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REVIEW ARTICLE

Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: A systematic review

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Abstract

Background: Exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) is ubiquitous in most regions of the world. The most commonly studied PFASs are perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Animal studies indicate that maternal PFAS exposure is associated with reduced fetal growth. However, the results of human studies are inconsistent. *Objectives:* To summarize the evidence of an association between exposure to PFASs, particularly PFOS and PFOA, and human fetal growth. *Methods*: Systematic literature searches were performed in MEDLINE and EMBASE. We included original studies on pregnant women with measurements of PFOA or PFOS in maternal blood during pregnancy or the umbilical cord and associations with birth weight or related outcomes according to the PFAS level. Citations and references from the included articles were investigated to locate more relevant articles. Study characteristics and results were extracted to structured tables. The completeness of reporting as well as the risk of bias and confounding were assessed. *Results*: Fourteen studies were eligible. In utero PFOA exposure was associated with decreased measures of continuous birth weight in all studies, even though the magnitude of the association differed and many results were statistically insignificant. PFOS exposure and birth weight were associated in some studies, while others found no association. *Conclusions:* Higher PFOS and PFOA concentrations were associated with decreased average birth weight in most studies, but only some results were statistically significant. The impact on public health is unclear, but the global exposure to PFASs warrants further investigation.

Keywords

birth weight, small for gestational age, epidemiology, humans, perfluorooctane sulfonate, perfluorooctanoate, perfluoroalkyl acids, perfluorinated chemicals

History

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Table of Contents

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Introduction

Several studies have investigated the association between exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) and human fetal growth, but the results have been inconsistent. Johnson et al. (2014) recently reviewed the association between perfluorooctanoate (PFOA) and fetal growth. The most recent review concerning both PFOA and perfluorooctane sulfonate (PFOS) was done by Olsen et al. in 2009. Nine epidemiological studies have been conducted since this publication, and as exposure is still widespread, an updated systematic review is warranted to summarize the evidence.

PFASs are a subgroup of the persistent organic pollutants (POPs). Their production started in the 1950s and is still

continuing, though some compounds have been phased out (Environment Canada 2010, European Parliament 2006, UNEP 2009, USEPA 2000, 2006). Due to their water and oil repelling properties, PFASs are found in products such as carpets, furniture, shampoo, shoes, clothes, non-stick cookware, and food packaging (Butenhoff et al. 2006, Kantiani et al. 2010). The most widely studied PFASs, PFOS and PFOA, have serum half-lives of approximately 5 and 3.5 years in humans, respectively (Olsen et al. 2007), and accumulate in various environmental media and organisms, including humans (Buck et al. 2011). Humans absorb PFASs after oral intake, inhalation, and dermal exposure (Shoeib et al. 2011). PFASs are mainly distributed in plasma, bound to albumin with varying association constants, and in tissues with high perfusion such as the liver and kidney (Han et al. 2012). In pregnant women, PFASs pass the placenta and reach the fetal circulation (Fei et al. 2007, Inoue et al. 2004, Kim et al. 2011, Midasch et al. 2007). The data obtained from populations sampled during different time periods in the National Health and Nutrition Examination Survey (NHANES), designed to be representative of US general population exposures, indicate that even though serum concentrations of PFOS and PFOA showed a downward trend from 1999 to 2003, PFOA concentrations did not decrease further during 2003–2008 (Calafat et al. 2007, Kato et al. 2011). In 2003–2008, the NHANES median serum concentrations were approximately 12 ng/mL for PFOS and 3 ng/mL for PFOA, respectively, in nonpregnant women aged 17–39 years old (Jain 2013).

Developmental effects of PFASs have been investigated in animal studies. Several rodent (mainly rat and mouse) studies observed reduced birth weight in offspring exposed to PFOS or PFOA in utero (Butenhoff et al. 2004, Grasty et al. 2003, Luebker et al. 2005, Thibodeaux et al. 2003, Wolf et al. 2007). In some studies, decreases in birth weight were at least partly attributable to toxic maternal doses causing reductions in food consumption and pregnancy weight gain (Lau et al. 2003). Exposure levels used in experimental studies were more than 1000 times higher than general human background exposure levels illustrated by NHANES data (Olsen et al. 2009), and furthermore, differences in half-lives and metabolism of PFASs across species complicate the interpretation of animal studies in relation to human health. In addition, differences in gestational duration, placental transfer etc. complicate extrapolation from animal studies to human risk assessment. However, the results from animal studies and the fact that exposure is ubiquitous in humans indicate a potential human health risk.

Currently, the exact impact of PFASs on human health is unclear, but adverse effects are a potential concern, particularly in the fetus who is exposed during a period of high vulnerability to toxicological impacts. Thus, the objective of this paper was to investigate the evidence of an association between exposure to PFASs and human fetal growth by systematic review of the existing literature. We focused on PFOS and PFOA as the majority of the published literature did so, and we assessed birth weight and related measures of the newborns' size at birth as proxies of fetal growth.

Different pathways for the biological effects of PFASs have been suggested, for example hormone disruption. Estrogen has been demonstrated to be important in promoting fetal growth (Kaijser et al. 2000). PFASs influence the expression of estrogen-responsive genes in animal studies (Benninghoff et al. 2011, Tilton et al. 2008, Wei et al. 2007), and PFAS-induced changes in sex hormone biosynthesis have been reported *in vitro* (Du et al. 2013, Kraugerud et al. 2011). PFASs, including PFOS and PFOA, have been shown to interfere with the estrogen receptor in human *in vitro* studies (Benninghoff et al. 2011, Henry and Fair 2011, Kjeldsen and Bonefeld-Jørgensen 2013). Thyroid hormones are pivotal for normal fetal growth and development, and maternal hypothyroidism is related to low birth weight (Blazer et al. 2003). Animal studies demonstrated alterations in thyroid hormone signaling with PFAS exposure (Du et al. 2013, Lau et al. 2003, Luebker et al. 2005, Martin et al. 2007, Thibodeaux et al. 2003, Yu et al. 2009a, b). Long et al. (2013) showed that PFASs interfered with thyroid hormone function. However, human studies concerning PFAS exposure and adult or fetal thyroid hormone function are not consistent (Emmett et al. 2006, Inoue et al. 2004, Kim et al. 2011, Olsen et al. 2003, Olsen and Zobel 2007, Wang et al. 2013). Some animal studies have demonstrated changes in lipid metabolism with exposure to PFOS and PFOA (Haughom and Spydevold 1992, Kennedy et al. 2004, Loveless et al. 2006, Thibodeaux et al. 2003). However, Apelberg et al. (2007) found no association between PFOS and PFOA concentrations in cord serum and total serum cholesterol, triglycerides or total lipids. Finally, immunotoxicity and susceptibility to infections in pregnant women may be a potential mechanism of fetal growth impairment. Adverse effects on the immune system have been demonstrated *in vitro*, in animals, and in children (DeWitt et al. 2012, Grandjean et al. 2012), but to our knowledge, such effects in pregnant women have not been evaluated. Overall, several pathways by which PFASs may impair fetal growth are plausible, but the mechanisms have not been established in humans.

Methods

Reporting was done in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Moher et al. 2009).

Search strategy

The electronic databases MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.embase.com) were systematically searched. The strategy was decided after identification of MeSH/Emtree terms and key words not covered by these terms. Searches included different terms for PFASs and fetal growth and development. No language, time period restrictions, or filters were applied. Abstracts and unpublished studies were not included. The latest searches were performed on June 12 2014. Titles and/or abstracts were screened using the selection criteria stated below, and articles were excluded if sufficient information was available in the titles or abstracts to determine that the studies were not eligible. The full text of the remaining studies was read, and the studies were included if found eligible. The electronic database Scopus (http://www.scopus.com) was searched for citations and references for all included articles on June 14 2014. Complete search strategies for MEDLINE and EMBASE are available in the Supplementary Material (see Supplementary material available online at

http://informahealthcare.com/doi/abs/10.3109/10408444.2014.952400, page 1).

Study selection criteria

The selection criteria were based on the PICOS (participants, interventions/exposures, comparators, outcomes, and study design) criteria (Liberati et al. 2009). *Participants:* Pregnant women were eligible. *Exposures:* Populations with all exposure levels were included (i.e. both populations with background exposure levels and highly exposed populations). Exposure was assessed as PFOS or PFOA measured in biological material such as blood, from either pregnant women or the umbilical cord. Studies estimating exposure indirectly (e.g. based on residence near a polluted water source) were excluded.

Comparators: Groups categorized according to individual PFAS levels or comparison of continuous PFAS levels. *Outcomes:* Birth weight on the continuous scale was the primary outcome. Other outcomes derived from birth weight, such as the birth weight z-score (birth weights standardized for gender and gestational age), low birth weight (LBW; birth weight below 2500 g), and small for gestational age (SGA; birth weight below the 10th percentile for gestational age), were also included. *Study design:* Original human cohort, cross sectional, and case-control studies were eligible. Editorials, comments, review articles, and meta-analyses were excluded.

Data extraction, completeness of reporting, and risk of bias and confounding

Data from included studies were extracted and added to structured forms with columns titled as follows: Author and year, design, population, exposure assessment (specific PFASs, sample, method), exposure levels, outcomes, specific problems (including confounders, and ways of addressing them), and results. The study characteristics and results are displayed in Tables 1–4. Each article was assessed for completeness of reporting, as suggested by Bonzini et al. (2007). This approach determines whether studies are described sufficiently in order for replication to be possible. The study design, sampling procedure, inclusion and exclusion criteria, distribution of participant characteristics, numbers of participants and response rates, assessment of exposure, ascertainment of outcomes, statistical analysis and quantitative risk estimates with 95% confidence intervals were evaluated. Each of the 9 criteria were assigned a value of 1 if fulfilled and given equal weight. A sum of ≥ 7 was considered sufficient for completeness of reporting (Bonzini et al. 2007). The risks of selection and information biases as well as confounding were assessed. Potential confounders, primarily covariates from multiple regression analyses of PFOA and PFOS exposure and birth weight variables, were extracted and evaluated (Table 5).

Results

Study selection

After removal of duplicates from the two database searches, 138 studies remained (Supplementary Material, Supplementary Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.952400). These were screened from their title (91 were excluded), abstract (30 were excluded) and full text content (3 were excluded). The reasons for exclusion at each stage are stated in Supplementary Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.952400. The remaining 14 studies fulfilled the eligibility criteria. We investigated citations and references in Scopus, which yielded no additional articles. A total of 14 peer-reviewed articles published between 2004, August and 2013, December were included in our review.

Characteristics of included studies

Ten studies investigated continuous birth weight. Other birth weight - related outcomes were low birth weight (five studies), birth weight z-score (two studies), small for gestational age (four studies), and birth weight dichotomized at the median level (one study) (Table 1). Stein et al. (2009) used maternal reports of outcomes, while all other studies assessed outcomes gathered from medical records, birth records, or national registries. Ten studies assessed PFASs in blood from women during pregnancy or at birth (Darrow et al. 2013, Fei et al. 2007, Hamm et al. 2010, Lee et al. 2013, Maisonet et al. 2012, Monroy et al. 2008, Stein et al. 2009, Washino et al. 2009, Whitworth et al. 2012, Wu et al. 2012), and six studies used umbilical cord blood samples (Apelberg et al. 2007, Arbuckle et al. 2013, Chen et al. 2012, Inoue et al. 2004, Lee et al. 2013, Monroy et al. 2008). No eligible studies measured PFASs in other biological material such as placental tissue. The specific time points for exposure assessment are listed in Tables 2 and 3. All studies used similar laboratory techniques to measure PFAS exposure. PFOA was included in all studies except for the one by Inoue et al. (2004), and PFOS was assessed in all studies except for the one by Wu et al. (2012). Four studies included exposure in regression models as the natural logarithm of the concentration of the exposure (Apelberg et al. 2007, Chen et al. 2012, Darrow et al. 2013, Hamm et al. 2010), and three used $\log_{10}$-transformations (Arbuckle et al. 2013, Washino et al. 2009, Wu et al. 2012). Fei et al. (2007), Inoue et al. (2004), and Monroy et al. (2008) modeled untransformed continuous exposure levels, and the studies by Lee et al. (2013), Stein et al. (2009), Maisonet et al. (2012), and Whitworth et al. (2012) used categories of exposure (dichotomized at median level, tertiles, and quartiles, respectively). Fei et al. (2007) also used categories in their analyses of LBW and SGA. In most studies, PFAS levels were the independent variables and measures of birth weight were considered the dependent variables. However, in the studies by Arbuckle et al. (2013), Lee et al. (2013), and Monroy et al. (2008), measures of birth weight were the independent variables and PFAS levels were analyzed as the dependent variables.

The studies by Fei et al. (2007) and Whitworth et al. (2012) were national population-based studies. The other studies were cohort or cross-sectional studies based on populations from restricted geographical areas or hospitals. No eligible case-control studies were published. The studies by Darrow et al. (2013), Stein et al. (2009), and Wu et al. (2012) were conducted in areas with high PFOA exposure. The populations studied originated from nine different countries (Taiwan, Japan, China, South Korea, Canada, Norway, Denmark, USA, and Great Britain) with study periods from 1991 to 2011. The sample sizes ranged from 15 to 5262.

Table 1. Characteristics of studies on perfluorooctanoate, perfluorooctane sulfonate, and measures of fetal growth.

Study	Location/setting	Design	N	Study period	PFASs	Outcomes	Ascertainment of outcomes
Inoue et al. (2004)	Japan (Hokkaido, hospital-based)	Cross sectional	15	2003	PFOS	BW	Not stated
Apelberg et al. (2007)	USA (Maryland, hospital-based)	Cross sectional	293	2004–2005	PFOA, PFOS	BW	Medical records
Fei et al. (2007)	Denmark (nationwide)	Birth cohort (Danish National Birth Cohort)	1400	1996–2002	PFOA, PFOS	BW, LBW, SGA	Registry
Monroy et al. (2008)	Canada (Ontario)	Cohort of pregnant women from standard prenatal care	89	2004–2005	PFOA, PFOS, PFHxS, PFNA	BW	Birth records
Stein et al. (2009)	USA (Ohio & West Virginia communities surrounding chemical plant)	Cross sectional (C8 Health Project)	1845 (PFOA) 5262 (PFOS)	2000–2006	PFOA, PFOS	LBW	Self-report
Washino et al. (2009)	Japan (hospital-based)	Cohort (Hokkaido Study on Environment and Children's Health)	428	2002–2005	PFOA, PFOS	BW	Medical records
Hamm et al. (2010)	Canada (Alberta, hospital-based)	Cohort of pregnant women undergoing second trimester screening	252	2005–2006	PFOA, PFOS, PFHxS	BW, BW z-score, SGA	Delivery records
Chen et al. (2012)	Taiwan (Taipei and New Taipei)	Birth cohort (Taiwan Birth Panel Study),	429	2004–2005	PFOA, PFOS, PFNA, PFUA	BW, LBW, SGA	Medical records
Maisonet et al. (2012)	Great Britain (three health districts of Avon county)	Cohort (Avon Longitudinal Study of Parents and Children)	447	1991–1992	PFOA, PFOS, PFHxS	BW	Medical records
Whitworth et al. (2012)	Norway (nationwide)	Birth cohort (Norwegian Mother and Child Cohort Study)	901	2003–2004	PFOA, PFOS	BW z-score, SGA	Birth registry
Wu et al. (2012)	China (Guiyu (e-waste recycling area) & Chaonan)	Cross sectional	167	2007	PFOA	BW	Birth records
Arbuckle et al. (2013)	Canada (Ottawa, hospital-based)	Cross sectional	100	2005–2008	PFOA, PFOS, PFHxS, PFNA	LBW	Medical records
Darrow et al. (2013)	USA (Ohio & West Virginia communities surrounding chemical plant)	Cohort (C8 Health Project)	1630 children 1330 women	2005–2010	PFOA, PFOS	BW, LBW	Birth records
Lee et al. (2013)	South Korea (Gyeongbok county)	Cross sectional	59	2011	PFOA, PFOS, PFHxS	BW dichotomized at median level	Medical records

PFOS perfluorooctane sulfonate, *PFOA* perfluorooctanoate, *PFNA* perfluorononanoic acid , *PFUA* perfluoroundecanoic acid, *PFHxS* perfluorohexane sulfonate, *BW* birth weight, *LBW* low birth weight, *SGA* small for gestational age.

The study by Maisonet et al. (2012) was restricted to girls, and all other studies included both sexes. All included studies except the one by Inoue et al. (2004) achieved completeness of reporting scores ≥ 7 (see Supplemental Material, Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.952400). Graphs illustrating regression coefficients of continuous birth weight by the range of PFOA and PFOS levels in individual studies are provided (Figures 1 and 2).

PFOA and PFOS concentrations and birth weight

The eight studies that investigated the association between PFOA exposure and birth weight on a continuous scale (Apelberg et al. 2007, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Hamm et al. 2010, Maisonet et al. 2012, Washino et al. 2009, Wu et al. 2012) all demonstrated lower birth weight with increasing exposure levels; however, only the studies by Fei et al. (2007), Wu et al. (2012) and Maisonet et al. (2012) were statistically significant (Table 2). Not all these studies had high average exposure levels compared to the other included studies (Table 2). Monroy et al. (2008) and Lee et al. (2013) investigated birth weight as a predictor of PFAS levels. Monroy et al. (2008) found no association between birth weight and PFOA, and Lee et al. (2013) found higher PFOA with lower birth weight (both dichotomized at the median level, not statistically significant).

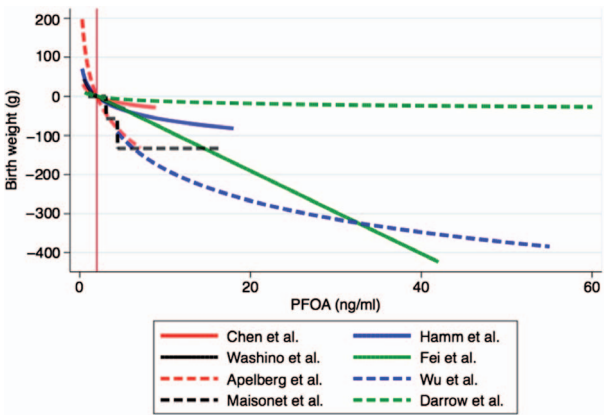

Figure 1. Illustration of the association between perfluorooctanoate and birth weight. Regression coefficients for changes in continuous birth weight by the range of perfluorooctanoate (PFOA) levels in individual studies. Plots are centered on the same average PFOA level (2 ng/ml). We were not able to include Lee et al. (2013) and Monroy et al. (2008) since they reversed exposure and outcome in their analyses.

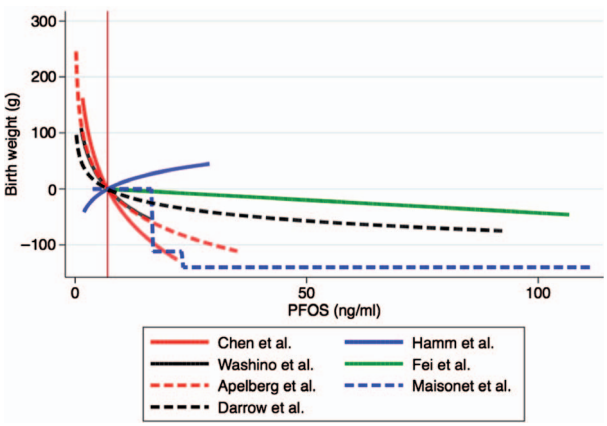

Figure 2. Illustration of the association between perfluorooctane sulfonate and birth weight. Regression coefficients for changes in continuous birth weight by the range of perfluorooctane sulfonate (PFOS) levels in individual studies. Plots are centered on the same average PFOS level (7 ng/ml). The upper range was 459.5 ng/ml in the study by Darrow et al. (2013), but to enhance visualization at lower exposure levels, this was cut off at 60 ng/ml similar to the other included studies. We were not able to include Lee et al. (2013) and Monroy et al. (2008) since they reversed exposure and outcome in their analyses. Inoue et al. (2004) did not provide an estimate and that study could therefore not be graphically displayed either.

The association between PFOS exposure and continuous birth weight was investigated in eight studies (Apelberg et al. 2007, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Hamm et al. 2010, Inoue et al. 2004, Maisonet et al. 2012, Washino et al. 2009). Six studies found lower birth weight with increasing PFOS exposure (Apelberg et al. 2007, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Maisonet et al. 2012, Washino et al. 2009, see Table 3). However, the associations were only statistically significant in the studies by Washino et al. (2009), Chen et al. (2012), and Maisonet et al. (2012). These three studies did not all have high average exposure levels compared to the other included studies. Inoue et al. (2004) reported no association, and provided no estimates. Monroy et al. (2008) and Lee et al. (2013) found no clear association between birth weight and PFOS.

PFOA and PFOS concentrations and low birth weight

Four studies found increased odds for LBW with PFOS exposure (Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Stein et al. 2009). However, only the result by Stein et al. (2009) was statistically significant (Table 4). Arbuckle et al. (2013) performed multiple stepwise regression analyses of PFOS and its potential predictors such as LBW, but LBW was omitted from the analyses due to the value of $p > 0.1$. No studies found statistically significant associations for PFOA and LBW (Arbuckle et al. 2013, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Stein et al. 2009), and only the point estimates in the studies by Fei et al. (2007) and Arbuckle et al. (2013) were above unity.

PFOA and PFOS concentrations and small for gestational age

SGA was defined as a birth weight below the 10th percentile for gestational age (Chen et al. 2012). In the studies by Whitworth et al. (2012), Hamm et al. (2010), and Fei et al. (2007), this was gender-specific, and in the latter, parity-specific as well. Fei et al. (2007) used all singleton live births of the same sex who fulfilled the sampling criteria in the Danish National Birth Cohort as reference, and Chen et al. (2012) used national Taiwanese data. Hamm et al. (2010) and Whitworth et al. (2012) did not report their reference population. Chen et al. (2012) found increased odds for SGA with higher PFOS exposure, but Fei et al. (2007) and Whitworth et al. (2012) found results close to unity, and Hamm et al. (2010) found decreased odds for SGA with higher PFOS (Table 4). The results concerning PFOA exposure and SGA were close to unity and statistically insignificant (Chen et al. 2012, Fei et al. 2007, Hamm et al. 2010, Whitworth et al. 2012).

Table 2. Results from included studies of perfluorooctanoate and birth weight on a continuous scale.

Study	Sample (gestational week of blood sample)	Exposure scale	Mean PFOA (ng/mL)	Median PFOA (ng/mL)	Geometric mean PFOA (ng/mL)	PFOA range (ng/mL)	Adjusted beta (95% CI)
Apelberg et al. (2007)	Cord serum	ln		1.6		0.3–7.1	− 104 (− 213, 5)
Fei et al. (2007)	Plasma taken during pregnancy (median 8, range 4–14)	ng/mL	5.6			< LLOQ-41.5 (LLOQ = 1.0)	− 10.6 (− 20.8, − 0.5)*
Monroy et al. (2008)	Maternal serum at delivery	ng/mL	2.2	1.8		1.3–2.6	0.0002 ($p = 0.7$)
Washino et al. (2009)	Serum taken in third trimester (72%) or after delivery (28%)	$\log_{10}$	1.4		1.2	< LOD-5.3 (LOD = 0.5)	− 75.1 (− 191.8,41.6)
Hamm et al. (2010)	Serum taken during pregnancy (15–16)	ln	2.1	1.5	1.3	< LOD-18 (LOD = 0.25)	− 37.4 (− 86.0, 11.2)
Chen et al. (2012)	Cord plasma	ln			1.8		− 19.2 (− 63.5, 25.1)
Maisonet et al. (2012)	Serum taken during pregnancy (median 15, IQR: 10–28)	Tertiles (1 = reference)		3.7		1.0–16.4	2 vs. 1: − 56.8 (− 153.1, 39.4) 3 vs. 1: − 133.0 (− 237, − 30)*
Wu et al. (2012)	Maternal serum taken at delivery	$\log_{10}$	18.3 (Guiyu) 9.8 (Chaonan)	17.0 (Guiyu) 8.7 (Chaonan)		5.5–58.5 (Guiyu) 4.4–30.0 (Chaonan)	− 267.3 (− 573.3, − 37.2)*
Darrow et al. (2013)	Maternal serum 3 3/4 years before to 1 1/2 years after birth	ln	31.0		16.2	0.6–459.5	− 8 (− 28, 12)
Lee et al. (2013)	Maternal serum at delivery	Dichotomized at median (< median = reference)	2.7			1.2–5.7	0.5 (0.2–3.0)

95% CI 95% confidence interval, *IQR* interquartile range, *ln* natural logarithm, *log 10* common logarithm, *LOD* limit of detection, *LLOQ* lower limit of quantification, *PFOA* perfluorooctanoate.
Adjusted betas represent changes in birth weight in g/unit exposure increase. Results are reported with one decimal except for Darrow et al. (2013) and Apelberg et al. (2007), who provided results without decimals. Lee et al. (2013) and Monroy et al. (2008) reversed exposure and outcome in their analyses. In the study by Lee et al. (2013) birth weight was dichotomized at the median level, and the group below the median was used as reference. Lee et al. (2013) and Monroy et al. (2008) also had cord blood samples, but we only reported maternal results since they were similar. Monroy et al. (2008) stated no confidence intervals.
*Statistical significance ($p < 0.05$).

Table 3. Results from included studies of perfluorooctane sulfonate and birth weight on a continuous scale.

Study	Sample (gestational week of blood sample)	Exposure scale	Mean PFOS (ng/mL)	Median PFOS (ng/mL	Geometric mean PFOS (ng/mL)	PFOS range (ng/mL)	Adjusted beta (95% CI)
Inoue et al. (2004)	Cord serum	ng/mL					Estimates not shown
Apelberg et al. (2007)	Cord serum	ln		5		< LOD- 34.8 (LOD = 0.2)	− 69 (− 149, 10)
Fei et al. (2007)	Maternal plasma (median 8, range 4–14)	ng/mL	35.3			6.4–106.7	− 0.5 (− 2.3, 1.4)
Monroy et al. (2008)	Maternal serum at delivery	ng/mL	16.2	14.5		9.2–20.2	0.0009 ($p = 0.7$)
Washino et al. (2009)	Maternal serum third trimester (72%) or after delivery (28%)	$\log_{10}$	5.6		4.9	1.3–16.2	− 148.8 (− 297.0, − 0.5)*
Hamm et al. (2010)	Maternal serum (15–16)	ln	9.0	7.8	7.4	< LOD-35 (LOD = 0.25)	31.3 (− 43.3, 105.9)
Chen et al. (2012)	Cord plasma	In			5.9		− 110.2 (− 176.0, − 44.5)*
Maisonet et al. (2012)	Maternal serum during pregnancy (median 15, IQR: 10–28)	Tertiles (1 = low (reference)		19.6		3.8–112.0	2 vs. 1: − 111.7 (− 208.2, − 15.2)* 3 vs. 1: − 140.0 (− 238, − 42)*
Darrow et al. (2013)	Maternal serum 3 3/4 years before to 1 1/2 years after birth	In	15.6		13.2	< LOD- 92.9 (LOD = 0.25)	− 29 (− 66, 7)
Lee et al. (2013)	Maternal serum at delivery	Dichotomized at median (< median = reference)	10.8			2.4–35.2	1.0 (0.3–3.0)

95% CI 95% confidence interval, *ln* natural logarithm, *log 10* common logarithm, *PFOS* perfluorooctane sulfonate, *LOD* limit of detection, *IQR* interquartile range.
Adjusted betas represent changes in birth weight in g/unit exposure increase. Results are reported with one decimal except for Darrow et al. (2013) and Apelberg et al. (2007) who provided results without decimals. Lee et al. (2013) and Monroy et al. (2008) reversed exposure and outcome in their analyses. In the study by Lee et al. (2013) birth weight was dichotomized at the median level, and the group below the median was used as reference. Lee et al. (2013) and Monroy et al. (2008) also had cord blood samples, but we only reported maternal results since they were similar. Monroy et al. (2008) stated no confidence intervals.
*Statistical significance ($p < 0.05$).

PFOA and PFOS concentrations and birth weight z-scores

Hamm et al. (2010) and Whitworth et al. (2012) found no statistically significant associations between exposure to PFOS or PFOA and birth weight z-scores (Table 4).

Discussion

We summarized the evidence addressing exposure to PFASs and measures of fetal growth. Higher PFOA levels were associated with lower average birth weight in eight studies of a total of 5046 pregnancies, even though the magnitude and significance of associations differed. Data are insufficient to determine a safe lower PFOA exposure level, but statistically significant associations were only demonstrated when median serum or plasma levels during pregnancy were above approximately 3 ng/mL (Fei et al. 2007, Maisonet et al. 2012, Wu et al. 2012). However, one study with median levels above this level found no significant association (Darrow et al. 2013). The value of 3 ng/mL is similar to the present day average PFOA exposure in US women in the fertile age (Jain 2013).

Table 4. Results concerning perfluorooctane sulfonate or perfluorooctanoate and low birth weight, small for gestational age, and birth weight z-score.

	Exposure variable	Number of cases (%)	OR (95% CI)
Low birth weight			
Fei et al. (2007)	PFOS quartiles (1 = reference)	24 (1.7)	2 vs. 1: 3.4 (0.4, 31.2) 3 vs. 1: 6.0 (0.7, 49.3) 4 vs. 1: 4.8 (0.56, 41.16)
	PFOA quartiles (1 = reference)	24 (1.7)	2 vs. 1: 4.3 (0.5, 36.5) 3 vs. 1: 3.7 (0.4, 32.5) 4 vs. 1: 2.4 (0.3, 22.3)
Stein et al. (2009)	PFOS above vs. below median	243 (5.3)	1.5 (1.1, 1.9)*
	PFOA above vs. below median	80 (5.0)	0.7 (0.5, 1.2)
Chen et al. (2012)	lnPFOS	26 (6.1)	2.6 (0.9, 8.0)
	lnPFOA	26 (6.1)	0.5 (0.2, 1.6)
Arbuckle et al. (2013)	logPFOS	3 (3)	No estimate
	logPFOA	3 (3)	0.6 (p = 0.09)
Darrow et al. (2013)	lnPFOS	88 (5.5)	1.1 (0.8, 1.7)
	lnPFOA	88 (5.5)	0.9 (0.8, 1.2)
Small for gestational age			
Fei et al. (2007)	PFOS quartiles (1 = reference)	121 (8.6)	2 vs. 1: 0.7 (0.4, 1.3) 3 vs. 1: 0.7 (0.4, 1.2) 4 vs. 1: 1.0 (0.6, 1.7)
	PFOA quartiles (1 = reference)	121 (8.6)	2 vs. 1:1.2 (0.7, 2.0) 3 vs. 1: 1.1 (0.6, 1.8) 4 vs. 1: 1.0 (0.6, 1.7)
Hamm et al. (2010)	PFOS tertiles (1 = reference)	16 (6.3)	2 vs. 1: 0.6 (0.2, 1.8) 3 vs. 1: 1.0 (0.3, 3.9)
	PFOA tertiles (1 = reference)	16 (6.3)	2 vs. 1: 1.0 (0.3, 3.6) 3 vs. 1: 0.3 (0.1,0.7)
Chen et al. (2012)	lnPFOS	26 (6.1)	2.3 (1.3, 4.2)*
	lnPFOA	26 (6.1)	1.2 (0.8, 2.1)
Whitworth et al. (2012)	PFOS quartiles (1 = reference)	60 (6.7)	2 vs. 1: 1.2 (0.5, 3.0) 3 vs. 1: 2.2 (1.0, 5.1) 4 vs. 1: 1.3 (0.5, 3.4)
	PFOA quartiles (1 = reference)	60 (6.7)	2 vs. 1: 0.8 (0.3, 2.3) 3 vs. 1: 1.3 (0.5, 3.2) 4 vs. 1: 1.0 (0.3, 2.8)

Birth weight z-score	Exposure variable	Regression coefficient (95% CI)
Hamm et al. (2010)	lnPFOS	0.1 (− 0.1, 0.2)
	lnPFOA	− 0.08 (− 0.2, 0.03)
Whitworth et al. (2012)	PFOS quartiles (1 = reference)	2 vs. 1: − 0.1 (− 0.3, 0.1), 3 vs. 1: − 0.2 (− 0.4, 0.1) 4 vs. 1: − 0.2 (− 0.4, 0.1)
	PFOA quartiles (1 = reference)	2 vs. 1: − 0.1 (− 0.3, 0.2), 3 vs. 1: − 0.3 (− 0.3, 0.2) 4 vs. 1: − 0.2 (− 0.5, 0.0)

95% CI 95% confidence interval, *ln* natural logarithm, log_{10} common logarithm, *PFOS* perfluorooctane sulfonate, *PFOA* perfluorooctanoate.

Arbuckle et al. (2013) reversed exposure and outcome in their analyses. The stated estimate (β) therefore indicates that low birth weight is associated with higher PFOA. They stated no CI. Birth weight was omitted from the PFOS model due to a *p*-value above 0.1. In that study, the cord serum median PFOS (range) was 5.0 ng/mL (< LOD-21.7), and the geometric mean was 4.4 ng/mL. For PFOA, median PFOA (range) was 1.6 ng/mL (0.3–5.2) and the geometric mean was 1.5 ng/mL. In the study by Whitworth et al. (2012), the median PFAS levels (interquartile range) were 13.0 ng/mL (10.3–16.6) for PFOS and 2.2 ng/mL (1.6–3.0) for PFOA. In the study by Stein et al. (2009), the median PFAS levels (interquartile range) were 13.6 ng/mL (9.4–18.7) for PFOS and 21.2 ng/mL (10.3–49.8) for PFOA. Average PFAS levels in the other studies are listed in Tables 2 and 3.

*Statistical significance ($p < 0.05$).

Six out of eight studies equivalent to 4627 out of 4894 pregnancies found lower average birth weight with higher levels of PFOS, but most of the results were not statistically significant, and in studies with high average exposure levels, there was not a higher proportion of significant associations. Studies that examined birth weight as a predictor of PFOA and PFOS levels provided little evidence of an association (Lee et al. 2013, Monroy et al. 2008). We found some suggestion that PFOS might be associated with LBW, but overall, the evidence concerning associations between PFOS or PFOA and other proxy measures of fetal growth restriction such as LBW, SGA, and birth weight z-scores was limited. This may be due to relatively small associations with birth weight as well as underpowered samples that were insufficient to demonstrate observable differences in dichotomized outcomes.

The consistency of results within the study differed for studies that included more than one outcome (Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Hamm et al. 2010, Whitworth et al. 2012). Chen et al. (2012) found consistent associations between PFOS exposure and birth weight, SGA, and LBW, significant for the two first outcomes and very close to significance for LBW. However, with PFOA, no statistically significant association was found for any of the outcomes. Darrow et al. (2013) found an association between PFOS and birth weight that did not reach significance, and no association was apparent for LBW. For PFOA, they found no association with any of the outcomes. Fei et al. (2007) found an association between PFOA and birth weight that was partly supported by their result on LBW (they found large odds ratios though they were not statistically significant), but not SGA. For PFOS, they found no association with SGA or birth weight, but a tendency towards an association with LBW. The results by Hamm et al. (2010) and Whitworth et al. (2012) did not support an association between either compound and birth weight z-score or birth weight or SGA, respectively.

Differences existed across studies. Most populations originated from smaller geographical areas representing different countries. The investigated time period spanned 20 years, during which exposure changed. The exposure levels as well as biological material (plasma or serum from pregnant women or the umbilical cord) and the timing of exposure measurement varied widely between and within studies. Statistical approaches including treatment of exposure measures and control for confounding also differed, which made the comparison of studies difficult. No patterns were evident in the results from individual studies according to these characteristics and thus, their impact in terms of modifying the results is unknown.

Our research question is highly relevant from a public health perspective due to the widespread exposure to PFASs in general populations. We applied a broad search strategy in order to achieve high sensitivity. Specificity was obtained through the narrow inclusion criteria with specific definitions of exposures and outcomes. The included studies were well suited to address our research question, and the completeness of reporting was sufficient in all studies except one. However, a major limitation was our inability to perform meta-analysis. This was impossible mainly due to differences in handling the exposure measures ($\log_{10}$, natural logarithm, untransformed continuous concentrations, or different categories) and outcomes, and in the choice of covariates. We contacted some of the authors in order to acquire estimates that were comparable with the remaining studies, but unfortunately, we did not achieve any useful results.

We restricted our study to address only PFOS and PFOA, because too few studies have addressed other PFASs (Arbuckle et al. 2013, Chen et al. 2012, Hamm et al. 2010, Lee et al. 2013, Maisonet et al. 2012, Monroy et al. 2008). In addition to PFOA and PFOS, Chen et al. (2012) reported associations for perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUA) that were not statistically significant. They found a change in birth weight of 6 g and -25 g, per natural log increase in PFNA and PFUA concentrations respectively. Monroy et al. (2008) stated that they found no association between birth weight and levels of PFNA and perfluorohexane sulfonate (PFHxS), but they provided no estimates. Arbuckle et al. (2013) performed multiple stepwise regression analyses of PFNA and PFHxS and potential predictors of their concentrations such as LBW, but LBW was omitted from the analyses due to the value of $p > 0.1$. In the study by Hamm et al. (2010), each natural log increase of the PFHxS concentration was associated with a statistically insignificant change in birth weight of 22 g, but Maisonet et al. (2012) found lower birth weight with increasing PFHxS (for the second tertile compared with the first: -9 g, and for the third compared with the first: -108 g. The latter result was statistically significant). Lee et al. (2013) found a statistically insignificant odds ratio for birth weight above the median of 0.6 with PFHxS above the median in maternal blood. Based on the limited evidence concerning other PFASs rather than PFOS and PFOA, an association with birth weight cannot be excluded.

Assessment of fetal growth

Birth weight may, especially when gestational age is taken into account, be regarded as a proxy measure of fetal growth, and is also closely related to neonatal morbidity and mortality (Wilcox 2010). According to the fetal programming hypothesis, birth weight may also be a predictor of adult disease (Wilcox 2010). However, true fetal growth restriction is present only when the fetus fails to obtain its genetically determined growth potential. Unfortunately, the individual fetal growth potential is unknown. Accordingly, a newborn with a low birth weight is not necessarily growth restricted, and a newborn with normal weight may be growth restricted (Wilcox 2010).

Even if there is a causal relationship between the exposure to PFASs and fetal growth measured by birth weight, modest shifts in average birth weight do not necessarily reflect pathology, as shifts in the birth weight distribution in a population may mainly occur within the normal range of birth weight (Olsen et al. 2009, Savitz 2007). However, even small shifts in population birth weight with environmental exposures may be a sensitive marker of potential pathology and adverse effects, which has been demonstrated for lifestyle exposures such as smoking.

Outcome assessment

For the 12 studies where information on outcomes was retrieved from medical records or national registries, the exposure status could not plausibly have affected outcome

ascertainment (Apelberg et al. 2007, Arbuckle et al. 2013, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Hamm et al. 2010, Lee et al. 2013, Maisonet et al. 2012, Monroy et al. 2008, Washino et al. 2009, Whitworth et al. 2012, Wu et al. 2012). Any measurement error or misclassification concerning outcomes is therefore most likely non-differential. Inoue et al. (2004) did not state how they assessed exposure. Stein et al. (2009) investigated a population in a PFOA contaminated area with maternal report of previous birth outcomes. Thus, in this study, it is possible that the reporting of outcomes was affected by exposure status. However, they found no association between PFOA and low birth weight.

Exposure assessment

PFASs were measured by variations of liquid chromatography-tandem mass spectrometry in all studies. With modern methods, 100 µl of serum or plasma are typically used for the analyses. Some research groups use high-throughput methods consisting of on-line cleanup on a small solid phase extractor and the direct injection of elute into the liquid chromatography-tandem mass spectrometer. Internal standards, consisting of two or more isotope-labeled compounds, are always used. Recently, labeled PFASs have become available to cover multiple analytes. Inclusion of more PFASs is more expensive, since more labeled compounds are needed, but the time spent on extraction and analysis is the same, independent of the number of PFASs. More time is required for the interpretation of results when more compounds are analyzed. Contamination can occur if Teflon is used, and adsorption of PFAS can occur if glass is used, but this is presumably taken into account by all chemists that measure PFAS content.

Most studies provided measures of repeatability [this was not stated in the study by Stein et al. (2009)]. Arbuckle et al. (2013), Darrow et al. (2013), Monroy et al. (2008), and Washino et al. (2009) participated in intercalibration with other laboratories. Laboratories, personnel and equipment differed between studies, but even if systematic differences existed, these would only create problems if detection limits differed markedly from one laboratory to another. In all studies, very few PFOS or PFOA levels were below detection limits.

We excluded four studies that estimated PFOA exposure indirectly instead of using concentrations measured in serum or plasma (Grice et al. 2007, Nolan et al. 2009, Savitz et al. 2012a, b). They found no association between PFOA exposure and fetal growth measures.

The ratios between serum and plasma measurements for PFOS and PFOA are 1:1 (Ehresman et al. 2007). PFASs measured in blood sampled during pregnancy are strongly correlated with levels in umbilical cord blood (Aylward et al. 2014). However, the ability to pass the placenta differs for different PFASs. This calls for careful interpretation of the magnitude of fetal exposure derived from levels measured during pregnancy. Ratios between cord and maternal plasma of approximately 0.3 for PFOS and 0.8 for PFOA have been demonstrated (Apelberg et al. 2007, Fei et al. 2007, Fromme et al. 2010, Lee et al. 2013, Midasch et al. 2007). Based on the differences between maternal and fetal blood, larger fetal transfer of PFOA may be part of the explanation for the somewhat stronger association with birth weight for PFOA than for PFOS, but differences in toxicity or windows of exposure are other potential explanations.

PFAS levels in maternal blood decrease throughout pregnancy; declines of 11% for PFOS and 16% for PFOA have been demonstrated from the first to the third trimester (Glynn et al. 2012). The measurements of PFASs in cord blood indicate that part of this decline may be due to fetal transfer, but dilution in the maternal body probably contributes as well, when maternal blood volume increases during pregnancy. The decline during pregnancy indicates that comparison of exposure between studies, with measures at different time points before, during, or after pregnancy, may be complicated. In order to eliminate the influence of toxicodynamics and toxicokinetics on results, a narrow window of interest might increase the validity within studies and the comparability between studies. It may not be appropriate to directly compare samples taken at different time points within the same analysis. Arbuckle et al. (2013), Chen et al. (2012), Fei et al. (2007), Hamm et al. (2010), Inoue et al. (2004), Lee et al. (2013), Monroy et al. (2008), and Wu et al. (2012) applied narrow blood sampling intervals according to gestational age. However, in the study by Maisonet et al. (2012), the interquartile range of exposure measurement spanned 18 gestational weeks. It is not plausible that the timing of blood sampling is related to birth weight, and misclassification would most likely be non-differential. Washino et al. (2009) primarily determined exposure during the third trimester. However, 25% of the samples were collected after delivery due to anemia. Anemia is not likely to affect measured PFAS levels, since these measurements were carried out in serum or plasma in all studies, but anemic pregnant women may have an increased risk of having a child with low birth weight (Xiong et al. 2000), which may lead to bias away from an association between PFAS exposure and lower birth weight, as PFAS levels are lower after delivery.

The relative decrease in PFOA levels during pregnancy is larger than seen for PFOS (Glynn et al. 2012). Thus, the potential bias would most likely affect the association for PFOA and birth weight. Washino et al. (2009) adjusted for the time of blood sampling, but this may still leave some residual confounding. The fact that Stein et al. (2009) assessed exposure up to five years after pregnancy is a major limitation, since pregnancy as well as breastfeeding reduce the maternal PFAS body burden, but PFASs also accumulate over time in individuals while time trends are decreasing (Brantsæter et al. 2013, Glynn et al. 2012). Similarly, Darrow et al. (2013) attempted to adjust for exposure assessment years before and after pregnancy. Overall, it is not clear when it is the best time to measure exposure; there were no systematic differences in the results based on when exposure was measured in relation to pregnancy and birth. Even though theoretical problems exist, their impact may be limited due to the stability and long half-lives of PFASs.

Selection bias, confounding, and effect modification

In the studies by Stein et al. (2009) and Darrow et al. (2013), the participants were aware of their exposure levels. However, in the remaining studies, individual knowledge about exposure category seems unlikely. Therefore, we do not consider selection bias to be very likely, even though it cannot be ruled

out that selection depended on other factors associated with both PFAS levels and birth weight.

We considered parity, body mass index (BMI), and socio-economic status to be the most important potential confounders, as these are associated with both exposure and outcome in the literature. Most included studies considered several potential confounders (Table 5), but as in all observational studies, residual confounding cannot be excluded. The magnitude of observed associations was small and therefore more likely to be explained by confounding or bias than strong associations, even if the extent of this was modest. Overall, crude estimates failed to change substantially when adjustments were made in multivariate models. In most studies, associations became somewhat stronger with adjustments. However, a few studies did not include some of the potential confounders we considered to be important. Apelberg et al. (2007), Arbuckle et al. (2013), Hamm et al. (2010), Inoue et al. (2004), Lee et al. (2013), Maisonet et al. (2012), and Monroy et al. (2008) failed to consider socio-economic status in their analyses of PFOA or PFOS and birth weight. It was previously demonstrated that women in higher socio-economic groups tend to have higher PFAS levels (Brantsæter et al. 2013). As women with high socio-economic status often give birth to children with higher birth weights (Luo et al. 2004, Moser et al. 2003), a lack of adjustment for socio-economic status may potentially explain the higher birth weight associated with higher PFOS (although statistically insignificant) in the study by Hamm et al. (2010). A lack of adjustment could have obscured a potential decrease in birth weight with PFOA exposure (Apelberg et al. 2007, Arbuckle et al. 2013, Hamm et al. 2010, Lee et al. 2013, Maisonet et al. 2012, Monroy et al. 2008) or PFOS exposure (Apelberg et al. 2007, Inoue et al. 2004, Lee et al. 2013, Maisonet et al. 2012, Monroy et al. 2008). Adjusting for socio-economic status is likely to be insufficient to control for behavioral factors such as smoking and alcohol consumption, but associations for PFASs with such behaviors have not been established.

Only Apelberg et al. (2007) adjusted for maternal weight gain during pregnancy, which is probably a relevant proxy for the size of plasma volume expansion during pregnancy. Poor plasma expansion as well as low pregnancy weight gain is associated with impaired fetal growth (Salas et al. 1993, Viswanathan et al. 2008), but may also cause higher PFAS concentrations due to a smaller distribution volume (Apelberg et al. 2007, Olsen et al. 2009). Thus, if blood samples are taken in late pregnancy or from cord blood, in utero exposure might be overestimated in smaller fetuses and vice versa, thereby creating a noncausal association between PFAS exposure and birth weight. Adjusting for maternal weight gain during pregnancy may not solve the problem, due to collinearity. On the other hand, if two pregnant women initially (e.g. at conception) have the same PFAS concentrations, a woman with lower pregnancy weight gain will probably preserve a higher concentration later in pregnancy, resulting in higher fetal PFAS exposure. With early pregnancy PFAS measurements, overall pregnancy exposure might thus be systematically underestimated in women with less gestational weight gain that may carry smaller fetuses and cause bias against no association. However, there were no systematic differences in the study results depending on the timing of exposure assessment.

Other physiologic and metabolic changes during pregnancy may also impact the association between PFAS levels and fetal growth parameters. No studies adjusted for maternal glomerular filtration rate (GFR). Since renal excretion of PFASs is proportional to the GFR and higher maternal GFR during pregnancy is associated with higher birth weight (Morken et al. 2014), GFR may be an important confounder for the association between PFAS exposure and birth weight. Morken et al. (2014) investigated the association between PFOA exposure and birth weight in a group of participants from the Norwegian Mother and Child Cohort Study [different from the group studied by Whitworth et al. (2012)], and found that adjusting for maternal GFR attenuated the estimate by 66%.

High pre-pregnancy BMI has been shown to be associated with higher birth weight (Papachatzi et al. 2013, Wahabi et al. 2013), and higher BMI might be associated with higher levels of PFASs (Brantsæter et al. 2013). Thus, a lack of adjustment for pre-pregnancy BMI can potentially bias the association towards no association. However, Wu et al. (2012) and Stein et al. (2009) found associations between PFOA and birth weight, and PFOS and LBW, respectively, even though they did not adjust for pre-pregnancy BMI. Maternal diet during pregnancy is another potential confounder. Fish contains considerable amounts of PFASs (Brantsæter et al. 2013, Haug et al. 2010, Rylander et al. 2010), but ingestion during pregnancy has been associated with increased birth weight as well (Brantsæter et al. 2012). Only Fei et al. (2007) attempted to control for diet, but they did not include it in their main analysis.

All studies except those by Arbuckle et al. (2013), Darrow et al. (2013), Inoue et al. (2004), Lee et al. (2013), and Monroy et al. (2008) adjusted for parity. Since average PFASs levels are lower in parous women (Brantsæter et al. 2013), and higher parity is associated with increased birth weight (Wilcox et al. 1996), lack of adjustment for parity could create a noncausal association between higher PFAS exposure and lower birth weight, but none of the studies that did not adjust for parity demonstrated any statistically significant associations.

All studies except those by Arbuckle et al. (2013), Darrow et al. (2013), Inoue et al. (2004), Monroy et al. (2008), and Stein et al. (2009), adjusted for gestational age. However, Darrow et al. (2013) and Monroy et al. (2008) restricted the study population to term births. Fei et al. (2007) also did this in supplementary analyses, and this did not change the result. It would be interesting to discover whether PFASs cause reduced fetal growth or whether a low birth weight may be due to a shorter gestational duration. However, it is debated whether adjustment for gestational age is appropriate when studying impacts on pregnancy outcomes (Wilcox et al. 2011). A way to distinguish effects on birth weight from effects on gestational age is to consider gestational age as an outcome. Many of the studies included in this review investigated associations between PFOS or PFOA and gestational age (Apelberg et al. 2007, Chen et al. 2012, Hamm et al. 2010, Maisonet et al. 2012, Wu et al. 2012) or preterm birth (Arbuckle et al. 2013, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Stein et al. 2009, Whitworth et al. 2012). Chen et al. (2012) found lower gestational age and higher odds for preterm birth with PFOS exposure, but not with PFOA exposure, and Wu

Table 5. Covariates adjusted for in multiple regression analyses of perfluorooctanoate or perfluorooctane sulfonate and birth weight.

	Inoue et al. (2004)	Apelberg et al. (2007)	Fei et al. (2007)	Monroy et al. (2008)	Stein et al. (2009)	Washino et al. (2009)	Hamm et al. (2010)	Chen et al. (2012)	Maisonet et al. (2012)	Whitworth et al. (2012)[a]	Wu et al. (2012)	Arbuckle et al. (2013)	Darrow et al. (2013)	Lee et al. (2013)
Maternal age		X	X		X	X	X	X		X	X		X	X
Pre-pregnancy BMI		X	X			X		X	X	X			X	
Maternal weight							X							
Maternal height		X					X							
Socio-economic status			X		X	X		X		X	X		X	
Delivery mode								X				X		
Parity		X	X		X	X	X	X	X	X	X			
Gravidity												X		
Infant sex		X	X			X	X	X		X	X			
Gestational age/preterm birth		X	X	X[b]		X	X	X	X	X	X		X[b]	X
Smoking during pregnancy		X	X		X	X	X	X	X		X		X	
Cord blood cotinine								X						
Partner smoking											X			
Race		X					X						X	
Gestational age at blood sampling			X			X							X	
Weight gain during pregnancy		X												
Weight gain at 17 weeks										X				
Diabetes		X											X	
Hypertension		X												
Catching cold during pregnancy											X			
History of premature delivery											X			
Spontaneous abortion history											X			
Consumption of lean fish										X				
Interpregnancy interval										X				
Albumin level										X				

Birth weight-scores included information on gestational age and infant gender (Hamm et al. 2010, Whitworth et al. 2012).

[a]In Whitworth et al. (2012), albumin concentration, lean fish consumption, maternal education and interpregnancy interval were only included in the perfluorooctane sulfonate model. Weight gain at 17 weeks of gestation was only included in the perfluorooctanoate model.

[b]Monroy et al. (2008) and Darrow et al. (2013) restricted estimates to term births. Monroy et al. (2008) only presented unadjusted estimates restricted to term births, but they stated that estimates were unchanged when adjusting for parity, gestational age, BMI, gender and smoking.

et al. (2012) found lower gestational age with higher PFOA. Arbuckle et al. (2013) found an association between term gestational age and higher PFOS. However, in the other studies, there was no significant association between PFOA or PFOS and gestational length or preterm birth, and no tendency for estimates to point in a certain direction. In three out of four studies corresponding to 992 out of 1421 pregnancies, there was no association between PFOS and gestational age, and in five out of six studies corresponding to 9293 out of 9722 pregnancies there was no association between PFOS and preterm birth. For PFOA, four out of five studies corresponding to 1421 out of 1588 pregnancies did not demonstrate any association with gestational age, and in five studies of 6205 pregnancies there was no association with preterm birth. Therefore, it is not very likely for lower birth weight with PFAS exposure to be caused by lower gestational age.

Most studies controlled for infant sex. However, if PFASs affect sex hormone homeostasis, it is possible that the potential effects of PFASs on birth weight differ between boys and girls. Only Washino et al. (2009) stratified data by the sex of the newborn. They found no association between PFOS and birth weight in boys, but a statistically significant decrease in birth weight was found in girls (adjusted beta = − 269.4 (− 465.7, − 73.0) per 10-fold increase in PFOS). Sex-stratified estimates were similar for the association between PFOA and birth weight. Maisonet et al. (2012) restricted their analysis to girls and found statistically significant lower birth weight of at least 130 g when comparing the highest with the lowest tertile of PFOA and PFOS. Girls may be more vulnerable to PFASs with respect to birth weight, which implies the need to consider effect modification by infant sex.

Other systematic reviews on the topic

The review by Olsen et al. (2009) provided no firm conclusions on the association between exposure to PFOA and PFOS and human fetal growth. A recent systematic review and meta-analysis by Johnson et al. (2014) applied the Navigation Guide systematic review methodology to investigate the association between exposure to PFOA and human fetal growth. Their inclusion criteria were less restrictive compared to ours; for instance, they included studies with estimated PFOA concentrations and other outcomes in addition to birth weight (birth length, head circumference, and ponderal index). Therefore, they included more studies than us (n = 18). However, since they conducted literature searches in the spring of 2012, they did not include the two most recent studies (Darrow et al. 2013 and Lee et al. 2013). Another difference between the review by Johnson et al. (2014) and our work is the approach to the risk of bias in individual studies. Johnson et al. (2014) decided that maternal age and gestational age were the most important confounders and concluded that studies were at low risk of confounding if they accounted for both in their design or analysis, or if they reported that neither of these influenced the associations between PFOA and fetal growth outcomes. These authors were more successful than us in retrieving raw data or comparable estimates from the authors of original articles. Therefore, they were able to perform a meta-analysis of 9 studies on PFOA concentrations and birth weight. They found an overall estimate of − 18.9 (95% CI: − 29.8, − 7.9) grams of birth weight per ng/mL increase in serum or plasma PFOA, and concluded that there is sufficient evidence for an association between PFOA exposure and reduced fetal growth.

Recommendations for future studies

Future studies should investigate populations with high exposure contrasts, exposure should be assessed in serum or plasma using a validated method in a narrow time window to enhance comparability within the study, or even better, during multiple windows to determine the critical window of exposure. Most existing studies modeled exposure as continuous untransformed, natural log or $\log_{10}$-transformed variables, assuming a linear relationship with the outcome, and thus a monotonic dose-response relationship. More complex models are necessary in order to investigate potential non-monotonic dose-response relationships, i.e. using categorical scales or splines. The literature has mainly focused on PFOA and PFOS. They are to a large extent substituted by other PFASs whose adverse effects need to be considered. Furthermore, future research should focus on mixtures of PFASs and other environmental toxicants (Sarigiannis and Hansen 2012). In terms of outcomes, birth weight remains a good proxy variable for early life pathology associated with environmental exposures. For outcomes such as LBW or SGA, existing studies have been underpowered to detect significant changes, and larger sample sizes are needed. Future studies should carefully choose which covariates to include in their analyses. In our opinion, at least parity, socio-economic status and BMI should be considered in the analyses of PFASs and birth weight. Furthermore, gender differences should be explored. The role of pregnancy-related metabolic and physiologic changes is a promising emerging area of research that incorporates the use of physiologically-based pharmacokinetic models in the epidemiological investigation of PFASs and birth weight (Loccisano et al. 2013).

Conclusions

While high PFOA and PFOS exposures in pregnancy were associated with lower average birth weights in human newborns in most studies, not all results were statistically significant. The existing data is insufficient to confirm or reject a certain association between PFASs exposure and fetal growth. Knowledge on the influence of PFASs other than PFOS and PFOA on fetal growth is sparse and needs to be investigated in future studies. Although any risk to the individual pregnant woman and her child due to PFOS and PFOA exposures seems small based on the limited information available, the widespread environmental presence of these and other PFASs warrants continued investigation.

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Declaration of interest

Affiliations for the authors are as shown on the cover page. All authors contributed to the conception and design of the study.

C.C.B drafted the article and all authors critically revised the article and approved the final manuscript. The authors declare that they have no actual or potential competing financial interests. The authors have not appeared in or submitted comments for regulatory or legal proceedings considering PFASs. The review strategy, the conduct of the review, and the interpretation and synthesis of the findings were exclusively the work of the authors. The work was supported by the Danish Council for Strategic Research (10-092818) and the Danish Research Council (10-082745).

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Supplementary material available online

Supplementary materials, Figure 1, Table 1.