of OC use (≤ 3 years) and PFAS concentrations were observed for three compounds: PFOA, PFOS, and PFHpS. Effects of short duration of OC use on PFOA and PFOS concentrations appear to be isolated to recent OC users, although interaction between short duration and recency was observed only for PFOS ($p < 0.10$). We observed relatively large increased blood concentrations of PFHpS among both recent and past OC users who reported the shortest duration of OC use. Among women with the longest duration of OC use, effect estimates for recent users were greater than for past users. However, the magnitude of these differences was not large and estimates appear imprecise, with overlapping confidence intervals. Statistically significant interaction between long duration of OC use and recency was observed only for PFOA.

We observed similar patterns of effect after adjustment for inter-pregnancy interval (Table A2) and separately, duration of breastfeeding (Table A3). Overall, our conclusions were unchanged when we considered analyses using the imputed dataset. However, in some cases (e.g., for PFHpS and PFHxS), the relation between characteristics of OC use and PFAS concentrations were strengthened (Table A4). Also, the results for PFDA appeared more consistent with those for the other PFASs. No meaningful changes in point estimates or CIs were noted

Table 2
Distribution of plasma concentrations (ng/ml) of perfluoroalkyl substances (PFASs) among 1090 women in the Norwegian Mother and Child Cohort (MoBa) Study, 2003–2007.

	Values ≥ LOQ[a]			Measured values < LOQ	Values ≥ LOQ + measured values < LOQ
	n (%)	Median	IQR	*n* (%)	*n* (%)
PFOA	1090 (100.0)	2.48	1.82, 3.30	0 (0.0)	1090 (100.0)
PFNA	1089 (99.9)	0.45	0.33, 0.63	0 (0.0)	1089 (99.9)
PFDA	812 (74.5)	0.13	0.09, 0.19	195 (17.9)	1007 (92.4)
PFUnDA	993 (91.1)	0.22	0.14, 0.32	73 (6.7)	1066 (97.8)
PFHxS	1086 (99.6)	0.65	0.46, 0.91	1 (0.1)	1087 (99.7)
PFHpS	927 (85.0)	0.15	0.11, 0.22	67 (6.1)	994 (91.2)
PFOS	1090 (100.0)	12.83	9.83, 16.53	0 (0.0)	1090 (100.0)

IQR: interquartile range; LOQ: limit of quantification; PFDA: perflurodecanoic acid; PFHpS: perfluoroheptane sulfonate; PFHxS: perfluorohexane sulfonate; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate; PFUnDA: perfluoroundecanoic acid.

[a] LOQ = 0.05 ng/mL.

Table 3
Estimates of adjusted percent change[a] (95% confidence intervals) of perfluoroalkyl substance (PFAS) concentrations associated with characteristics of oral contraceptive (OC) use among 1090 women from the Norwegian Mother and Child Cohort (MoBa), 2003–2007.

	PFOA	PFNA	PFDA	PFUnDA	PFHxS	PFHpS	PFOS
OC use[b]	*n* = 977	*n* = 976	*n* = 906	*n* = 954	*n* = 974	*n* = 893	*n* = 977
No	REF	REF	REF	REF	REF	REF	REF
Yes	11.8 (6.2, 17.8)	6.9 (0.3, 14.0)	3.4 (−9.3, 17.8)	7.8 (−3.1, 20.0)	5.7 (−1.9, 13.8)	7.1 (−1.9, 16.9)	14.6 (8.5, 21.0)
Recency of OC use	*n* = 977	*n* = 976	*n* = 906	*n* = 954	*n* = 974	*n* = 893	*n* = 977
Never-users	REF	REF	REF	REF	REF	REF	REF
Recent users	25.4 (14.5, 37.4)	13.3 (1.2, 26.9)	−1.5 (−22.3, 25.0)	4.5 (−13.5, 26.2)	12.9 (−1.2, 29.1)	35.7 (15.4, 59.6)	28.6 (16.7, 41.6)
Past users	14.7 (4.8, 25.6)	7.2 (−4.2, 20.0)	−5.5 (−25.4, 19.7)	−3.7 (−20.2, 16.2)	8.3 (−5.1, 23.7)	32.1 (12.6, 55.1)	14.8 (4.3, 26.4)
Duration of OC use	*n* = 963	*n* = 962	*n* = 893	*n* = 943	*n* = 961	*n* = 878	*n* = 963
Never-users	REF	REF	REF	REF	REF	REF	REF
≤ 3 years	15.2 (4.6, 27.0)	7.3 (−4.8, 20.9)	−2.6 (−24.3, 25.3)	−5.3 (−22.4, 15.5)	5.0 (−8.6, 20.7)	27.1 (7.1, 50.7)	13.1 (2.1, 25.3)
4–6 years	17.7 (6.8, 29.8)	10.2 (−2.3, 24.3)	−7.5 (−28.3, 19.3)	6.7 (−12.7, 30.4)	10.2 (−4.2, 26.7)	31.9 (11.1, 56.7)	20.0 (8.2, 33.0)
7–9 years	22.3 (10.8, 35.0)	7.9 (−4.5, 21.9)	−12.9 (−32.7, 12.7)	1.9 (−16.8, 24.8)	10.6 (−4.0, 27.5)	33.7 (12.4, 59.1)	26.3 (13.8, 40.2)
≥ 10 years	32.0 (19.1, 46.3)	18.9 (4.8, 35.0)	16.0 (−11.1, 51.4)	3.8 (−15.9, 28.1)	18.9 (2.6, 37.8)	46.2 (22.0, 75.2)	31.9 (18.3, 47.0)
	n = 940	*n* = 939	*n* = 877	*n* = 918	*n* = 938	*n* = 863	*n* = 940
Age at first OC use	−0.7 (−1.5, 0.1)	−0.4 (−1.4, 0.5)	−1.1 (−3.1, 1.0)	0.9 (−0.8, 2.6)	−0.2 (−1.4, 0.9)	−0.2 (−1.5, 1.2)	0.4 (−0.5, 1.2)

PFDA: perfluorodecanoic acid, PFHpS: perfluoroheptane sulfonate, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, PFOA: perfluorooctanoic acid, PFOS: perfluorooctane sulfonate, PFUnDA: perfluoroundecanoic acid.

[a] Adjusted for age, menstrual cycle length, parity, and education.

[b] In the 12 months preceding the baseline interview.

when a four-category parity variable was used (data not shown) nor when results were adjusted for sub-study (data not shown).

4. Discussion

These data suggest that recency and longer duration of OC use predict higher plasma concentrations of multiple PFASs. Women who reported OC use in the 12 months preceding the baseline interview had increased plasma PFAS concentrations compared with non-users, though longer duration of OC use appeared to have an even greater impact, even among those for whom OC use was not recent.

Previous studies have reported that menstrual patterns are associated with PFAS concentrations, but the results have not been consistent, and HC use was not considered in these studies. HCs are commonly used to regulate menstruation in women, and are used to treat endometriosis (Derouich et al., 2015). Two studies have found higher PFAS concentrations in the blood of women with endometriosis compared with controls (Louis et al., 2012; Campbell et al., 2016). A study that applied physiologically-based pharmacokinetic (PBPK) models to data from the National Health and Nutrition Examination Survey reported that 13–16% of the association between endometriosis and blood PFAS concentrations might be explained by OC use (Ngueta et al., 2017), demonstrating the importance of considering OC use when examining the relationship between reproductive factors of PFAS blood concentrations.

In our primary analysis, PFDA and PFUnDA appeared to relate differently to characteristics of OC use than the other PFASs analyzed. These two compounds have the longest carbon chains of the PFASs included in the present analysis (10 and 11 carbons, respectively). The pharmacokinetics of PFASs with longer carbon chains may be different than PFASs with shorter carbon chains (Fujii et al., 2012). Uncertainty due to low concentrations of PFDA and PFUnDA may also contribute to differences in observed associations. PFDA also had a large number of missing observations and when we analyzed the imputed dataset, the associations between OC use and PFDA appeared more similar to the other PFASs.

The most obvious mechanism through which OCs might increase body burden of PFAS concentrations is alteration of menstruation as menstrual fluid loss is an important excretion route for PFASs (Wong et al., 2014; Verner and Longnecker, 2015). OCs in use today have been associated with a 44% reduction in menstrual fluid loss among normal women (Larsson et al., 1992) and 64% reduction in menstrual fluid loss in women with heavy or prolonged menstrual bleeding (Fraser et al., 2011). Excessive menstrual fluid loss is associated with iron-deficiency anemia. Among middle-aged women who are OC users, the prevalence of iron-deficiency anemia is consistently lower than in non-OC users (Burkman et al., 2004; Galan et al., 1998; Haile et al., 2016), which is consistent with reduced menstrual fluid loss. Another possible

Table 4
Estimates of adjusted percent change[a] (95% confidence intervals) of perfluorinated alkyl substance (PFAS) concentrations associated with duration and recency of oral contraceptive (OC) use among women from the Norwegian Mother and Child Cohort (MoBa), 2003–2007.

Duration	Recency	PFOA	PFNA	PFDA	PFUnDA	PFHxS	PFHpS	PFOS
		n = 815	*n* = 912	*n* = 911	*n* = 845	*n* = 892	*n* = 910	*n* = 834
Never-users		REF	REF	REF	REF	REF	REF	REF
≤ 3 years	Past users	11.0 (−0.5, 23.8)	6.8 (−6.7, 22.3)	1.0 (−24.0, 34.3)	−13.7 (−31.2, 8.4)	1.5 (−13.3, 18.9)	25.8 (3.9, 52.4)	7.7 (−4, 20.8)*
	Recent users	19.8 (7.2, 33.9)	7.1 (−6.7, 22.9)	−6.3 (−29.8, 25.1)	−0.2 (−20.7, 25.4)	9.4 (−6.8, 28.3)	30.2 (7.5, 57.7)	19.7 (6.5, 34.5)*
4–6 years	Past users	12.4 (0.5, 25.8)*	6.2 (−7.6, 22.1)	−12 (−34.3, 17.9)	6.3 (−15.8, 34.1)	7.8 (−8.2, 26.7)	35.0 (11.3, 63.8)	12.0 (−0.4, 26)*
	recent users	23.3 (10.4, 37.7)*	15.5 (0.8, 32.5)	−3.9 (−27.8, 28)	8.0 (−14.1, 35.6)	13.3 (−3.3, 32.8)	31.9 (8.9, 59.8)	28.6 (14.6, 44.4)*
7–9 years	Past users	23.6 (9.6, 39.3)	6.4 (−8.2, 23.4)	−15 (−37.7, 16.0)	2.9 (−19.6, 31.7)	18.7 (0.0, 41)	39.6 (13.7, 71.4)	26.7 (11.7, 43.6)
	Recent users	23.9 (11.2, 38)	9.8 (−4.0, 25.5)	−12.3 (−33.7, 16.0)	3.5 (−17.2, 29.3)	8.3 (−7.3, 26.4)	33.7 (10.9, 61.2)	30.9 (16.9, 46.6)
≥ 10 years	Past users	21.3 (6.3, 38.3)*	11.7 (−5.0, 31.5)	15.7 (−17.8, 63.0)	−4.3 (−26.9, 25.2)	13.2 (−6.2, 36.7)	39.4 (11.1, 75)	24.0 (8.1, 42.3)
	Recent users	36.0 (21.7, 52.0)*	21.6 (5.9, 39.6)	20.3 (−9.5, 60.1)	9.2 (−13.2, 37.3)	20.0 (2.3, 40.9)	45.3 (19.9, 76.2)	35.3 (20.4, 52.1)

PFDA: perfluorodecanoic acid, PFHpS: perfluoroheptane sulfonate, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, PFOA: perfluorooctanoic acid, PFOS: perfluorooctane sulfonate, PFUnDA: perfluoroundecanoic acid.

* Statistically significant interaction between duration and recency at $p < 0.1$.

[a] Adjusted for age, menstrual cycle length, parity, and education.

mechanism is that OCs might decrease excretion via glomerular filtration, though the evidence for this is based only on increased serum creatinine among OC users (Wang et al., 2016; Oelkers et al., 1995). On the other hand, the use of OCs has been associated with metabolic changes including decreased plasma albumin (Wang et al., 2016), which might be expected to decrease PFAS concentrations. In the present analysis, the focus was on PFASs in relation to characteristics of OC use. Detailed data on characteristics of non-oral HC use was not available in MoBa and only a small number of women ($n = 43$) in this study reported the use of non-oral HCs. Though our results to do directly inform associations between all forms of HCs and PFASs concentrations, it is possible that the associations observed in the present study may hold for HCs in general.

The most likely source of bias in this analysis was from potential misclassification of OC use characteristics. Reported characteristics of OC use may be affected by imprecise recall, although misreporting of OC use is unlikely to vary according to levels of PFASs. Studies have measured the accuracy of women's self-reported history of contraceptive use. Coulter et al. found that 80% of self-reported OC start dates were accurate within six months of the clinically recorded start date; this study also found that the reported duration of contraceptive use was highly correlated with the clinical record ($r = 0.91$) (Coulter et al., 1986). Glass et al. also found high accuracy in self-reported duration of OC use (correlation statistics not reported) (Glass et al., 1974). Because these results were affected by imprecision in measurements, the underlying associations may be somewhat larger than observed.

4.1. Conclusions

Overall, this analysis shows that recency and, particularly, duration of oral contraceptive use may be important to consider when investigating the relationships between reproductive outcomes and plasma PFAS concentrations in women. Thus, it would be beneficial for future studies investigating women's reproductive health impacts of PFAS to collect detailed information about the types of hormonal contraceptives women use as well as on the timing and duration of use as our analyses indicate these variables may be potentially important covariates.

Conflicts of interest and source of funding

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Author contributions

ER conducted data analyses, prepared tables, and edited the manuscript; ABS contributed to data analyses and manuscript editing; LSH and AS conducted chemical analyses and edited the manuscript; MPL conceived of the study, contributed to data analyses, data interpretation, and manuscript editing; ES contributed to data interpretation and manuscript editing; KWW conceived of and designed the study, directed the data analyses, data interpretation, and manuscript preparation.

Table A1
Estimates of percent change (95% confidence intervals) of perfluoroalkyl substance (PFAS) concentrations associated with oral contraceptive (OC)[a] use in the 12 months preceding the baseline interview among 1090 women from the Norwegian Mother and Child Cohort (MoBa), 2003–2007.

	n (%)	Model		
		Crude	Age-adjusted	Fully adjusted[b]
PFOA	470 (43.1)	20.1 (13.7, 27.0)	19.0 (12.4, 25.9)	11.8 (6.2, 17.8)
PFNA	470 (43.1)	11.7 (4.6, 19.4)	13.6 (6.2, 21.5)	6.9 (0.3, 14.0)
PFDA	447 (40.0)	1.1 (−11.0, 14.9)	8.8 (−4.5, 23.9)	3.4 (−9.3, 17.8)
PFUnDA	448 (41.1)	−2.6 (−12.2, 8.2)	7.6 (−3.0, 19.5)	7.8 (−3.1, 20.0)
PFHxS	470 (43.1)	8.7 (1.0, 17.0)	10.3 (2.3, 19.0)	5.6 (−1.9, 13.8)
PFHpS	440 (40.4)	17.6 (7.6, 28.6)	16.2 (6.0, 27.3)	7.1 (−1.9, 16.9)
PFOS	470 (43.1)	14.6 (8.8, 20.7)	15.2 (9.2, 21.5)	14.6 (8.5, 21.0)

PFDA: perfluorodecanoic acid, PFHpS: perfluoroheptane sulfonate, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, PFOA: perfluorooctanoic acid, PFOS: perfluorooctane sulfonate, PFUnDA: perfluoroundecanoic acid.

[a] OCs include: pill, mini-pill.

[b] Adjusted for age, menstrual cycle length, parity, and education.

Table A2
Estimates of adjusted percent change[a] (95% confidence intervals) of perfluoroalkyl substance (PFAS) concentrations associated with characteristics of oral contraceptive (OC) use among women from the Norwegian Mother and Child Cohort (MoBa), 2003–2007, additionally adjusted for inter-pregnancy interval.

	PFOA	PFNA	PFDA	PFUnDA	PFHxS	PFHpS	PFOS
OC use[b]	*n* = 975	*n* = 974	*n* = 904	*n* = 952	*n* = 972	*n* = 891	*n* = 975
No	REF	REF	REF	REF	REF	REF	REF
Yes	12.6 (7.1, 18.4)	7.2 (0.6, 14.2)	3.2 (− 9.4, 17.5)	7.2 (− 3.7, 19.2)	5.9 (− 1.7, 14.1)	7.6 (− 1.4, 17.5)	14.9 (8.9, 21.4)
Recency of OC use	*n* = 975	*n* = 974	*n* = 904	*n* = 952	*n* = 972	*n* = 891	*n* = 975
Never-users	REF	REF	REF	REF	REF	REF	REF
Recent users	25.7 (15.0, 37.4)	13.2 (1.2, 26.7)	− 1.6 (− 22.3, 24.7)	4.0 (− 13.9, 25.6)	13.3 (− 0.9, 29.4)	35.8 (15.5, 59.7)	28.6 (16.8, 41.6)
Past users	14.1 (4.5, 24.6)	6.8 (− 4.4, 19.4)	− 5.4 (− 25.2, 19.6)	− 3.6 (− 20.0, 16.3)	8.4 (− 5.1, 23.7)	31.5 (12.0, 54.3)	14.5 (4.0, 25.9)
Duration of OC use	*n* = 961	*n* = 960	*n* = 856	*n* = 941	*n* = 959	*n* = 876	*n* = 961
Never-users	REF	REF	REF	REF	REF	REF	REF
≤ 3 years	15.6 (5.2, 27.0)	7.1 (− 4.8, 20.5)	− 8.0 (− 29.0, 19.2)	− 6.2 (− 23.0, 14.4)	5.2 (− 8.4, 20.9)	27.2 (7.3, 50.7)	13.1 (2.2, 25.2)
4–6 years	16.9 (6.3, 28.5)	9.3 (− 2.9, 23.2)	− 16.6 (− 35.8, 8.4)	6.1 (− 13.1, 29.6)	9.9 (− 4.5, 26.4)	31.0 (10.4, 55.5)	19.4 (7.8, 32.3)
7–9 years	22.5 (11.2, 34.8)	8.0 (− 4.3, 21.8)	− 18.3 (− 37.2, 6.4)	1.9 (− 16.8, 24.7)	11.0 (− 3.7, 27.9)	34.0 (12.7, 59.3)	26.4 (14.0, 40.3)
≥ 10 years	31.8 (19.3, 45.6)	18.6 (4.6, 34.5)	9.5 (− 16.7, 43.9)	3.9 (− 15.7, 28.2)	19.0 (2.7, 37.9)	45.3 (21.3, 74.1)	31.6 (18.2, 46.6)
	n = 938	*n* = 937	*n* = 875	*n* = 916	*n* = 936	*n* = 861	*n* = 938
Age at first OC use	− 0.5 (− 1.2, 0.3)	− 0.4 (− 1.3, 0.6)	− 1.1 (− 3.2, 1.0)	0.6 (− 1.1, 2.7)	− 0.2 (− 1.3, 1.0)	0.0 (− 1.3, 1.4)	0.5 (− 0.3, 1.4)

PFDA: perfluorodecanoic acid, PFHpS: perfluoroheptane sulfonate, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, PFOA: perfluorooctanoic acid, PFOS: perfluorooctane sulfonate, PFUnDA: perfluoroundecanoic acid.

[a] Adjusted for age, menstrual cycle length, parity, education, and interval between pregnancy.

[b] In the 12 months preceding the baseline interview.

Table A3
Estimates of adjusted percent change[a] (95% confidence intervals) of perfluoroalkyl substance (PFAS) concentrations associated with characteristics of oral contraceptive (OC) use among women from the Norwegian Mother and Child Cohort (MoBa), 2003–2007, additionally adjusted for duration of breastfeeding.

	PFOA	PFNA	PFDA	PFUnDA	PFHxS	PFHpS	PFOS
OC use[b]	*n* = 967	*n* = 966	*n* = 896	*n* = 944	*n* = 964	*n* = 883	*n* = 967
No	REF	REF	REF	REF	REF	REF	REF
Yes	11.8 (6.2, 17.6)	6.6 (0.0, 13.6)	3.6 (− 9.2, 18.1)	7.4 (− 3.5, 19.6)	5.5 (− 2.1, 13.7)	6.7 (− 2.3, 16.6)	14.5 (8.4, 20.9)
Recency of OC use	*n* = 967	*n* = 966	*n* = 896	*n* = 944	*n* = 964	*n* = 883	*n* = 967
Never-users	REF	REF	REF	REF	REF	REF	REF
Recent users	23.3 (12.6, 35.1)	11.8 (− 0.3, 25.3)	− 1.6 (− 22.7, 25.2)	4.1 (− 14.1, 26.0)	11.0 (− 3.0, 27.0)	32.3 (12.3, 55.9)	27.7 (15.9, 40.9)
Past users	12.5 (2.8, 23.1)	5.9 (− 5.5, 18.6)	− 5.9 (− 25.9, 19.6)	− 3.7 (− 20.4, 16.4)	6.27 (− 7.03, 21.48)	28.7 (9.4, 51.4)	14.0 (3.5, 25.7)
Duration of OC use	*n* = 955	*n* = 954	*n* = 885	*n* = 935	*n* = 953	*n* = 870	*n* = 955
Never-users	REF	REF	REF	REF	REF	REF	REF
≤ 3 years	12.4 (2.0, 23.8)	5.5 (− 6.5, 19.1)	− 2.5 (− 24.5, 26.0)	− 6.0 (− 23.1, 15.0)	2.6 (− 10.9, 18.1)	23.4 (3.7, 46.8)	12.1 (1.1, 24.3)
4–6 years	16.4 (5.6, 28.3)	9.4 (− 3.81 23.3)	− 7.5 (− 28.5, 19.7)	6.6 (− 13.0, 30.4)	8.3 (− 6.0, 24.7)	30.1 (9.3, 54.7)	19.6 (7.8, 32.6)
7–9 years	20.5 (9.21, 33.0)	6.9 (− 5.4, 20.9)	− 12.6 (− 32.6, 13.4)	1.9 (− 16.9, 25.1)	8.7 (− 5.7, 25.4)	31.4 (10.2, 56.6)	25.5 (13.0, 39.4)
≥ 10 years	29.3 (16.7, 43.3)	17.4 (3.3, 33.4)	16.6 (− 10.9, 52.7)	4.0 (− 15.9, 28.5)	16.2 (0.1, 34.8)	42.7 (18.8, 71.5)	30.6 (17.1, 45.6)
	n = 931	*n* = 930	*n* = 868	*n* = 909	*n* = 929	*n* = 854	*n* = 931
Age at first OC use	− 0.5 (− 1.3, 0.3)	− 0.3 (− 1.3, 0.7)	− 1.1 (− 3.2, 1.0)	0.8 (− 1.0, 2.5)	0.1 (− 1.1, 1.3)	0.2 (− 1.2, 1.6)	0.6 (− 0.3, 1.4)

PFDA: perfluorodecanoic acid, PFHpS: perfluoroheptane sulfonate, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, PFOA: perfluorooctanoic acid, PFOS: perfluorooctane sulfonate, PFUnDA: perfluoroundecanoic acid.

[a] Adjusted for age, menstrual cycle length, parity, education, and duration of breastfeeding.

[b] In the 12 months preceding the baseline interview.

Table A4
Estimates of adjusted percent change[a] (95% confidence intervals) of perfluorinated alkyl substance (PFAS) concentration associated with characteristics of oral contraceptive (OC) use among 1090 women from the Norwegian Mother and Child Cohort (MoBa), 2003–2007, using multiple imputation.

	PFOA	PFNA	PFDA	PFUnDA	PFHxS	PFHpS	PFOS
OC use[b]	*n* = 999	*n* = 999	*n* = 999	*n* = 999	*n* = 999	*n* = 999	*n* = 999
No	REF	REF	REF	REF	REF	REF	REF
Yes	10.9 (5.3, 16.9)	6.9 (0.1, 14.2)	10.7 (−4.4, 28.3)	9.1 (−2.0, 21.6)	7.0 (−1.1, 15.7)	16.2 (5.8, 27.7)	12.3 (6.3, 18.6)
Recency of OC use	*n* = 999	*n* = 999	*n* = 999	*n* = 999	*n* = 999	*n* = 999	*n* = 999
Never-users	REF	REF	REF	REF	REF	REF	REF
Recent users	25.0 (14.2, 37.0)	13.5 (1.2, 27.2)	16.2 (−10.0, 50.0)	4.6 (−14.0, 27.2)	16.5 (1.7, 33.5)	63.0 (37.5, 93.4)	27.4 (15.7, 40.3)
Past users	14.0 (4.1, 24.8)	6.7 (−4.8, 19.5)	4.1 (−19.3, 34.3)	−6.7 (−23.3, 13.3)	10.0 (−4.0, 26.0)	47.1 (24.1, 74.3)	14.6 (4.1, 26.1)
Duration of OC use	*n* = 987	*n* = 987	*n* = 987	*n* = 987	*n* = 987	*n* = 987	*n* = 987
Never-users	REF	REF	REF	REF	REF	REF	REF
≤ 3 years	15.1 (4.6, 26.8)	7.6 (−4.6, 21.4)	6.5 (−18.9, 39.7)	−7.3 (−24.5, 13.7)	8.0 (−6.2, 24.4)	45.2 (21.3, 73.8)	13.3 (2.4, 25.4)
4–6 years	17.5 (6.6, 29.5)	9.6 (−2.9, 23.8)	7.0 (−18.4, 40.4)	4.2 (−15.3, 28.2)	13.5 (−1.5, 30.8)	54.1 (28.6, 84.8)	20.6 (8.9, 33.5)
7–9 years	22.1 (10.6, 34.7)	7.9 (−4.6, 22.0)	−0.1 (−24.0, 31.4)	1.1 (−18.0, 24.6)	14.4 (−1.0, 32.0)	57.8 (31.4, 89.5)	25.4 (13.1, 39.0)
≥ 10 years	32.3 (19.4, 46.6)	19.9 (5.4, 36.3)	36.1 (2.17, 81.3)	7.4 (−13.6, 33.5)	23.8 (6.54, 43.8)	72.4 (42.4, 108.8)	32.4 (18.9, 47.4)
	n = 965	*n* = 965	*n* = 965	*n* = 965	*n* = 965	*n* = 965	*n* = 965
Age at first OC use	−0.8 (−1.6, 0.0)	−0.5 (−1.5, 0.4)	−1.2 (−3.4, 1.0)	0.3 (−1.4, 2.0)	−0.4 (−1.5, 0.8)	−0.6 (−2.0, 0.9)	0.2 (−0.6, 1.0)

PFDA: perfluorodecanoic acid, PFHpS: perfluoroheptane sulfonate, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, PFOA: perfluorooctanoic acid, PFOS: perfluorooctane sulfonate, PFUnDA: perfluoroundecanoic acid.

[a] Adjusted for age, menstrual cycle lengths, parity, and education.

[b] In the 12 months preceding the baseline interview.

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