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First-trimester maternal concentrations of polyfluoroalkyl substances and fetal growth throughout pregnancy

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ABSTRACT

Background: Several studies have investigated the possible association between prenatal exposure to perfluoroalkyl substances (PFASs) and birth anthropometry. However, none has assessed fetal size longitudinally. We studied the possible association between PFASs and fetal biometry.

Methods: In 1230 mother–child pairs of three cohorts from the Spanish INMA-Project, we analyzed perfluorohexanesulfonic acid (PFHxS), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) in first-trimester maternal plasma (collection: 2003–2008). We measured abdominal circumference (AC), femur length (FL), biparietal diameter (BPD), and estimated fetal weight (EFW) by ultrasounds at 12, 20, and 34 gestational weeks. We conducted multivariable linear regression analyses between $\log_2$-transformed (PFASs) and SD-scores of fetal parameters in each cohort and subsequent meta-analysis. We also assessed effect modification by sex and maternal smoking.

Results: PFHxS, PFOA, PFOS, and PFNA medians were: 0.58, 2.35, 6.05, and 0.65 ng/mL, respectively. There were no associations for the whole population in any trimester of pregnancy. However, we found an indication that maternal smoking modified the effect in different directions depending on the PFAS. Among smokers (31%), we found negative associations between both PFOA and PFNA and FL or EFW at week 20 (% change ranging between −6.8% and −5.7% per twofold PFAS increase) and positive associations between PFHxS or PFOS and BPD at week 34 (6.8% and 6.3%, respectively).

Conclusions: Results did not suggest an overall association between prenatal PFASs and fetal growth. The results among smokers should be taken with caution and further studies are warranted to elucidate the possible role of smoking in this association.

Abbreviations: AC, abdominal circumference; AIC, Akaike Information Criterion; BMI, body mass index; BPD, biparietal diameter; CI, confidence interval; DAG, directed acyclic graphs; df, degrees of flexibility; EFW, estimated fetal weight; eGFR, estimated glomerular filtration rate; FL, femur length; GAM, generalized additive model; HCB, hexachlorobenzene; Hg, total mercury; INMA, INfancia y Medio Ambiente (Environment and Childhood); LMP, last menstrual period; LOQ, limit of quantification; NO_2, nitrogen dioxide; OR, odds ratio; P, percentile; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFASs, perfluoroalkyl substances; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; Ref, reference group; SD, standard deviation; SGA, small for gestational age

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1. Introduction

Perfluoroalkyl substances (PFASs), such as perfluorohexanesulfonic acid (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA), are synthetic chemicals which have been widely used in a variety of industrial and commercial applications (WHO, 2013). They are ubiquitously present in the environment and food, the latter being an important route of exposure (Domingo and Nadal, 2017; Manzano-Salgado et al., 2016). Detectable blood levels of these PFASs have been reported in pregnant women and women of reproductive age from different regions worldwide (Ballesteros et al., 2017; Kannan et al., 2004; Manzano-Salgado et al., 2016; Mondal et al., 2012). Their transfer across the placenta has also been reported (Manzano-Salgado et al., 2015). PFASs have high persistence, bioaccumulation capability, and long half-lives in humans (WHO, 2013), making them a potential threat to humankind.

The fetal period is one of the most vulnerable windows for exposure to chemicals with suspected endocrine disrupting capacity, such as the PFASs, since it is a time of great change and rapid development (Mallozzi et al., 2016). Epidemiologic evidence on possible fetal growth impairment due to PFOA exposure has been reviewed on several occasions (Bach et al., 2015; Johnson et al., 2014; Negri et al., 2017; Steenland et al., 2018). In the most recent meta-analysis (Steenland et al., 2018) conducted using data from 24 studies (n = 13,000 births), a modest inverse association was found between concentrations of PFOA and birth weight when considering studies with measured levels of this contaminant in maternal or cord blood samples (change in birth weight of −10.5 g [95% confidence interval (CI): −16.7, −4.4] for every ng/mL of PFOA). However, little evidence of an association was found (−1.0 g; [−2.4, 0.4]) when including a large study with estimated PFOA levels from a model (Savitz et al., 2012). Human evidence on possible birth weight impairment due to PFOS has also been reviewed (Bach et al., 2015; Negri et al., 2017). The most recent review found a change in birth weight of −0.92 g [−3.4, 1.6] for each ng/mL of untransformed PFOS measured in maternal or cord blood (n = 8 studies) and a change of −46.1 g [−80.3, −11.9] for each unit of log-transformed ng/mL PFOS (i.e., for an increase of approximately 2.7 times in PFOS-untransformed levels) (n = 8 studies). Regarding PFHxS and PFNA, information about the possible effects on reproductive outcomes is still too sparse to reach a conclusion and further research is warranted (Bach et al., 2015).

The potential impact of exposure to PFASs on fetal development is of concern for public health since altered fetal growth has been associated with an increased risk of multiple diseases later in life, including hypertension, obesity, cardiovascular diseases, and diabetes (Gluckman et al., 2008; Varvarigou, 2010; Zheng et al., 2016). We therefore aimed to investigate the relation between maternal plasma PFAS concentrations and longitudinal measures of fetal growth in the INMA–INfancia y Medio Ambiente (Environment and Childhood) Project (Spain).

2. Material and methods

2.1. Study design

The INMA-Project is a mother-and-child cohort study established in 2003–2008 in different areas of Spain following a common protocol (Guxens et al., 2012). The Ethics Committees of each center of recruitment approved the research protocol, and all mothers gave their written informed consent prior to inclusion.

We recruited a total of 2150 eligible women in the first trimester of pregnancy in three INMA cohorts (Gipuzkoa: n = 638; Sabadell: n = 657; and Valencia: n = 855, participation rate: 54–68%). A total of 2000 (93%) women with two or more valid ultrasounds were followed up to delivery (2004–2008). In the present study, the sample size was 1230 mothers and their children with available maternal plasma samples for PFAS determinations (see flowchart in Fig. S1).

2.2. PFAS analysis

At the end of the first trimester (mean: 13.5 weeks of gestation; standard deviation [SD]: 1.7) maternal blood was collected, aliquoted, and stored (−80 °C) by trained professionals, applying the same protocol in the three cohorts (Guxens et al., 2012). Maternal plasma samples were analyzed at the Institute for Occupational Medicine, RWTH Aachen University, Germany, as described elsewhere (Manzano-Salgado et al., 2015). Briefly, PFAS plasma concentrations were determined by column-switching high-performance liquid chromatography (Agilent 1100 Series HPLC apparatus) coupled to tandem mass spectrometry (Sciex API 3000 LC/MS/MS system in ESI-negative mode). The limit of quantification (LOQ), determined as a signal-to-noise ratio of six in the vicinity of the analytes, was 0.2 ng/mL for PFHxS, PFOS, and PFOA and 0.1 ng/mL for PFNA.

We carried out the calibration by spiking bovine serum with the analytes in the range concentration of 1–100 ng/mL for PFOA and PFOS and 0.1–10 ng/mL for PFHxS and PFNA. Quality control was prepared by spiking bovine serum at a 4 ng/mL concentration for PFOA and PFOS and 0.4 ng/mL for PFHxS and PFNA. Moreover, we used the aliquoted plasma of a 41-year-old German male for additional quality control. This was included in every analytical series. The between-day imprecision for the spiked bovine samples (n = 42) ranged from 6.4% for PFOA (4.0 ng/mL) to 12.6% for PFHxS (0.4 ng/mL). In the human plasma, the between-day imprecision ranged from 8.7% for PFHxS (0.7 ng/mL) to 11.1% for PFNA (0.7 ng/mL).

To guarantee the accuracy of our results, we participated biannually in successful round robins for the determination of PFASs in plasma organized in Germany (www.g-equas.de). During the study period, certified material from this round robin was included in every analytical series with all results in the acceptable range.

2.3. Fetal outcomes

Ultrasound scans were routinely scheduled for gestational weeks 12, 20, and 34, and were performed by specialized obstetricians following standardized procedures. We considered the following fetal parameters: abdominal circumference (AC), biparietal diameter (BPD), femur length (FL), and estimated fetal weight (EFW) calculated using the Hadlock algorithm (Hadlock et al., 1985). We assessed fetal size during the first, second and third trimesters of pregnancy (specifically at 12, 20, and 34 weeks of gestation) by SD-scores. Calculation of SD-scores was based on longitudinal growth curves for the four fetal parameters, obtained by linear mixed models that account for constitutional growth potential and gestational age (Pinheiro and Bates, 2000). These customized models provide individual rather than population-based fetal growth standards that are expected to better identify intrauterine growth retardation (Mamelle et al., 2001). We used 6041 ultrasounds obtained during the three trimesters of pregnancy (mean ± SD: 12.4 ± 0.8, 20.8 ± 0.9, and 33.4 ± 1.7 weeks of gestation) to construct these longitudinal growth curves. A detailed description of the rationale, parameterization of the models, and calculation of SD-scores has been published previously (Iniguez et al., 2016; Lopez-Espinosa et al., 2015; Lopez-Espinosa et al., 2016) and it is also briefly summarized in Supplementary material and Table S1.

2.4. Covariates

We obtained information on parental sociodemographic and anthropometric characteristics, as well as lifestyle, through two questionnaires administered during the first and third trimesters of pregnancy by trained interviewers. We considered the following maternal variables: age, pre-pregnancy body mass index (BMI), country of origin, zone of residence, studies, employment during pregnancy, social class, parity, consumption of tobacco during the first trimester of pregnancy, passive smoking, and season of last menstrual period (LMP).

Additionally, we considered paternal BMI, cohort, and sex of the fetus (Iniguez et al., 2016; Lopez-Espinosa et al., 2015; Lopez-Espinosa et al., 2016).

During the first trimester, we also collected information on diet by using a food frequency questionnaire (Vioque et al., 2013) and we considered the following as covariates: beverages containing alcohol, and energy-adjusted intake of eggs, dairy products, cereals and pasta, vegetables and legumes, fruits, seafood, and meat products. The items included in each food group have been described previously (Costa et al., 2016).

We also considered pre- or perinatal concentrations of some contaminants (Ballester et al., 2018; Iniguez et al., 2016; Llop et al., 2017; Lopez-Espinosa et al., 2015; Lopez-Espinosa et al., 2016): total mercury (Hg) in cord blood; first-trimester maternal serum levels of the sum of three polychlorinated biphenyls (ΣPCBs: PCB−138, −153, and −180); hexachlorobenzene (HCB); the sum of five polybrominated diphenyl ethers (ΣPBDEs: BDE−47, −99, −153, −154, and −209) measured in first-trimester maternal serum (Valencia cohort) or colostrum collected at 48–96 h postpartum (Gipuzkoa and Sabadell cohorts); and individual exposure to air pollution by estimating nitrogen dioxide (NO_2) exposure throughout pregnancy (Estarlich et al., 2011). We also considered albumin and estimated glomerular filtration rate (eGFR), the latter calculated using the Cockroft-Gault formula. See Supplementary material for details of covariates.

2.5. Statistical analysis

Logistic regression models adjusted by cohort were used to explore the differences in study variables between the excluded and included women. Cohort-adjusted Pearson's partial correlations between PFASs and the rest of the contaminants, albumin, and eGFR were performed and a heatmap was also generated to display the correlations. We present numbers (percentages) for categorical variables, mean ± SD for continuous variables, and percentage ≥ LOQ and percentiles (P25, P50, and P75) for PFASs.

We used multivariable linear regression models to assess the relation between PFAS concentrations (log_2-transformed to account for right-skewed distributions) and fetal outcomes. We selected the candidate covariates using a directed acyclic graph (DAG) (Fig. S2) accounting for all the potential determinants of maternal PFAS concentrations and anthropometric outcomes at birth identified in the INMA cohort (Manzano-Salgado et al., 2015, 2016). Subsequently, candidate variables were selected to prevent overfitting from accounting for their predictive ability of the outcome and their confounding role. Firstly, we built a core model for each SD-score in each trimester of pregnancy by including the variables related at the $p < 0.2$ level in crude analyses (only adjusted by cohort). Variables not related at $p < 0.1$ (F test) were excluded following a backward procedure. Each exposure variable was then incorporated and potential confounders were added to the final models if their inclusion changed the contaminant coefficient by > 10% after inclusion of this variable. In all resulting models, we included the following variables regardless of their statistical significance: cohort, parity, and maternal age and country of birth, since they were either strongly associated with PFASs in the INMA-Project (Manzano-Salgado et al., 2016) or due to the relation with the outcome and exposure in the present study (parity). Finally, we assessed the homoscedasticity and normality of regression residuals, and we excluded extreme outliers (studentized residuals ≥4) or highly influential observations (Cook's distance > 0.5) from the final models (n ≤ 1 in all models).

We also explored the shape of the relation by generalized additive models (GAMs) including natural splines as smoothers. Several degrees of flexibility (df = 1, 2, 3), including linearity, were evaluated on the basis of the Akaike Information Criterion (AIC). Results from the GAMs did not provide any evidence of a non-linear pattern for the relation between maternal PFAS concentrations and fetal outcomes (data not shown).

We used multiple imputation with chained equations (Sterne et al., 2009) to deal with missing values in covariates and with values < LOQ in exposure (PFASs) and other variables included in sensitivity analyses (Hg, PCBs, HCB, and PBDEs), avoiding fixed imputation by assuming a log-normal distribution of censored variables and conditioning the imputation to the range: 0, LOQ. We generated 50 complete datasets using the *mice* package for R (Van Bauren and Groothuis-Oudshoorn, 2011) and we used Rubin's rules for multiple imputation to combine the estimates on each dataset (Little and Rubin, 2002). For further information see Supplementary material and Table S2.

Final models were applied to each cohort separately using imputed data and the resulting estimates were combined by means of meta-analysis. Random effects models were applied when heterogeneity was detected (i.e., I-squared statistic [Higgins et al., 2003] > 50%). Parameter estimates were expressed as the % change in the outcome with respect to the mean and its 95% CI associated with a twofold increase in PFAS concentrations.

We also investigated possible differences by sex and smoking by including the product interaction term of each of these variables with the contaminants in the individual cohort models and subsequent meta-analysis.

Different sensitivity analyses were also performed to evaluate the robustness of the results. First, we conducted analyses restricted to individuals with complete data (hereafter called 'complete case analysis'). Second, we added the eGFR to the main analysis since the association between PFASs and fetal growth could be confounded by maternal eGFR during gestation (Verner et al., 2015). Third, since PFASs bind to albumin (Sagiv et al., 2015), we also included this variable in the main analysis. Fourth, we conducted a multi-pollutant analysis including the four PFASs in the main analysis simultaneously. Fifth, as exposure to other contaminants was related to impaired fetal growth in our cohort (Ballester et al., 2018; Iniguez et al., 2016; Lopez-Espinosa et al., 2015; Lopez-Espinosa et al., 2016), we re-ran analyses including (i) NO_2; and the following log-transformed contaminants and lipids: (ii) ΣPCBs plus lipids, (iii) HCB plus lipids, (iv) Hg, and (v) ΣPBDEs plus lipids. Sixth, we excluded special cases from the main analysis, i.e., either preterm births (n = 48) or women whose self-reported date of the LMP was not confirmed by ultrasound, stated as a difference ≥ 7 days with respect to the estimation based on an early crown–rump length measurement (n = 145).

We conducted the statistical analysis with the software R.3.4.0 (R Core Team, 2014). Where associations are referred to as statistically significant, this implies a $p < 0.05$. We drew our DAG using DAGitty version 3.0 (Textor, 2011). All results presented (except Table 1 and Fig. S3) were based on pooled estimates from a multiple imputed dataset.

3. Results

3.1. Study population and PFAS concentrations

Mothers included in our study (n = 1230) were more likely to be older, born in Spain, working during pregnancy, and non-smokers, to have a higher educational level or social class, and intake more dairy products compared to excluded mothers (n = 920) (Table 1). No differences were found regarding outcomes between the two groups, except in EFW at 12 weeks of gestation (lower in participants, see Table S3).

The mean ± SD age of the included mothers was 31 ± 4 years, most of them were born in Spain (93%), 31% smoked during the first trimester of pregnancy, and 49% gave birth to a girl (Table 1). PFOS and PFOA were quantified in all maternal samples, whereas PFHxS and PFNA were quantified in 96% and 99%, respectively. Median concentrations were 0.58, 2.35, 6.05, and 0.65 ng/mL for PFHxS, PFOA, PFOS, and PFNA, respectively (Table 2). Among PFASs, correlations

Table 1
Characteristics of the INMA-Project population by exclusion and inclusion in the current study (2003–2008, Spain).

Variable	Excluded (n = 920)	Included (n = 1230)	OR[a]	p[a]
Maternal variable				
Age (years)	30 ± 4.8	31 ± 4.0	1.05	< 0.001
Height (cm)	163 ± 6.4	163 ± 6.1	1.01	0.17
BMI[b] (kg/m^2)	23 ± 4.4	24 ± 4.3	1.01	0.44
Cohort:				< 0.001
Gipuzkoa	318(34)	320(26)	Ref	
Sabadell	255(28)	402(33)	1.57	
Valencia	347(38)	508(41)	1.46	
Country of birth:				< 0.001
Spain	770(87)	1145(93)	Ref	
Other	119(13)	83(7)	0.42	
Zone of residence:				0.31
No rural	876(96)	1175(96)	Ref	
Rural	35(4)	54(4)	1.30	
Studies:				< 0.001
Up to primary	283(32)	280(23)	Ref	
Secondary	346(39)	516(42)	1.64	
University	260(29)	431(35)	2.06	
Employment[c]:				< 0.001
No	154(17)	152(12)	Ref	
Yes	738(83)	1078(88)	1.53	
Social class:				< 0.001
I (highest)	225(25)	430(35)	Ref	
II	211(24)	327(27)	0.73	
III (lowest)	456(51)	473(38)	0.48	
Parity:				0.33
0	479(54)	689(56)	Ref	
≥1	411(46)	539(44)	0.92	
Smoking[d]:				0.04
No	514(66)	835(69)	Ref	
Yes	268(34)	382(31)	0.82	
Passive smoking[c]:				0.95
No	272(35)	410(34)	Ref	
Yes	505(65)	800(66)	0.99	
Alcohol intake[d]:				0.30
No	749(85)	1054(86)	Ref	
Yes	130(15)	169(14)	0.88	
Energy-adjusted intake (g/day) of:				
Eggs	19.8 ± 9.3	19.9 ± 8.7	1.01	0.30
Dairy products	425 ± 205.2	442 ± 220.1	1.00	0.02
Cereals and pasta	95.4 ± 48.8	97.8 ± 45.9	1.00	0.76
Veg. and legumes	251 ± 110.5	252 ± 112.9	1.00	0.40
Fruits	310 ± 194.1	312 ± 190.8	1.00	0.38
Seafood	78.9 ± 35.7	79.8 ± 35.2	1.00	0.27
Meat products	115 ± 43.4	119 ± 42.2	1.00	0.29
Paternal variable				
Age (years)	32 ± 5.4	33 ± 4.7	1.03	< 0.001
Height (cm)	176 ± 7.0	176 ± 7.1	1.02	0.02
BMI (kg/m^2)	26 ± 3.4	26 ± 3.4	0.99	0.38
Child variable				
Sex:				0.94
Girl	381(49)	597(49)	Ref	
Boy	405(51)	633(51)	0.99	

BMI: Body mass index; SD: Standard deviation; Social class I: Managerial jobs, senior technical staff, and commercial managers, II: Skilled non-manual workers, and III: Manual and unskilled workers; OR: Odds ratio; Ref: Reference group. Veg: Vegetables.
Sample size and percentage (n[%]) are presented for categorical variables and mean ± SD for continuous variables. [a]Inclusion OR and *p-value* from logistic models adjusted by cohort; [b]Before pregnancy; [c]During pregnancy; [d]First trimester of pregnancy.

ranged between 0.47 and 0.74 ($p < 0.05$). We found weak levels of correlations between PFASs and the families of other chemicals or the estimations of air pollution, being higher between PFOS and both ΣPCBs and Hg (r: 0.28 and 0.21; $p < 0.05$). The correlation was close to null between PFASs and albumin ($p < 0.05$ only for PFOA) and weak and negative (r range: −0.16 to −0.11, $p < 0.05$) between the contaminants and eGFR (Fig. S3).

Table 2
First-trimester maternal plasma concentrations of PFASs (ng/mL; n = 1230). The INMA-Project, 2003-2008 (Spain).

PFAS	≥LOQ	Concentration		
	%	P25	P50	P75
PFHxS	96.3	0.41	0.58	0.82
PFOA	100	1.63	2.35	3.30
PFOS	100	4.52	6.05	7.82
PFNA	99.4	0.49	0.65	0.90

LOQ: Limit of quantification; P: Percentile; PFASs: Polyfluoroalkyl substances; PFHxS: Perfluorohexanesulfonic acid; PFNA: Perfluorononanoic acid; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctane sulfonate.

3.2. Prenatal PFAS exposure and fetal parameters

We found no evidence of an association between $\log_2$(PFAS) concentrations and fetal growth for the whole population (see Fig. 1 and Table S4). Heterogeneity was found in only 6 out of 48 cases (BPD-20 weeks, LF-12 weeks, AC-12 weeks, and EFW-12 weeks vs. PFHxS; BPD-12 weeks vs. PFOA; and FL-34 weeks vs. PFOS). Random effects models were applied in these cases.

We did find an indication that maternal smoking modified the effect in different directions depending on the PFAS (see Fig. 1 and Table S5). Among smokers (31%), we found inverse associations between PFOA or PFNA and LF or EFW at week 20. Specifically, at week 20 among smokers, the estimates for the associations between PFOA and FL or EFW were −6.8% [−12.4, −1.0%] and −5.7% [−11.4, 0.1%], respectively, and between PFNA and FL or EFW they were −6.3% [−11.9, −0.5%] and −6.0% [−11.6, −0.3%], respectively. This pattern was also observed at week 12, although with estimates of lower magnitude. Conversely, we found positive associations between PFHxS or PFOS and BPD at week 34 among smokers (6.8% [0.5, 12.9%] and 6.3% [0.1, 12.3%], respectively). These associations were in the same direction at week 20 and for FL and EFW at week 34 (Fig. 1 and Table S5).

Although no clear differential effect between sexes was found (*p-interaction* > 0.05 except for PFOA and BPD at week 12), a pattern suggestive of lower estimates for the association between PFOA and PFNA and the four fetal parameters was observed among boys during the first two trimesters of pregnancy (Fig. S4).

No remarkable changes in results were found when restricting analyses to individuals with available data (complete case analysis) or in the other sensitivity analyses (Figs. S5-S8).

4. Discussion

Overall, we did not find an association between these contaminants and fetal growth. Estimates in the main analysis did not differ markedly when adding eGFR, albumin, other contaminants, or excluding special cases (i.e., preterm newborns or women whose self-reported LMP was not confirmed by ultrasounds). We did not find a clear differential effect between sexes but one was found for maternal smoking.

In this study, maternal plasma PFOA concentrations were not associated with fetal growth for the whole population. Although fetal and neonatal biometric parameters are not directly comparable, these results are in line with a meta-analysis of 24 studies from different countries (Steenland et al., 2018). Following a suggestion in a previous study by Verner et al. (2015), authors of the review divided studies on birth weight and prenatal PFOA exposure according to time of sampling. They found an inverse association only when blood was sampled late in pregnancy and/or at birth (n = 7563 pregnancies; −17.8 g [−25.0, −10.6] for every ng/mL of PFOA). Restriction to studies with

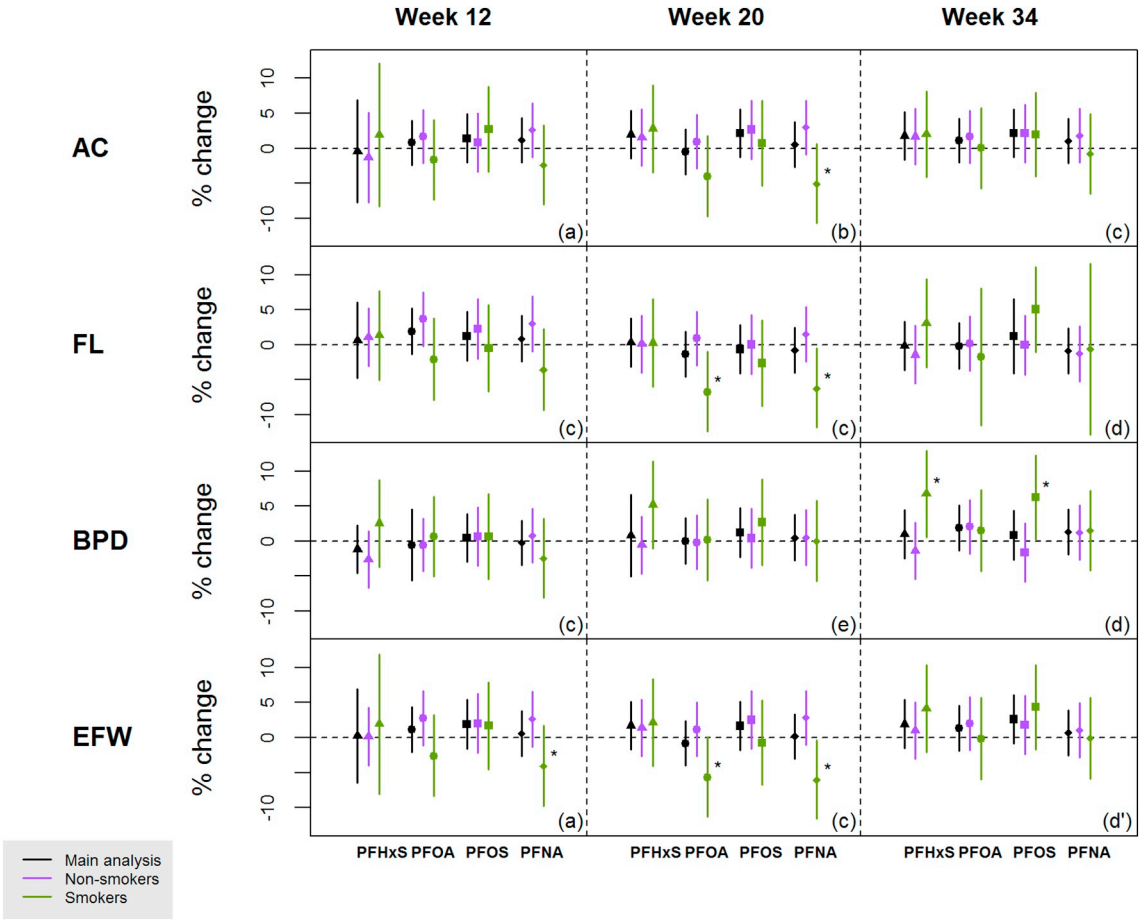

Fig. 1. Combined estimates of the association between maternal PFAS concentrations and fetal growth measurements (main analysis) and results for effect modification by maternal smoking during pregnancy. The INMA-Project, 2003–2008 (Spain).
%change and 95% confidence intervals in fetal measurements associated with a twofold increase in PFAS concentrations.
Total sample size: n = 1230; 31% smokers.
AC: Abdominal circumference; BPD: Biparietal diameter; EFW: Estimated fetal weight; FL: Femur length; PFASs: Polyfluoroalkyl substances; PFHxS: Perfluorohexanesulfonic acid; PFNA: Perfluorononanoic acid; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctanesulfonic acid. **p-interaction* < 0.05.
Covariates of adjustment in models (a): Cohort, parity, and maternal age, country of birth, studies; (b): Cohort, parity, and maternal age, country of birth, studies, and season of last menstrual period; (c): Cohort, parity, and maternal age and country of birth; (d): Cohort, parity, and maternal age, country of birth, and smoking at week 12; (d´): variables in (d) for all the contaminants except for PFNA (in the latter: variables in (d) plus maternal pre-pregnancy body mass index); (e): Cohort, parity, and maternal age, country of birth, working in pregnancy, studies, and passive smoking.

blood sampling conducted early in pregnancy or shortly before conception showed no association between the contaminant and birth weight (−3.3 g [−9.6, 3.0]; n = 5393 participants) (Steenland et al., 2018). INMA bloods samples were obtained at around 13.5 weeks of gestation which could explain the lack of association reported in the present study. In a recent review on animal data, an inverse association between PFOA and both fetal and birth weight has been reported only at very high doses, far above the levels of human exposure (Negri et al., 2017).

For the other PFASs, no overall association with fetal growth was apparent in the present study, since the direction of the associations was inconsistent throughout pregnancy and some of the associations were close to null. Regarding previous reviews on PFOS, authors reported that the evidence of the association between this contaminant and birth weight was insufficient tending to moderately likely (Negri et al., 2017). In animals, fetal and birth weights decreased following oral exposure of pregnant animals to PFOS, but at much higher doses than in humans (Negri et al., 2017). To date, prenatal PFHxS and PFNA exposure has been addressed less and no review of the evidence has yet been published. Among previous studies, the directions of the associations do not seem to be consistent, since some studies reported non-statistically significant associations (Ashley-Martin et al., 2017; Manzano-Salgado et al., 2017), and others found positive associations between birth length and PFHxS (Shi et al., 2017) or PFNA (Chen et al., 2012), and negative associations between PFHxS and birth weight (Maisonet et al., 2012), birth length (Cao et al., 2018) or waist circumference (Buck Louis et al., 2018) in neonates.

We did not observe any associations for the whole population, but a differential effect by smoking was found for some outcomes. Among smokers, the association was inverse for both PFOA and PFNA and all parameters except BDP at mid-pregnancy, and positive for PFHxS or PFOS and BPD during the third trimester of pregnancy. Smoking may be a relevant effect modifier to be considered in the association between contaminants and fetal growth since it is a well-known risk factor for fetal growth impairment during pregnancy (Palma-Gudiel et al., 2018). In previous analyses, smoking modified the association between PFOS and small for gestational age (SGA) babies with higher odds of SGA in the newborns of mothers who smoked during pregnancy and decreased odds among non-smokers (Govarts et al., 2018). In another study, prenatal exposure to PFNA may have attenuated the inverse association of smoking on birth weight-for-gestational age (Rokoff et al., 2018). Finally, greater decreases in birth weight were reported in infants from smokers compared to non-smokers associated to prenatal PFOA exposure (Lenters et al., 2016).

One biological mechanism by which both PFASs and smoking could affect fetal growth is epigenetic changes. In a previous study, both smoking during pregnancy and PFOA (but not PFOS) exposure were inversely correlated with global DNA hypomethylation in umbilical cord serum of newborns (Guerrero-Preston et al., 2010). In our study, the difference in the direction of the associations between PFASs and outcomes among smokers (inverse for PFOA and PFNA and positive for PFHxS and PFOS) is intriguing. Since multiple estimates were derived and we only found some evidence of an association between fetal growth and PFASs among smokers, with the associations running in different directions depending on the contaminant, results should be taken with caution because these statistically significant associations could result from chance. The estimates of the coefficients and their CIs should be taken as a global picture of the pattern of the relations between the variables involved in the study (Rothman, 1990) and our results remain to be investigated in further studies.

Sex-specific differences in the development of reproductive organs and physiology may result in sex-specific responses to a given toxicant (Bach et al., 2015). Overall, we did not find a clear differential effect between sexes, with only one interaction being significant (PFOA and BPD during the first trimester of pregnancy). However, we found some suggestions of boys being more sensitive to PFOA and PFNA than girls, but the estimates were not significant in all cases. In the previous INMA study on anthropometry at birth, PFOS concentrations were associated with boys having higher odds of being born with low birth weight compared to girls (Manzano-Salgado et al., 2017). Previous literature is not consistent, since both girls (Cao et al., 2018; Kishi et al., 2015; Washino et al., 2009) and boys (Shi et al., 2017) have been reported to be more vulnerable to chemical exposure, and other studies did not find any sex-specific differences (Bach et al., 2016; Fei et al., 2007).

As reported in a pharmacokinetic model assessing the role of GFR in the epidemiological association between simulated maternal (at 0, 3, 6 months of pregnancy, and at birth) and cord PFAS levels and fetal growth, confounding has arisen as a possible concern, since GFR is an indicator of the rate at which the mother can clear chemicals from the body (Verner et al., 2015). In a Norwegian study, the coefficient of the association between PFOA and birth weight did attenuate 66% after GFR inclusion (creatinine measured during the second trimester of pregnancy) (Morken et al., 2014). However, in the INMA-Project, adjustment for first-trimester maternal eGFR did not influence the association between maternal PFASs measured at around 13.5 weeks of gestation and fetal biometry (present study) or neonatal anthropometry (Manzano-Salgado et al., 2017). Differences in the time of measurements of GFR (which has been reported to increase from 40% to 50% during pregnancy (Cheung and Lafayette, 2013)), as well as the way it was measured (in our case we calculated eGFR by using the Cockroft-Gault formula instead of measuring clearance of insulin directly) could account for discrepancies among studies. In addition, reverse causality with GFR was discarded as a possible cause of bias with insufficient evidence to explain the inverse associations between contaminants and fetal growth (Vesterinen et al., 2015).

Albumin, a marker of plasma volume expansion, has been strongly correlated with serum PFASs (Sagiv et al., 2015). In our study, the correlation was close to null. When we incorporated this variable in the models our results did not change, in line with some previous studies (Whitworth et al., 2012). As for GFR, measurements of plasma albumin were performed in early pregnancy, when the changes in this variable during gestation may not yet be marked (Steenland et al., 2018).

Some limitations of our study should be considered. Firstly, the included vs. excluded population (because of missing information on PFASs or the study outcomes) was more likely to contain women born in Spain, non-smokers, working at beginning of pregnancy, older, and with higher education and social class. Differences were also found in the outcome EFW at week 12. Therefore, we cannot rule out the possibility of our population not being representative of some population subgroups. Nevertheless, the difference between included and excluded in terms of smoking was small, since there were only 3% more non-smokers in the included group. Both PFASs and the first measure of the outcome were simultaneous in time. Finally, since multiple estimates were derived and we found opposite directions of associations among smokers depending on the contaminant, the statistically significant results may point to a chance finding.

The main strengths of our study are its large sample size; prospective design; the use of repeated measurements of several parameters of fetal biometry, allowing the identification of fetal periods when effects could occur as well as possible fetal body segments affected; the careful assessment of fetal growth, considering the individual growth potential of each fetus; and the availability and quality of the information at the individual level, collected using standardized protocols. In addition, participants might have been simultaneously exposed to a huge variety of contaminants that may have synergetic or accumulative effects. This cohort has information on prenatal exposure to NO_2, Hg, PBDEs, HCB, or PCBs, which have previously been related with fetal growth impairment in the same cohort (Ballester et al., 2018; Iniguez et al., 2016; Lopez-Espinosa et al., 2015; Lopez-Espinosa et al., 2016), thereby allowing us to test whether exposure to these contaminants may have affected our results. Nevertheless, we found a low correlation between maternal concentrations of PFASs and the other chemicals (range: −0.01 to 0.12). Finally, preterm babies were also excluded and no differences in results were found.

5. Conclusions

In this study population, overall we found no evidence of an association between first-trimester maternal concentrations of PFASs and fetal growth. We found an effect modification by maternal smoking during pregnancy, with different directions of the associations depending on the contaminant. Caution should be taken when interpreting the results among smokers, and further studies using ultrasound measurements need to be conducted to obtain a clearer understanding of the possible role that smoking may play in this association.

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Research ethics and informed consent

This study has been reviewed and approved by the accredited committees of the following institutions: The Municipal Institute of Sanitary Assistance of Barcelona, La Fe University Hospital of Valencia, and The Donostia Hospital of the Basque Country. All mothers gave their written informed consent prior to inclusion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.024.

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