# Serum Perfluorooctanoic Acid and Birthweight

## *An Updated Meta-analysis With Bias Analysis*

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**Background:** A recent meta-analysis of 15 studies found a change in birthweight of −12.8 g (95% CI = −23.1, −2.38) per ng/ml PFOA in maternal or cord blood and −27.1 g (−50.6, −3.6) per log ng/ml PFOA. Almost all studies were done in low-exposed populations. There are nine new studies, adding 6,019 births to the previous 6,937 births.

**Methods:** We conducted a meta-analysis of 24 studies. To combine all results, we approximated results for untransformed PFOA from nine studies using log-transformed PFOA. We also included another large study, excluded from previous analyses, in a sensitivity analysis.

**Results:** We found a change of birthweight of −10.5 g (−16.7, −4.4) for every ng/ml PFOA in maternal or cord blood. After adding one previously excluded large study, we found little evidence of an association (−1.0 g; 95% CI = −2.4, 0.4). Restricting to studies where blood was sampled from mothers early in the pregnancy or shortly before conception (5,393 births), we found little association of PFOA with birthweight (−3.3 g [−9.6, 3.0]). In studies where blood was sampled late in the pregnancy (7563 pregnancies), lower birthweight was associated with higher PFOA (−17.8 [−25.0, −10.6]).

**Conclusion:** Present human evidence provides only modest support for decreased birthweight with increasing PFOA. Studies with a wide range of exposure, and studies with blood sampled early in pregnancy, showed little or no association of PFOA with birthweight. These are studies in which confounding and reverse causality would be of less concern.

**Keywords:** PFOA, birthweight, meta-analysis

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Perfluorooctanoic acid (PFOA) is a synthetic and environmentally persistent perfluorinated compound that has been used in the manufacture of fluoropolymers since the 1940s. PFOA has been used in a variety of products (e.g., Teflon, Goretex) for its stain, grease, and water resistance and its surfactant properties. PFOA, once absorbed into the body through inhalation or ingestion, accumulates in the serum, kidneys, and liver, with a half-life of about 3 years. It persists indefinitely in the environment, is ubiquitous, and has been detected consistently in the serum of the general US population.[1]

PFOA production, and most use, ended in the United States as of 2015 based on an agreement between the Environmental Protection Agency (EPA) and the largest eight producers/users (www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program). However, over the past few years, dozens of communities in the United States located near industries or military bases have detected PFOA in their drinking water (e.g., http://www.al.com/news/huntsville/index.ssf/2015/10/decatur_companies_leaking_canc.html, http://www.timesunion.com/7dayarchive/article/Hoosick-Falls-meeting-11231034.php, http://www.mynbc5.com/article/19-more-north-bennington-wells-test-above-vt-standard-for-pfoa-sampling-area-expands/3326821, https://www.delawareonline.com/story/money/2016/04/01/delaware-c8-contamination-blamed-firefighting-foam/81538418/). There are an estimated 6 million US inhabitants exposed to levels above EPA drinking water guidelines.[2]

Toxicologic studies show reproductive effects in mice and rats such as reduced birth weight, neonatal death, and reduced postnatal growth, but at higher exposure levels than background exposure in human populations.[3] PFOA readily crosses the placental barrier.[4]

In 2014, Johnson et al[5] published a meta-analysis of PFOA and low birthweight in which they concluded that birthweight decreased −18.9 g (95% CI = −29.8, −7.9) for every ng/ml PFOA in maternal or cord blood measured at time of pregnancy, using a random-effects analysis with nine studies. Chance and bias were ruled out with reasonable confidence as an explanation for this finding. In 2017, Negri et al[6] updated this meta-analysis to include 15 studies and conducted a random-effects meta-analysis separately for untransformed and log-transformed PFOA. These investigators found a change in birthweight of −12.8 (95% CI = −23.1, −2.38) for each ng/ml of untransformed PFOA in maternal or cord blood (12 results) and a change of −27.1 (95% CI = −50.6, −3.6) for each unit

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Computer code is provided in a supplemental file for replication of analyses, and the data are public.

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of log-transformed ng/ml PFOA (10 results). Six studies gave results for both untransformed and log-transformed PFOA and were included in both of these summary estimates, results of which were, therefore, not independent.

Here, we update these meta-analyses with nine new studies, including an additional 6,019 births compared with 6,937 births in the earlier analysis by Negri et al.[6] In a sensitivity analysis, we add one large study (4,142 births) with a wide range of exposure levels, which was excluded in the two prior meta-analyses because it used modeled PFOA at time of pregnancy, rather than measured serum PFOA in either the pregnant mother's blood or cord blood. We also divide studies into those in which maternal blood was sampled earlier in pregnancy compared with later, following a suggestion in a prior study by Verner et al.[7]

## METHODS

We searched PubMed for English-language, full-text, peer-reviewed articles published from 1 January 2014 through 31 December 2017 to identify relevant articles published since Negri et al.[6] All searches required that at least two terms be identified in the title, abstract, or keywords of the article with one of the terms always being either "birthweight" or "reproduction." The second term used in searches included either: "PFOA," "PFAS," "PFC," "fluoroalkyl," or "fluorocarbon." Reference lists were also screened for other relevant articles that may have not shown up in the database search. The search identified 1,310 articles. We then excluded duplicates and studies that did not consider the relationship between PFOA and birthweight. This resulted in finding nine new studies with usable data (with 10 results for exposure–response coefficients).

We conducted a meta-analysis of all 24 studies to date (26 results) for birthweight in relation to either maternal or cord blood levels of PFOA, using a program in SAS based on DerSimonian and Laird[8] (see eAppendix, http://links.lww.com/EDE/B393, for the SAS program). Following standard practice, when a *P* value for a test for heterogeneity between studies was <0.05, we used a random-effects analysis, and otherwise, we used a fixed-effects analysis.[8] Weight for the meta-analyses for studies with fixed effects (little heterogeneity between coefficients) were the inverse of the variance of the coefficient for each study; weights for meta-analyses with random effects (substantial heterogeneity between coefficients) were based on the inverse of the variance of the coefficient of each study plus the addition of an extra component of variance between studies.[8]

When studies gave results for both untransformed and log-transformed PFOA, we used untransformed PFOA. For studies that gave results only for log-transformed PFOA (nine studies; 11 results), we approximated the results for an untransformed analysis by iteratively minimizing the squared deviation of a new linear curve from the original logarithmic one, over a scale of 0 to 10 ng/ml PFOA, typical of studies in the general population. We also minimized squared deviation of a linear upper and lower confidence limit from the original logarithmic confidence interval curves. For any given study, the iteration was conducted by minimizing the sum of squares of the difference between the candidate linear curve and the logarithmic curve reported in the literature, across 10 points, at 1, 2….through 10 ng/ml. Iteration began with an educated guess for a candidate linear curve that would approximate the logarithmic curves and proceeded by varying the candidate linear curve until the sum of squares of the differences were minimized.

There were 15 included studies using maternal blood and nine based on cord blood. Maternal and cord blood serum levels of PFOA are highly correlated. Kato et al[9] report a Spearman correlation of 0.88 between maternal serum and cord blood PFOA at the time of delivery, Yang et al[10] found a correlation of 0.81 in 157 mother/child pairs, and Fromme et al[11] found a correlation at delivery of 0.94 in 23 mother/child pairs. Two studies using maternal blood gave separate results for boys and girls, and we included both results separately.

Of the 24 included studies, 14 adjusted for gestational age of the child at delivery, five did not, two did not provide information, two had models with and without adjustment (we used the unadjusted results), and one was restricted to term births (Table). Adjustment was presumably done to control for possible confounding, as gestational age is strongly related to birthweight, and would also be associated with cumulative PFOA exposure to the fetus. On the other hand, gestational age might be an intermediate variable between PFOA and birthweight, and adjustment would bias a positive PFOA/birthweight association to the null.[12] However, four out of five studies that looked at PFOA in relation to preterm birth found no association, and nine out of ten studies that looked at PFOA and gestational age found no association (one found a weak correlation). These data suggest that gestational age is unlikely to be either a confounder or intermediate variable and also suggest that adjustment for it would not affect the PFOA/birthweight association. This is consistent with the finding of no difference in the PFOA/birthweight results in two studies that included analyses that either did or did not adjust for gestational age.

We conducted a second random-effects meta-analysis after adding a large study of a highly exposed population by Savitz et al,[13] which had been excluded from both prior meta-analyses on grounds of potential exposure measurement error, owing to the use of a model to estimate serum levels instead of serum measurements. Savitz et al[13] used a model to predict historical PFOA in women over time. The model had estimates of exposure, which were calibrated to a single observed measure of PFOA in 2005/2006, or estimates that were not calibrated. We used the model with uncalibrated estimates of past PFOA serum levels; the uncalibrated estimates have generally been the estimates used by the principal investigators of this population , and were well correlated with the 2005/2006 observed

**Table.** Studies of PFOA and Birthweight

| Study | Change in Birth Weight (g) by per ng/ml PFOA or log ng/ml PFOA | Change in Birthweight per ng/ml Estimated From Data per ln ng/ml | Sample Size (births) | Source of Measured PFOA During Pregnancy | Trimester Blood Sampled | Comment |
|---|---|---|---|---|---|---|
| Apelberg et al[38] | −64 (−125, −3) per ng/ml PFOA | | 293 | Cord blood | Third | Included; background levels[a], adjusted for gestational age |
| Fei et al[39] | −11 (−21, 1) per ng/ml PFOA | | 1,400 | Maternal blood | First | Included; background levels, adjusted for gestational age |
| Monroy et al[40] | No regression of birthweight on PFOA | | 101 | Maternal and cord blood | Third | Excluded. No regression results for birthweight regressed on PFOA |
| Washino et al[41] | −23 (−61, 16) per ng/ml PFOA | | 428 | Maternal blood | Third | Included; background levels, adjusted for gestational age |
| Hamm et al[42] | −12 (−33, 8) per ng/ml PFOA | | 252 | Maternal blood | Second | Included; background levels, adjusted for gestational age |
| Fromme et al[11] | −213 (−423, −2) per ng/ml PFOA | | 33 | Cord blood | Third | Included; background levels, not known whether adjusted for gestational age |
| Kim et al[20] | 154 (−84, 392) per ng/ml PFOA | | 43 | Cord blood | Third | Included; background levels, unknown whether adjusted for gestational age |
| Whitworth et al[31] | −28 (−60, 4) per ng/ml PFOA | | 849 | Maternal blood | Mostly second and third | Included; background levels, adjusted for gestational age |
| Maisonet et al[43] | −34 (−55, −14) per ng/ml PFOA | | 422 | Maternal blood | Mostly second | Included; background levels, adjusted for gestational age |
| Chen et al[44] | −11 (−26, 4) per ng/ml | | 429 | Cord blood | Third | Included; background levels, adjusted for gestational age |
| Wu et al[21] | −267 (−573, −37) per $\log_{10}$ ng/ml | −33 (−66, 5) | 158 | Maternal blood | Third | Included; background levels, adjusted for gestational age |
| Savitz et al[13] | −0.1 (−0.2, 0.02) per ng/ml | | 4,142 | Estimated maternal blood, using model, uncalibrated result | N.A. | Included in sensitivity analysis. Higher exposure cohort. PFOA estimated at time of pregnancy. Term births |
| Lee et al[45] | ≥median birth weight 2.38 ng/ml, <median birth weight 2.83 ($P = 0.04$) | | 59 | Maternal blood | Third | Excluded. No regression results for birth weight |
| Lee et al[45] | ≥median birth weight 2.10 ng/ml, <median birth weight 2.09 ($P = 0.99$) | | 59 | Cord blood | Third | Excluded. No regression results for birth weight |
| Darrow et al[22] | 0.1 (−0.4,0.5) per ng/ml | | 710 | Maternal blood measured preconception | Before or during conception | Included. Cohort with higher exposure (mean 31 ng/ml; range: 0.6–460). Term births, occurring after measurement of PFOA in maternal serum |
| Kishi et al[46] | No significant association between birthweight and PFOA | | 306 | Maternal blood | Second, third | Excluded. No quantitative data provided |
| Robledo et al[47] | −61.6 (−159.2, 35.9) girls<br>4.8 (−85.4, 95.0) boys<br>per standard deviation increase in ln(PFOA) | −38(−54, 12) girls<br>3 (−21, 27) boys | 117 girls<br>113 boys | Maternal preconception blood | Shortly before conception | Included. Background levels. Not adjusted for gestational age |
| Alkhalawi et al[48] | Regression trend test using quartile (1,2,3,4), −0.025 (−0.09, 0.04) | | 148 | Maternal and cord blood | Third | Excluded, no regression coefficient; background levels |

*(Continued)*

**Table.** (*Continued*)

| Study | Change in Birth Weight (g) by per ng/ml PFOA or log ng/ml PFOA | Change in Birthweight per ng/ml Estimated From Data per ln ng/ml | Sample Size (births) | Source of Measured PFOA During Pregnancy | Trimester Blood Sampled | Comment |
|---|---|---|---|---|---|---|
| Callan et al[49] | −48 (−203, 108) per ln(ng/ml) | −13 (−53, 28) | 98 | Maternal blood | Third | Included; background levels, adjusted for gestational age |
| de Cock et al[50] | −185 (−623, 253), 2nd tertile, boys<br>168 (−231, 576) 3rd tertile, boys<br>238 (−183, 659), 2nd tertile, girls<br>−11 (−489, 466), 3rd tertile, girls | | 91 | Cord blood | Third | Excluded, no regression coefficient; background levels |
| Bach et al[51] | 10 (−10, 20) per ng/ml | | 1,507 | Maternal blood | Mostly first | Included; background levels, model with and without adjustment for gestational age. We used unadjusted |
| Lee et al[52] | −30 (−25, 18) per ln(ng/ml) | −8 (−64, 48) | 85 | Cord blood | Third | Included; background levels, adjusted for gestational age |
| Wang et al[53b] | −80 (−180, 10) girls40 (−5, 120) boys per ln(ng/ml) | −21 (−43,3) girls<br>11 (−11, 33) boys | 106 girls<br>117 boys | Maternal blood | First | Included; background levels, not adjusted for gestational age |
| Lenters et al[54b] | −43 (−108, 23) per ln 1.18 ng/ml | −10 (−27, 8) | 1,250 | Maternal blood | Mostly third | Included; background levels, models with and without adjustment for gestational age. We used unadjusted |
| Minatoya et al[55b] | −197 (−391, −3) per $\log_{10}$ ng/ml | −52 (−105, 2) | 168 | Cord blood | Second, third | Included; background levels. A subset of Kishi et al[45], adjusted for gestational age |
| Shi et al[56b] | 16 (−12, 45) per ng/ml | | 170 | Cord blood | Third | Included; background levels, adjusted for gestational age |
| Li et al[57b] | −113 (−172, 54) per ln(ng/ml) | −30 (−75, 15) | 321 | Cord blood | Third | Included; background levels, adjusted for gestational age |
| Lind et al[58b] | No significant effect; data not provided | | 638 | Maternal blood | First | Excluded, no exposure–response coefficient given; background levels |
| Manzano-Salgado et al[59b] | −9(−39.8, 20) per ln(ng/ml) | −2 (−10, 5) | 1,185 | Maternal blood | First, second | Included; background levels, not adjusted for gestational age |
| Gyllenhammar et al[60b] | No significant effect | | 381 | Maternal blood | Postpartum | Excluded, maternal serum PFOA in ng/g in mothers 3 weeks after birth |
| Chen et al[61b] | −33 (−85, 14) per ng/ml | | 429 | Cord blood | Third | Included; background levels, not adjusted for gestational age |
| Starling et al[62b] | −51.4 (−97.2, −5.7) per ng/ml | | 628 | Maternal blood | Second, third | Included; background level, adjusted for gestational age |
| Sagiv et al[16b] | −4.9 (−11.9, 7.2) per ng/ml | | 1,645 | Maternal blood | First | Included; background levels, term birth weight, adjusted for gestational age |
| Woods et al[63b] | No significant effect | | 272 | Maternal blood | Second, third | Excluded; no comparable data; background levels |

[a]Background levels refers to low general population levels, e.g., <10 ng/ml.
[b]New studies not considered in prior meta-analyses by Johnson et al[5] and Negri et al[6], total 6,019 births (prior total 6,937).

measurement (r=0.67). The observed serum measurements in 2005/2006 in this population, which were used for calibration, were artificially low compared with levels just before 2005, owing to the widespread consumption of bottled water provided for free at that point in time in the Little Hocking water district, which was the most highly exposed community in this population. The interview data available to the investigators for the model building did not reflect this recent bottled water usage. In the Little Hocking water district, only 7% of subjects reported to investigators that they were drinking bottled water in 2005/2006, at a time when 81% of the household in Little Hocking were receiving free bottled water.[14] For this reason, we believe that the uncalibrated modeled exposures were a better estimate of historical exposures, which were of primary interest, rather than the calibrated modeled exposures. However, as a sensitivity analysis, we also conducted a meta-analysis using modeled exposure estimates calibrated in relation to the observed 2005/2006 measurement, as well as modeled exposure estimates calibrated via a Bayesian method. Traditional calibration multiplies all yearly model-generated serum estimates for an individual by the ratio of his/her measured to modeled PFOA serum levels in 2005/2006, whereas the Bayesian calibration give less weight to this correction as the modeled estimates are further away in time from the measured estimates.

Estimates were generated for subsets of studies that assessed biomarker levels before conception or early in pregnancy compared with those that considered late-pregnancy serum levels. Biomarker measures in pregnancy are vulnerable to distortion related to the health of the pregnancy.[15] Sagiv et al[16] have noted that the potential for reverse causality in which low plasma volume expansion, which is associated with lower fetal growth, generates a higher level of serum PFOA, is more plausible for late than early pregnancy measures.

We made funnel plots (with and without two outliers) to investigate possible publication bias,[17] although we did not conduct statistical tests of publication bias, nor attempt imputations of missing studies, owing to the inadvisability of these techniques when heterogeneity of results is present.[18,19]

## RESULTS

The Table provides descriptive data on all studies that reported on birthweight and PFOA, of which 24 were included because they generated exposure–response coefficients. The comment section indicates which studies were excluded and why. For two small studies (Kim et al[20] and Fromme et al[11]), we took results directly from Negri et al[6] but were unable to find the results in the original articles. We conducted the meta-analyses with these studies included, but in a sensitivity analysis, we also excluded them.

An example of approximating the association between log PFOA and birthweight via an association between untransformed (linear) PFOA and birthweight is shown graphically for one study[21] in Figure 1. Calculating the difference in birthweight estimates across all 10 points (1, 2….9, 10 ng/ml), between the estimated birthweight for the original log-transformed and the new linear curve, for this study, we found an average difference of −7.8 g, indicating that in this range of PFOA, the linear curve underestimated the change in birthweight found by using the original log-transformed curve by 8 g, a small amount given the predicted decrease for the log-transformed curve was −270 g going from 0 to 10 ng/ml PFOA. The analogous mean across all log-transformed

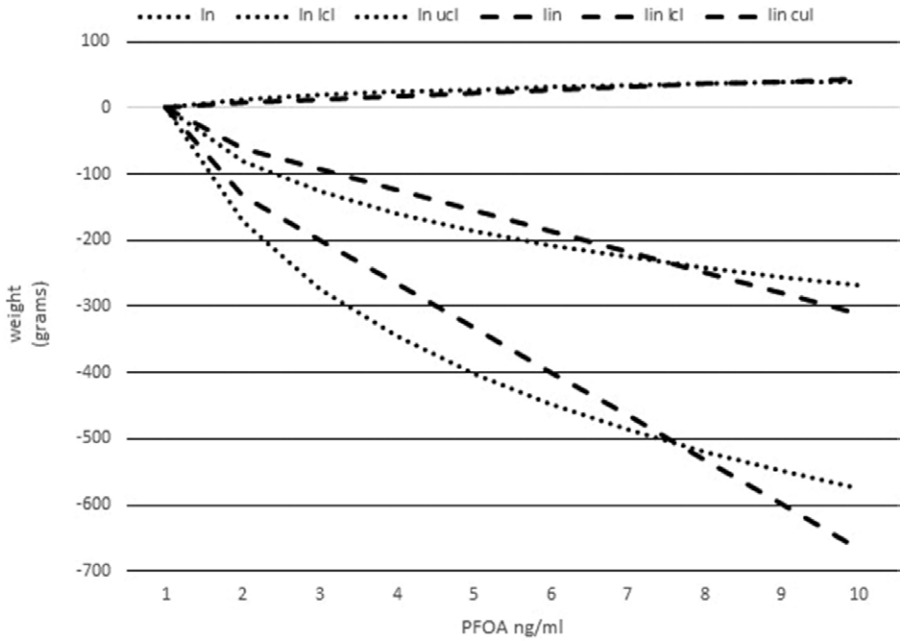


**Figure 1.** Example of approximation of a function of linear PFOA from given log PFOA exposure–response (Wu et al[21]).

studies, weighted by the number of births, showed that on average, the linear approximation underestimated the decrease in birthweight over the 0–10 ng/ml range by only −2.9 g. Hence, we believe the linear approximations were good ones, which allows us to combine all 24 studies.

Figure 2 shows a forest plot of the meta-analysis for all 24 studies (26 coefficients). We found a change of birthweight of −10.5 g (−16.7, −4.4) for every ng/ml of maternal or cord blood, using a random-effects analysis (which would be approximately a drop of 0.3% in weight per unit of serum PFOA, assuming a mean birthweight of about 3,500 g). Inclusion of one additional large study excluded in the earlier meta-analyses (Savitz et al,[13] using uncalibrated model results from Table 8 for change in birthweight by interquartile range) yielded a result showing no association between each unit of serum PFOA and birthweight (−1.0 g; 95% CI = −2.4, 0.4). Use of either traditionally calibrated model estimates or Bayesian calibrated estimates from Savitz et al resulted in a meta-analysis result of either −1.0 (−2.4, 0.4) or −1.1 (−2.5, 0.3).

Our results were little changed with the exclusion of two small studies by Kim et al[20] and Fromme et al,[11] for which we took results from Negri et al.[6] The corresponding results, excluding these two studies, were −10.3 (−16.3, −4.3) without Savitz et al[13] and −0.9 (−2.3, 0.4) with Savitz et al.[13]

Analyses of the 15 studies in the prior meta-analyses versus the nine new studies showed a reduced effect estimate in the newer studies. A random effects ($I^2$ 0.68; $P$ for heterogeneity <0.0001) of the 15 studies included in the prior meta-analyses resulted in a change in birthweight of −13.1 (−22.5, −3.8) per ng/ml serum PFOA, whereas a fixed-effects ($I^2$ 0.44; $P$ for heterogeneity 0.07) analysis of the nine newer studies found a change of −5.2 (−11, 0). A test for the difference between birthweight change between old and new studies yielded a $P$ value of 0.24, using a weighted meta-regression of the 26 coefficients, in which the outcomes were the coefficients for the association of PFOA and birthweight, the predictor variable was "prior" versus "new" study, and the weights for each coefficient were the same as those used in the respective meta-analyses.

When we compared maternal blood studies to cord blood studies, we found little difference. For the 15 maternal blood studies (17 coefficients), a random-effects analysis ($P$ for heterogeneity <0.0001; $I^2$ 0.66) found a change in birthweight of −9.2 (−15.6, −2.8) g per ng/ml serum PFOA, whereas a fixed-effects analysis ($P$ for heterogeneity 0.06; $I^2$ 0.47) of the nine cord blood studies found a change in birthweight of −13.3 (−24.7, −1.8) g per ng/ml.

We conducted subanalyses on studies in which the trimester of blood sampling was early (either the first, a mixture of first and second, or mostly/all preconception; seven studies, nine coefficients, 5,393 births) compared with studies in which the blood sampling was late (either second or third trimester, or a mixture of second/third trimester, 17 studies, 17

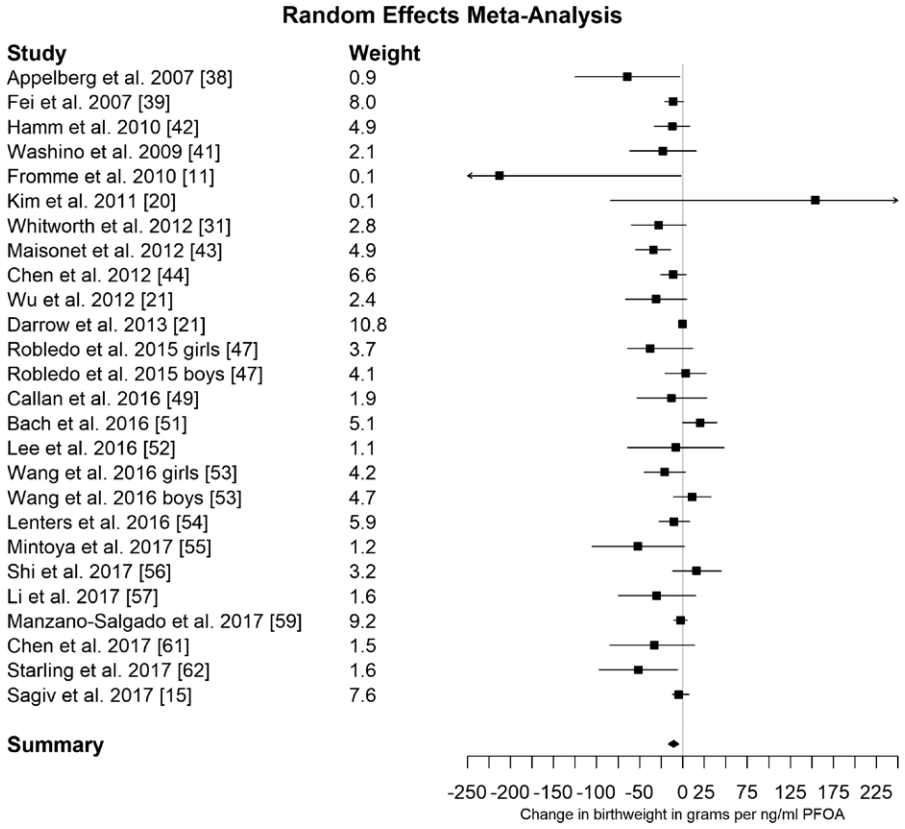


**Figure 2.** Forest plot of results across 26 estimates from 24 studies (summary coefficient [95% CI] using 24 studies: –10.5 [–16.7, –4.4]; Q for heterogeneity 66.8; df = 25; $P < 0.0001$; $I^2 = 0.63$).

coefficients, 7,563 births). Cord blood studies were included in this latter group. For the first group where blood was sampled early in gestation, we used a random-effects model that resulted in a slightly lower birthweight of −3.3 g (−9.6, 3.0) per ng/ml serum PFOA (Figure 3 shows the forest plots). Omitting Darrow et al,[22] a study with a wide range of exposure from this group had only a minor effect (−4.5 g, −13.5, 4.6) on this result.

For the second group in which the blood sampling was late in gestation, we used a fixed-effect model (*P* for heterogeneity 0.13; $I^2$ 0.29) and found an effect estimate of −17.8 g (−25.0, −10.6) per ng/ml serum PFOA (Figure 3 shows the forest plot). A test of the difference between the early and late-pregnancy studies yielded a *P* value of 0.02, in a weighted meta-regression of the 26 coefficients, in which the weights for each coefficient were taken from the respective meta-analyses.

efigure 1A (http://links.lww.com/EDE/B391; 24 studies) and efigure 1B (22 studies) show the funnel plot for the studies, with and without two outliers; efigure 1B (http://links.lww.com/EDE/B392) shows some suggestion of "missing" studies with positive coefficients for PFOA and low precision.

## DISCUSSION

We have conducted a meta-analysis of the relationship between maternal serum PFOA and birthweight using data from 24 studies and 13,000 births. We found a modest decrease in birthweight with increasing serum PFOA but only when omitting Savitz et al.[13] The study by Savitz et al[13] was omitted from the two prior meta-analyses, because of assumed mismeasurement of exposure. When we included it along with the other studies, there was virtually no effect of PFOA on birthweight.

There is a great deal of heterogeneity of results across the studies we considered, motivating a random-effects analysis when considering all studies combined. One possible source of heterogeneity is that samples of maternal blood were taken at different times during gestation, and PFOA levels differ by trimester, decreasing during pregnancy, presumably owing to the pregnancy-associated expansion of blood volume, or the parallel increase in glomerular filtration rate (GFR). Plasma volume increases by about 50% during pregnancy, peaking at 30–35 weeks gestation.[23] Glomerular filtration increases in parallel, increasing 40%–50% during pregnancy.[24] An increase in plasma volume and GFR would be expected to lead to a decrease in maternal serum PFOA concentration.[25] Kato et al[9] found a decrease in maternal mean serum PFOA from 4.8 to 3.3 ng/ml, comparing samples from 16 weeks of pregnancy to those at delivery (n = 71). Fromme et al[11] found a decrease in median maternal serum PFOA from 2.4 to 1.9 ng/ml from sometime in the third trimester until delivery (n = 38). Given that the magnitude of maternal blood volume expansion is related to fetal growth,[26] there is the potential for distortion

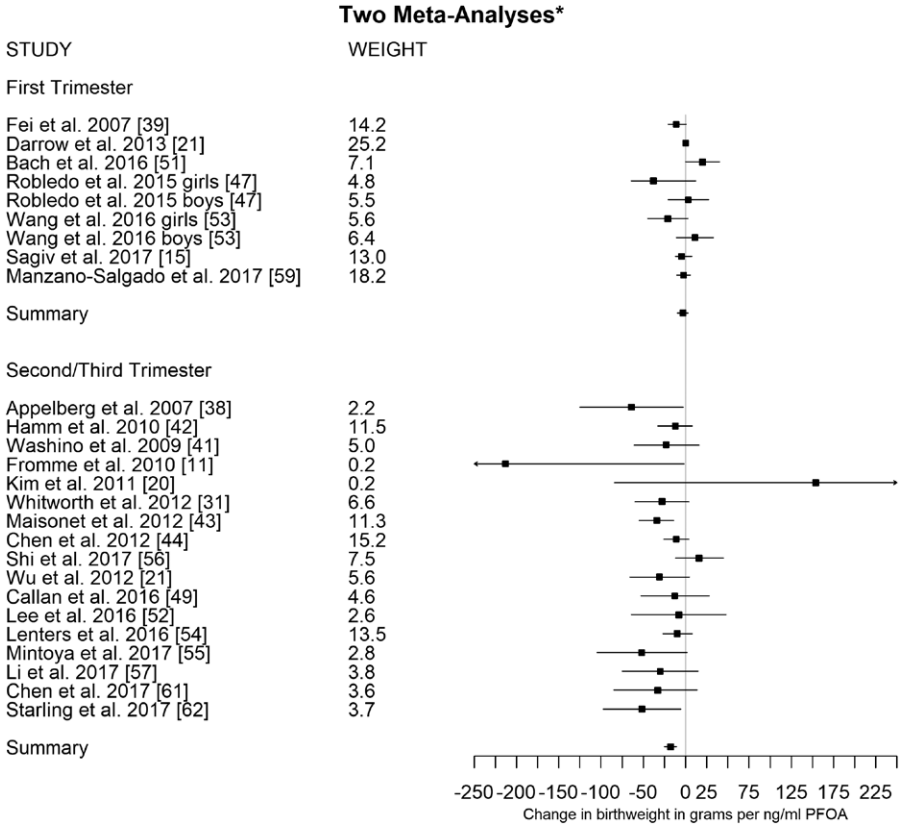


**Figure 3.** Forest plots stratified by trimester during which blood was sampled (summary coefficient [95% CI] for studies with primarily first-trimester sampling: −3.3 [−9.6, 3.0] using random-effects model [heterogeneity $P \leq 0.0001$; $I^2 = 0.68$]; for studies with second-/third-trimester sampling, summary coefficient: −17.8 [−25.0, −10.6] using fixed-effects model [heterogeneity $P \leq 0.13$; $I^2 = 0.29$]).

of the associations between measured PFOA and birthweight, depending on the time of sampling.

The timing of the maternal blood sample may also affect susceptibility to confounding by a low glomerular filtration rate (GFR). The potential role of confounding by low GFR (not controlled in any study included here), which affects both birthweight (lower GFR, lower birth weight) and the amount of serum PFOA (low GFR, high serum PFOA), has been studied by Verner et al.[7] The authors conducted simulations and estimated that confounding could account for a substantial proportion of the observed inverse association between birthweight and PFOA. The potential effect of confounding by low GFR might be expected to be greater when maternal blood is sampled later in pregnancy, when GFR should have increased 40%–50%. Indeed, in the simulations conducted by Verner et al,[7] the confounding effect of GFR was primarily seen late in pregnancy. These authors also conducted a meta-regression to assess the time of sampling on associations between birthweight and perfluoroalkyl substances (PFAS) and found that the association between perfluorooctane sulfuric acid (PFOS) was stronger later in pregnancy but did not find similar effect modification for PFOA, possibly owing to the small number of studies included in their meta-regression for PFOA (n = 7). These authors called for further meta-analyses when more studies became available, which could investigate the effect of sampling early or late in pregnancy.

Although much about gestational hemodynamics remains unknown, Figure 4A–4C explore possible pathways, under the assumption of no causal association between "true" maternal PFOA exposure (unaffected by reverse causality or confounding) and birthweight. Figure 4A pictures confounding by an unknown factor that results in (1) greater expansion of plasma blood volume, going hand in hand with increased GFR, which in turn results in low maternal serum PFOA and (2) increased fetal growth, which in turn leads to larger birthweight. Conceivably, the direction of the arrow between fetal growth and plasma expansion/high GFR might be switched, as in Figure 4B, such that larger fetuses (destined to have higher

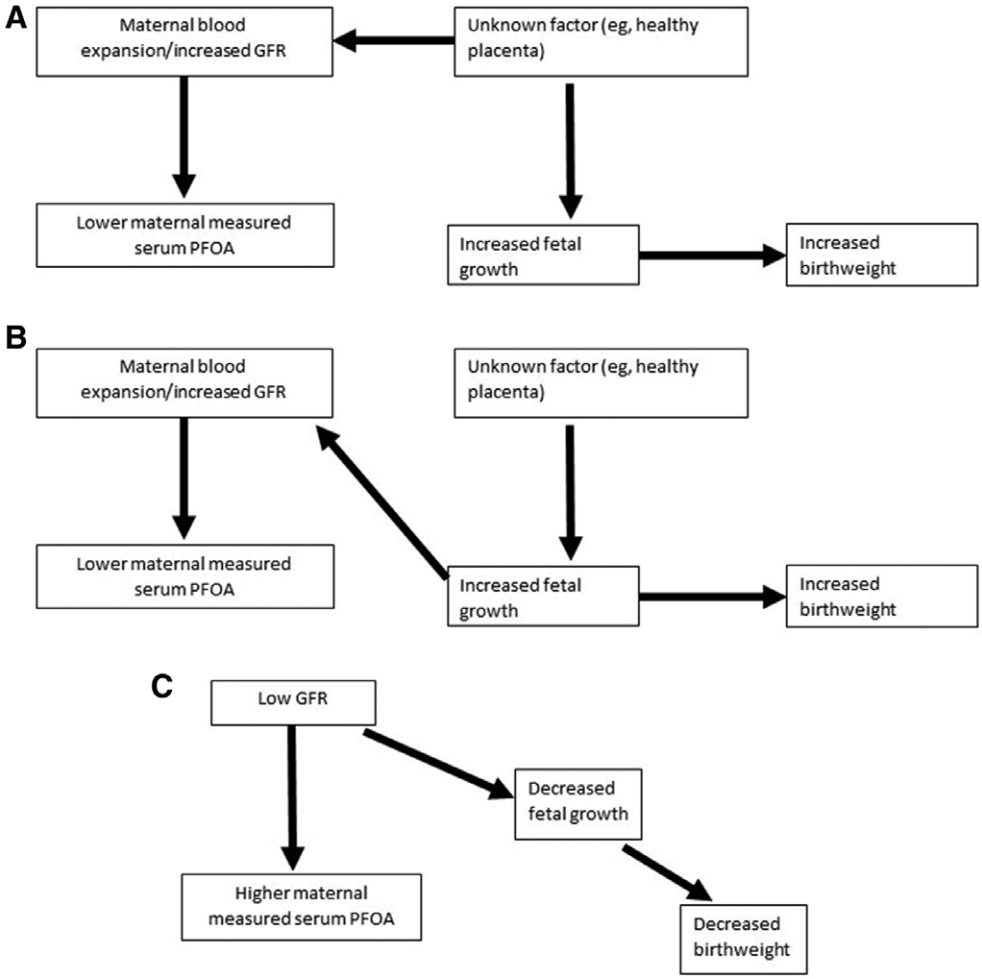


**Figure 4.** Directed acyclic graphs for perfluorooctanoic acid and birthweight. A, Confounding by unknown factor leading to increased maternal blood expansion/GFR. B, Reverse causality, increased fetal growth leading to increased maternal blood expansion/glomerular filtration rate (GFR). C, Confounding by low GFR.

birthweight) stimulate increased plasma volume and accompanying higher GFR, although the mechanism by which this might occur is unknown. Again, the increased plasma volume/higher GFR leads to lower serum PFOA, but this time, the relationship between birthweight and PFOA would be one of reverse causality. Evidence of other reverse causality in studies of serum PFOA has been shown for other outcomes, including kidney function,[27,28] and early menopause.[28] Savitz[29] and Savitz and Wellenius[15] have commented on the general problem of reverse causality during pregnancy. Figure 4C pictures confounding by abnormally low GFR, which as noted might be expected to be more severe when blood is sampled late in pregnancy and which results in turn in higher serum PFOA and lower birthweight.

Sagiv et al[30] have shown that plasma albumin, a marker of plasma volume expansion, and GFR were strongly correlated with serum PFOA. These same authors,[15] on the other hand, have recently shown that incorporating these variables into a regression of birthweight on serum PFOA did not change results, suggesting no confounding. There is, however, a caveat to this finding, noted by the authors. Measurements of plasma albumin and GFR were made in the first trimester (median 10 weeks; range 4–21 weeks), at time when changes in these variables during pregnancy may not yet be marked. Whitworth et al[31] also found that adjustment for plasma albumin had no confounding effect on the observed inverse PFOA–birthweight association (data not shown), for women sampled at mid-pregnancy (17 weeks), although plasma albumin did confound the PFOS–birthweight association, driving it toward the null. It is possible that 17 weeks is still too early to see marked effects of adjustment for plasma albumin on PFOA.

Our findings are consistent with a possible effect of reverse causality/confounding, which would be especially apparent in studies with blood taken later in pregnancy. We found an inverse association between birthweight and serum PFOA when the blood was taken late in pregnancy. In contrast, we found no effect of PFOA on birthweight in studies with blood taken early in pregnancy.

Furthermore, the possibility of reverse causality and/or confounding would be expected to be stronger in studies of low-exposed general populations in which a substantial proportion of the variation in PFOA serum concentration is owing to physiologic differences among individuals rather than differing environmental contact with PFOA.[14,23,25] It may be that reverse causality or confounding play an important role in the findings of an inverse relationship between birthweight and PFOA only in populations in which variation in exposure is in the background range.

It is noteworthy that the only two studies of populations with wide heterogeneity of exposure (Savitz et al[13] and Darrow et al[22]) showed no association between PFOA and birthweight. The mid-Ohio valley populations studied in both these studies had a mean of 86 ng/ml and a median of 26 ng/ml, with a 25th percentile of 13 and a 75th percentile of 68,[32] in measurements made in 2005/2006. Furthermore, both these studies are quite large. All the other published studies are of low-exposed populations, typically with a range of exposure of 0–10 ng/ml so that their effect estimates reflect much more limited variation in exposure. In neither of these two studies in the mid-Ohio valley was maternal PFOA measured primarily or at all during pregnancy, but instead either estimated from a model (Savitz et al[13]) or estimated based on measured PFOA primarily before pregnancy. Hence, these studies are not subject to reverse causality (Savitz et al.[13]), or only very slightly subject to it (Darrow et al.[22]). Both the modeled PFOA in Savitz et al[13] and the measured PFOA just before pregnancy, in Darrow et al,[22] may reflect the etiologic dose ("true" maternal PFOA), rather than blood sampled during pregnancy, especially later in pregnancy. Similarly, regarding confounding by plasma volume/GFR, it would be expected to be associated with relatively small increases in serum PFOA and should not play an important role in these two studies, given the higher PFOA levels present in the mid-Ohio population from a well-defined environmental source.

It is theoretically possible that there is an initial decrease in birthweight with increasing exposures at low doses, followed by a plateau as exposures increase beyond background levels. This "plateau" phenomenon (albeit in the opposite direction) has been observed, for example, in data with hypercholesterolemia and PFOA,[33] in the same highly exposed mid-Ohio valley cohort studied by Darrow et al[22] and Savitz et al[13] and would tend to result in a better fit for a model using log-transformed rather than untransformed PFOA. We re-ran both models, log-transformed and untransformed, for the data (n = 710) reported in Darrow et al[22] and found that both models fit the data about equally well, with a very slight improvement of fit for the linear model (QIC [QIC (a goodness of fit statistic analogous to the AIC (Akaike's Information Criterion)] 728.5 for the linear model vs. QIC of 728.7 for the log-transformed model). An appreciable number (206/710 = 29.0%) of the serum levels in this data set were below 10 ng/ml, suggesting that had a plateau effect been present it would have been detectable in these data.

Funnel plots show some modest suggestion of publication bias with possible omission of studies reporting positive coefficients but low precision. Along these lines, we note that the earlier studies included in the two prior meta-analyses had a stronger inverse relationship between PFOA and birthweight than the nine later studies added for this meta-analysis. It is possible that earlier results showing a stronger inverse effect of PFOA on birthweight were more likely to be published.

There are animal data supporting an inverse effect of PFOA on birthweight. Koustas et al[34] conducted a meta-analysis of animal studies and found that in eight mouse gavage studies, exposure of pregnant mice to increasing concentrations of PFOA was associated with a change in mean pup birth weight of −0.023 g (95% CI = −0.029, −0.016) per 1-unit increase in dose (milligrams per kilogram body weight

per day, equivalent to approximately 12 ppm or 12,000 ng/ml in the serum). Negri et al[6] included animal data in their meta-analyses and found similar results to Koustas et al,[34] based largely on the same set of mouse studies. There are two caveats here. In the animal studies, the effects on birthweight did not begin until animals' estimated serum level were on the order of 12,000 ng/ml, far above almost all human levels even in the high exposed populations in the mid-Ohio valley studies of Darrow et al[22] and Savitz et al.[13] Also, we know that rodent studies and human studies of PFOA may have contradictory results. Animal data show that PFOA decreases cholesterol in rodents.[3] In contrast, there are now abundant data—both cross-sectional and longitudinal[31]—that higher PFOA is associated with increased cholesterol in humans. We know that many effects of PFOA in rodents are owing to binding via the peroxisome proliferator–activated receptor-α (PPAR-α),[3] whereas in humans, this mechanism appears to be far less relevant as these receptors are less frequent in humans. Albrecht et al[35] have found that effects of PFOA on fetal loss in mice are no longer present in mice without the PPAR-α receptor or with humanized PPAR-α receptors. The relevance of animal studies of PFOA and birthweight to humans may be limited.

We have not conducted a formal risk-of-bias analysis to exclude some studies based on design or analysis flaws, as was done in the prior meta-analyses by Johnson et al[5] and Negri et al.[6] Although such risk-of-bias analyses have their advantages in identifying biases, using a quantitative score of bias as a basis to exclude studies ultimately includes subjective components. In the case of PFOA and birthweight, we note that Johnson et al[5] included the Savitz et al[13] study only in sensitivity analyses, and Negri et al[6] excluded it altogether. The very weaknesses used to exclude or downgrade this study, i.e., possible mismeasurement in estimating maternal serum levels from a model rather than via direct measurement, may in fact be a strength, in that the model-based method avoided reverse causality and confounding problems in measuring maternal serum PFOA, and estimates from the model have also been shown to be reasonably well-correlated measured levels in the large mid-Ohio valley population ($r = 0.67$). Furthermore, Avanasi et al[36] have shown in simulations that possible (classical) measurement error in the model (e.g., by using incorrect estimates of PFOA water contamination), which estimated past serum PFOA in the mid-Ohio valley residents, is unlikely to cause marked bias in exposure–response coefficients (i.e., relative risks per unit of exposure) given that the relative ranking of subjects by exposure level will be preserved regardless of relatively small plausible errors in individual serum exposure estimates. The large amount of variation in interindividual exposure estimates means that small errors in intraindividual exposures will have little effect on the relative risks. Weisskopf and Webster[37] have discussed in general the thesis that proxy exposures (e.g., model-based estimates of serum levels) may outperform more proximate measured exposures because they avoid confounding and/or reverse causation.

## CONCLUSIONS

Our meta-analysis including nine new studies, with an almost equal number of births as prior studies, shows a modest inverse association between maternal or cord PFOA and birthweight, with large heterogeneity across studies. The two studies with exposure above background levels showed no association, and similarly, restriction to studies with blood sampling conducted early in pregnancy or shortly before conception showed little or no association. These findings are consistent with confounding and/or reverse causality being responsible for the inverse association seen in studies with low background exposure levels and blood sampling conducted later in pregnancy, when confounding and/or reverse causality are likely to be more important.

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