Birth weight and perfluorooctanesulfonic acid (PFOS): A random-effects meta-regression analysis

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**Supplemental Digital Content**

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**Rationale for protocol amendments**

 In two studies (Lauritzen et al., 2017; Meng et al., 2018) a range of gestational weeks at blood draw was presented, without a mean or median.1,2 In these cases, we took the midpoint and treated it as the median in the meta-regression analyses. For Ashley-Martin et al. (2017), the authors said the specimens were from <14 weeks of gestation (Arbuckle et al., 2013), so we imputed a range of 6-13 weeks and took the midpoint.3,4

 The search algorithm registered with PROSPERO used quotation marks around all phrases, acronyms, or words in the search string. When we did the search, however, no quotation marks were used, which resulted in the identification of one additional study.

 The protocol said we would abstract the most-adjusted coefficient presented for the birth weight-PFOS association. In two instances we took adjusted coefficients that were adjusted like those in nearly all other studies, rather than ones that were further adjusted for glomerular filtration rate (Manzano-Salgado et al., 2017; Sagiv et al., 2018) or serum albumin (Sagiv et al., 2018).5,6 In the case of Manzano-Salgado et al., the less-adjusted coefficients were based on a larger number of subjects, and this was a study with blood drawn early in pregnancy with a fairly narrow range of gestational weeks at blood draw (mean 12, SD 6), we did not expect the adjustment to substantially affect the results (and it did not).5 In the case of Sagiv et al., the further adjusted models had the same number of subjects as those not adjusted for glomerular filtration rate or albumin, and the further adjustment had little effect on the regression coefficients.6 We used the more standard-adjusted results in the analysis for consistency. The median gestational weeks at blood draw in Sagiv et al. was 9, at which point we did not expect the adjustment to substantially affect the results.6

 The original protocol said the algorithmic optimization would be over the range of the 5th – 95th percentiles of the estimated PFOS distribution, at 10 percentile intervals (10 points). Based on the results of the validation substudy described in the main manuscript, we instead performed the algorithmic optimization over the 25th – 75th percentiles of the estimated PFOS distribution, at 10 percentile intervals (6 points).

 The original protocol did not specify whether we were going to use a fixed effects or random effects meta-regression. Based on Borenstein et al.’s recommendations, we decided to use a random effects meta-regression.7

 The original protocol included sensitivity analyses (analyses performed after excluding certain groups of studies), but it did not call for analyses after excluding studies that used cord blood for measurement of PFOS or studies from Asia. Neither did it call for sensitivity analyses where we added 1.26 g/ng/ml to β coefficients from studies using cord serum or plasma, because Verner et al. calculated that use of cord serum or plasma would bias βs by -1.26 g/ng/ml compared with maternal serum measurements at 40 weeks of gestation. Nor did we plan to do a subgroup analysis by continent. It was only after we had analyzed the data that we realized the value of such analyses.

 The original protocol did not include a plan to impute null results for the large study of Buck Louis et al.8 It said we would use the trim and fill method if no heterogeneity was present. However, heterogeneity was present, and it appeared that some small studies with positive associations were missing. Because of that, we felt the imputation of null results for Buck Louis would be a useful adjunct analysis.

**Search algorithm**

 Searches were conducted using the keywords (birth-weight or birth weight or birthweight or reproduction) and (PFOS or PFAS or PFC or fluoroalkyl or fluorocarbon) and were limited to studies published from November 20, 2015 through July 1, 2019. Searches were conducted using the PubMed filters for studies of human subjects published in the English language. Because very recently added publications may not have completed the MEDLINE indexing process in PubMed, they may be inadvertently excluded from searches using filters. To avoid missing these studies, we repeated our searches for January 1, 2019 through July 1, 2019 without the “Humans” and “English” filters.

**Method of re-expression of β coefficients**

 Our method for re-expression of β coefficients (to obtain a coefficient for change in g birthweight per ng/ml PFOS given a coefficient in terms of log-transformed ng/ml PFOS) was a variation on the method described in Steenland et al. (2018).9 The primary motivation for altering their approach was that the distributions of PFOS across studies were much more variable than the distributions of PFOA. While Steenland et al. (2018) were able to choose a range of concentration that was appropriate for all PFOA studies, there was no single range that could be used for all the studies for PFOS, and the range of concentration over which the re-expression was performed had a large effect on the re-expressed β.9 Thus, we needed a method of determining a range of values over which to perform the re-expression that depended on the study-specific distributions of PFOS. The method we used relied on a quantitative estimation of the study-specific distributions of PFOS which is described in a subsequent section (see below). Once the estimated distribution was determined from said procedure, the re-expression was performed within the range of the 25th – 75th percentiles of the PFOS distribution. The re-expressed β coefficient was determined by minimizing the sum of squared differences between the curves generated by the re-expressed β and the log-transformed β at 10 percentile intervals using the optim function in the statistical software package R. While the slope and intercept of the linear association were both optimized in this approach, only the slope (i.e., the β coefficient) was relevant for comparison of the study results.

In several cases, a log-transformed β coefficient was presented in units that were scaled by measures of variance, for example change in g birthweight per standard deviation log-transformed ng/ml PFOS or z-score change in birthweight per log-transformed ng/ml PFOS. In these cases, the unscaled log-transformed β coefficient was retrieved by multiplying or dividing by the measure of variance that was used in the scaling and then the unscaled log-transformed β coefficient was then re-expressed as an untransformed β coefficient.

 The validity of the method was evaluated using studies in which the authors presented associations of birthweight with both untransformed and log-transformed PFOS concentration (see Table 2 in the main report).

**Method of estimating the study-specific distribution of PFOS**

 We assumed that a log-normal distribution was appropriate to describe the study-specific distributions of PFOS. A log-normal distribution is described by two parameters, μ and σ, and these parameters were determined in a standardized fashion.

 When a median and interquartile range (IQR) were presented, we used ln(median) to estimate μ and the ln(75th percentile/25th percentile)/1.349 to estimate σ.55 A variant of this procedure was used when 5th and 95th percentiles rather than quartiles were presented.

 When the geometric mean (GM) and geometric standard deviation (GSD) were presented, we estimated the parameters as μ = ln(GM) and σ = ln(GSD).

 In the case where the arithmetic mean (AM) and standard deviation (ASD) were presented, we first estimated the geometric mean and geometric standard using the equations, $GM=AM/\sqrt{ω}$ and $GSD=exp\left(\sqrt{log⁡(ω)}\right)$, where $ω=1+\left(ASD/AM\right)^{2}$ (Limpert et al. 2001).

 In those instances where a median was presented without usable data on variance (e.g., range), we predicted σ based on μ, using a regression of σ on μ from studies where the median PFOS concentration was > 1 ng/ml. For studies with a median value > 1 ng/ml, the scatterplot clearly showed a linear relation of the two variables (not shown).

**Primer for statistics in meta-analysis**

In general, the goal of a meta-analysis is to calculate a quantitative summary of data about the variable under study, which is our case is a slope (β) relating birth weight to serum concentration of PFOS. The summary “effect” estimate is a weighted average of study results. The summary effect estimate can be either a fixed-effects summary or a random-effects summary. The fixed- and random-effects summaries differ in how the weighted average is calculated.7 Technical details are described in the next paragraph.

Assume we have reported regression coefficients yi from n studies, where i = 1, …, n, the number of studies. With each reported regression coefficient yi we have the reported standard error of yi, or SE(yi), the within-study sampling error. In a fixed-effects meta-analysis, we assume that each of the studies included are estimating the same underlying parameter y. In some settings this assumption might be plausible -- for example if the studies have all been conducted in the same population, they have used the same inclusion criteria, the treatments have been given in the same way, and outcomes have been measured consistently. The fixed-effects meta-analytic summary of the regression coefficients across studies can be written as a model:

yi=β0+*e*,

where β0=Σ yi∙SE(yi)2/Σ SE(yi)2, the summation is across studies, and *e*∼*N*(0,*v*), with *v* = 1/ Σ SE(yi)2. In the fixed-effects approach, the different effect estimates are attributed purely to random sampling error.

In contrast, in a random-effects meta-analysis, we assume that each study is estimating a study-specific true effect *u*i + β0, where β0 is an overall weighted mean of regression coefficients across studies and *u*i is the study-specific difference from the overall mean. Interest then lies in estimating the mean β0 = E(y) and variance Var(*u*i) = τ2 of these true effect sizes across the population of potential studies. In a random-effects meta-analysis, the observed heterogeneity in the estimates yi is attributed to two sources: 1) between-study heterogeneity in true effects, and 2) within-study sampling error. The mixed-effects meta-analysis model can be written as:

yi=β0+*u*i+*e*i,

where i indexes the study result, *u*i∼*N*(0,*τ*2) and *e*i∼*N*(0,*v*i), and *v*i are the (approximately) known sampling variances of the observed effect size estimates (squared values of standard errors of regression coefficients). The formula and weights used in calculating a random-effects summary estimate are different than in a fixed effects estimate, and are presented in Borenstein et al.7

Inclusion of covariates in a random-effect models yields is a meta-regression model, which can be written as:

yi=β0+β1xi1+β2xi2+…+βpxip+*u*i+*e*i,

where 1 … p index the number of covariates in the meta-regression model. The covariates can be fixed effect or random effects terms; in our application they are fixed-effects. In the models above, the β coefficients have a Z distribution and the standard errors of the coefficients for the covariates are used as in a standard regression model to evaluate whether the coefficients are statistically precise. After fitting a meta-regression model, the coefficients can be interpreted as follows. β0 is the overall summary slope when all the covariates have a value of zero. If, e.g., the only covariate in the model is weeks of gestation at blood draw, then the interpretation of β0 is the average slope of the birth weight-PFOS association at the beginning of pregnancy; β1 is the amount that the average slope increases per week of gestation. Thus, the average slope after 40 weeks of gestation is β0+40∙β1. β1 … βp are effect modification terms in meta-regression – they indicate how much the outcome-exposure association (slope in our case) changes according to level of the covariate.

 Tau is calculated as ((Q – df)/C)0.5, where Q = ΣWi∙(Yi-M)2, W is the study weight, Yi is the study effect size, M is the summary random effect, df = the number of studies - 1, and C = ΣWi – ΣWi2/ΣWi.



Unique records identified through PubMed

n=191

Records excluded n=164

Animal/cell/genetic (n=21)

Not a study (letter to the editor, case report) (n=5)

Wrong exposure (not PFOS or measured after birth) (n=24)

Wrong outcome (not birthweight) (n=108)

Meta/review (otherwise relevant) (n=6)



Records screened

n=191

Full-text articles excluded n=7

Same cohort included in another study (n=4)

PFOS results not reported because not statistically significant; include in sensitivity analyses (n=2)

Unable to re-express coefficient in g/ng/mL (n=1)



Full-text articles assessed for eligibility

n=27

Reports identified by search that were already being included because they had been in previous meta-analyses (n=10)

Reports identified by search (n=20)



eFigure 1. Flowchart showing how the studies identified by the PubMed search were classified according to inclusion, exclusion, and whether they had been included in previous meta-analyses of birth weight and PFOS.

New reports identified by search (n=10)



eFigure 2. Funnel plot for meta-analysis of birth weight in relation to serum concentration of PFAS

eTable 1. List of studies included in previous meta-analyses and newer studies identified by the literature searcha

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Previous meta-analyses | Not in Previous meta-analysesb |
|  |  | Johnsonet al 2014 | Verneret al 2014 | Negriet al 2014 | Steenlandet al 2014 |
| **Included Studies** | **Year** |  |  |  |  |  |
| Apelberg10 | 2007 | x | x | x | x |  |
| Monroy11 | 2008 |  |  | x |  |  |
| Washino12 | 2009 | x | x | x | x |  |
| Hamm13 | 2010 | x | x | x | x |  |
| Chen14 | 2012 | x | x | x | x |  |
| Maisonet15 | 2012 | x | x | x | x |  |
| Whitworth16 | 2012 | x | x | x | x |  |
| Darrow17 | 2013 |  |  | x | x |  |
| Robledo18 | 2015 |  |  | x | x |  |
| Bach19 | 2016 |  |  | x | x |  |
| Callan20 | 2016 |  |  |  | x |  |
| Govarts21 | 2016 |  |  |  |  | x |
| Kwon22 | 2016 |  |  |  |  | x |
| Lee23 | 2016 |  |  | x | x |  |
| Lenters24 | 2016 |  |  | x | x |  |
| Ashley-Martin3 | 2017 |  |  |  |  | x |
| Chen14 | 2017 |  |  |  | x |  |
| Lauritzen1 | 2017 |  |  |  |  | x |
| Li25 | 2017 |  |  |  | x |  |
| Lind26 | 2017 |  |  |  |  | x |
| Manzano-Salgado5 | 2017 |  |  |  | x |  |
| Shi27 | 2017 |  |  |  | x |  |
| Starling28 | 2017 |  |  |  | x |  |
| Valvi29 | 2017 |  |  |  |  | x |
| Cao30 | 2018 |  |  |  |  | x |
| Meng2 | 2018 |  |  |  |  | x |
| Sagiv6 | 2018 |  |  |  | x |  |
| Marks31 | 2019 |  |  |  |  | x |
| Wang32 | 2019 |  |  |  |  | x |

a Johnson et al. also include Fromme et al. 2010, Kim et al. 2011, and Fei et al. 2007.33–36 Johnson et al. likely contacted the original authors to get results for PFOA from Fromme et al. 2010 and Kim et al. 2011. Fei et al. 2007 was superceded by Meng et al. 2018.2,36 Verner et al. and Negri et al. also included Fei et al. 2007.36–38 Steenland et al. also included Fei et al. 2007, Fromme et al. 2010, Kim et al. 2011, Wu et al. 2012, Wang et al. 2016, and Minatoya et al. 2017.9,34–36,39–41 See manuscript for an explanation for why we did not include these studies.

b These were studies identified as eligible by our literature search.

eTable 2. Screened studies that were excluded and reason they were irrelevant or excluded

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | If not a relevant study, why? -> Animal/cell | If not a relevant study, why? -> Not a study (letter to the editor, case report, opinion/commentary) | If not a relevant study, why? -> Wrong exposure (not PFOS) | If not a relevant study, why? -> Wrong outcome (not birthweight) | If not a relevant study, why? -> Not health (studies of attitudes, beliefs, other non-health outcomes) | If not a relevant study, why? -> Meta/Review (only potentially relevant reviews related to exposure and endpoint of interest) |
| **Abuzeid,​ OM.,​ Hebert,​ J.,​ Ashraf,​ M.,​ Mitwally,​ M.,​ Diamond,​ MP.,​ Abuzeid,​ MI.** (2018). Pediatric Foley Catheter Placement After Operative Hysteroscopy Does Not Cause Ascending Infection. *Journal of minimally invasive gynecology*,​ 25(1). |   |   | Wrong exposure (not PFOS) |   |   |   |
| **Agrawal,​ J.,​ Ludwig,​ B.,​ Roy,​ B.,​ Dwivedi,​ Y.** (2019). Chronic Testosterone Increases Impulsivity and Influences the Transcriptional Activity of the Alpha-2A Adrenergic Receptor Signaling Pathway in Rat Brain. *Molecular neurobiology*,​ 56(6). | Animal/cell |   |   |   |   |   |
| **Ashley-Martin,​ J.,​ Dodds,​ L.,​ Arbuckle,​ TE.,​ Morisset,​ AS.,​ Fisher,​ M.,​ Bouchard,​ MF.,​ Shapiro,​ GD.,​ Ettinger,​ AS.,​ Monnier,​ P.,​ Dallaire,​ R.,​ Taback,​ S.,​ Fraser,​ W.** (2016). Maternal and Neonatal Levels of Perfluoroalkyl Substances in Relation to Gestational Weight Gain. *International journal of environmental research and public health*,​ 13(1). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Avanasi,​ R.,​ Shin,​ HM.,​ Vieira,​ VM.,​ Bartell,​ SM.** (2016). Variability and epistemic uncertainty in water ingestion rates and pharmacokinetic parameters,​ and impact on the association between perfluorooctanoate and preeclampsia in the C8 Health Project population. *Environmental research*,​ 146. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Avanasi,​ R.,​ Shin,​ HM.,​ Vieira,​ VM.,​ Bartell,​ SM.** (2016). Impacts of geocoding uncertainty on reconstructed PFOA exposures and their epidemiological association with preeclampsia. *Environmental research*,​ 151. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Avanasi,​ R.,​ Shin,​ HM.,​ Vieira,​ VM.,​ Savitz,​ DA.,​ Bartell,​ SM.** (2016). Impact of Exposure Uncertainty on the Association between Perfluorooctanoate and Preeclampsia in the C8 Health Project Population. *Environmental health perspectives*,​ 124(1). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bach,​ C.,​ Matthiesen,​ B.,​ Olsen,​ .,​ Henriksen,​ B.** (2018). Conditioning on Parity in Studies of Perfluoroalkyl Acids and Time to Pregnancy: An Example from the Danish National Birth Cohort. *Environmental health perspectives*,​ 126(11). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bach,​ CC.,​ Bech,​ BH.,​ Nohr,​ EA.,​ Olsen,​ J.,​ Matthiesen,​ NB.,​ Bossi,​ R.,​ Uldbjerg,​ N.,​ Bonefeld-Jørgensen,​ EC.,​ Henriksen,​ TB.** (2016). Response to letter to the editor regarding "Serum perfluoroalkyl acids and time to pregnancy in nulliparous women". *Environmental research*,​ 147. |   | Not a study (letter to the editor, case report, opinion/commentary) |   |   |   |   |
| **Bach,​ CC.,​ Vested,​ A.,​ Jørgensen,​ KT.,​ Bonde,​ JP.,​ Henriksen,​ TB.,​ Toft,​ G.** (2016). Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review. *Critical reviews in toxicology*,​ 46(9). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bakhireva,​ LN.,​ Garrison,​ L.,​ Shrestha,​ S.,​ Sharkis,​ J.,​ Miranda,​ R.,​ Rogers,​ K.** (2018). Challenges of diagnosing fetal alcohol spectrum disorders in foster and adopted children. *Alcohol (Fayetteville,​ N.Y.)*,​ 67. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Ballesteros,​ V.,​ Costa,​ O.,​ Iñiguez,​ C.,​ Fletcher,​ T.,​ Ballester,​ F.,​ Lopez-Espinosa,​ MJ.** (2017). Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. *Environment international*,​ 99. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Barrett,​ CE.,​ Kable,​ JA.,​ Madsen,​ TE.,​ Hsu,​ CC.,​ Coles,​ CD.** . The Use of Functional Near-Infrared Spectroscopy to Differentiate Alcohol-Related Neurodevelopmental Impairment. *Developmental neuropsychology*,​ 44(2). |   |   | Wrong exposure (not PFOS) |   |   |   |
| **Bell,​ EM.,​ Yeung,​ EH.,​ Ma,​ W.,​ Kannan,​ K.,​ Sundaram,​ R.,​ Smarr,​ MM.,​ Buck Louis,​ GM.** (2018). Concentrations of endocrine disrupting chemicals in newborn blood spots and infant outcomes in the upstate KIDS study. *Environment international*,​ 121(Pt 1). |   |   | Wrong exposure (not PFOS) |   |   |   |
| **Berg,​ V.,​ Nøst,​ TH.,​ Pettersen,​ RD.,​ Hansen,​ S.,​ Veyhe,​ AS.,​ Jorde,​ R.,​ Odland,​ JØ.,​ Sandanger,​ TM.** (2017). Persistent Organic Pollutants and the Association with Maternal and Infant Thyroid Homeostasis: A Multipollutant Assessment. *Environmental health perspectives*,​ 125(1). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bjerregaard-Olesen,​ C.,​ Bach,​ CC.,​ Long,​ M.,​ Ghisari,​ M.,​ Bech,​ BH.,​ Nohr,​ EA.,​ Henriksen,​ TB.,​ Olsen,​ J.,​ Bonefeld-Jørgensen,​ EC.** (2016). Determinants of serum levels of perfluorinated alkyl acids in Danish pregnant women. *International journal of hygiene and environmental health*,​ 219(8). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bjerregaard-Olesen,​ C.,​ Bach,​ CC.,​ Long,​ M.,​ Ghisari,​ M.,​ Bossi,​ R.,​ Bech,​ BH.,​ Nohr,​ EA.,​ Henriksen,​ TB.,​ Olsen,​ J.,​ Bonefeld-Jørgensen,​ EC.** (2016). Time trends of perfluorinated alkyl acids in serum from Danish pregnant women 2008-2013. *Environment international*,​ 91. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bjerregaard-Olesen,​ C.,​ Bossi,​ R.,​ Liew,​ Z.,​ Long,​ M.,​ Bech,​ BH.,​ Olsen,​ J.,​ Henriksen,​ TB.,​ Berg,​ V.,​ Nøst,​ TH.,​ Zhang,​ JJ.,​ Odland,​ JØ.,​ Bonefeld-Jørgensen,​ EC.** (2017). Maternal serum concentrations of perfluoroalkyl acids in five international birth cohorts. *International journal of hygiene and environmental health*,​ 220(2 Pt A). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Bjerregaard-Olesen,​ C.,​ Ghisari,​ M.,​ Bonefeld-Jørgensen,​ EC.** (2016). Activation of the estrogen receptor by human serum extracts containing mixtures of perfluorinated alkyl acids from pregnant women. *Environmental research*,​ 151. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Boronat,​ S.,​ Sánchez-Montañez,​ A.,​ Gómez-Barros,​ N.,​ Jacas,​ C.,​ Martínez-Ribot,​ L.,​ Vázquez,​ E.,​ Del Campo,​ M.** (2017). Correlation between morphological MRI findings and specific diagnostic categories in fetal alcohol spectrum disorders. *European journal of medical genetics*,​ 60(1). |   |   | Wrong exposure (not PFOS) |   |   |   |
| **Braun,​ JM.,​ Chen,​ A.,​ Romano,​ ME.,​ Calafat,​ AM.,​ Webster,​ GM.,​ Yolton,​ K.,​ Lanphear,​ BP.** (2016). Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: The HOME study. *Obesity (Silver Spring,​ Md.)*,​ 24(1). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Caserta,​ D.,​ Pegoraro,​ S.,​ Mallozzi,​ M.,​ Di Benedetto,​ L.,​ Colicino,​ E.,​ Lionetto,​ L.,​ Simmaco,​ M.** (2018). Maternal exposure to endocrine disruptors and placental transmission: a pilot study. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*,​ 34(11). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Chalkiadaki,​ K.,​ Velli,​ A.,​ Kyriazidis,​ E.,​ Stavroulaki,​ V.,​ Vouvoutsis,​ V.,​ Chatzaki,​ E.,​ Aivaliotis,​ M.,​ Sidiropoulou,​ K.** (2019). Development of the MAM model of schizophrenia in mice: Sex similarities and differences of hippocampal and prefrontal cortical function. *Neuropharmacology*,​ 144. | Animal/cell |   |   |   |   |   |
| **Chen,​ F.,​ Yin,​ S.,​ Kelly,​ BC.,​ Liu,​ W.** (2017). Chlorinated Polyfluoroalkyl Ether Sulfonic Acids in Matched Maternal,​ Cord,​ and Placenta Samples: A Study of Transplacental Transfer. *Environmental science & technology*,​ 51(11). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Chen,​ F.,​ Yin,​ S.,​ Kelly,​ BC.,​ Liu,​ W.** (2017). Isomer-Specific Transplacental Transfer of Perfluoroalkyl Acids: Results from a Survey of Paired Maternal,​ Cord Sera,​ and Placentas. *Environmental science & technology*,​ 51(10). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Chen,​ G.,​ Xu,​ LL.,​ Huang,​ YF.,​ Wang,​ Q.,​ Wang,​ BH.,​ Yu,​ ZH.,​ Shi,​ QM.,​ Hong,​ JW.,​ Li,​ J.,​ Xu,​ LC.** (2018). Prenatal Exposure to Perfluorooctane Sulfonate impairs Placental Angiogenesis and Induces Aberrant Expression of LncRNA Xist. *Biomedical and environmental sciences : BES*,​ 31(11). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Chen,​ J.,​ Wang,​ X.,​ Ge,​ X.,​ Wang,​ D.,​ Wang,​ T.,​ Zhang,​ L.,​ Tanguay,​ RL.,​ Simonich,​ M.,​ Huang,​ C.,​ Dong,​ Q.** (2016). Chronic perfluorooctanesulphonic acid (PFOS) exposure produces estrogenic effects in zebrafish. *Environmental pollution (Barking,​ Essex : 1987)*,​ 218. | Animal/cell |   |   |   |   |   |
| **Chen,​ L.,​ Deng,​ W.,​ Palacios,​ I.,​ Inglessis-Azuaje,​ I.,​ McMullin,​ D.,​ Zhou,​ D.,​ Lo,​ EH.,​ Buonanno,​ F.,​ Ning,​ M.** (2016). Patent foramen ovale (PFO),​ stroke and pregnancy. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research*,​ 64(5). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Chen,​ Q.,​ Huang,​ R.,​ Hua,​ L.,​ Guo,​ Y.,​ Huang,​ L.,​ Zhao,​ Y.,​ Wang,​ X.,​ Zhang,​ J.** (2018). Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study. *Environmental health : a global access science source*,​ 17(1). |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Chen,​ Q.,​ Zhang,​ X.,​ Zhao,​ Y.,​ Lu,​ W.,​ Wu,​ J.,​ Zhao,​ S.,​ Zhang,​ J.,​ Huang,​ L.** (2019). Prenatal exposure to perfluorobutanesulfonic acid and childhood adiposity: A prospective birth cohort study in Shanghai,​ China. *Chemosphere*,​ 226. |   |   |   | Wrong outcome (not birthweight) |   |   |
| **Cheng,​ DT.,​ Meintjes,​ EM.,​ Stanton,​ ME.,​ Dodge,​ NC.,​ Pienaar,​ M.,​ Warton,​ CMR.,​ Desmond,​ JE.,​ Molteno,​ CD.,​ Peterson,​ BS.,​ Jacobson,​ JL.,​ Jacobson,​ SW.** (2017). Functional MRI of Human Eyeblink Classical Conditioning in Children with Fetal Alcohol Spectrum Disorders. *Cerebral cortex (New York,​ N.Y. : 1991)*,​ 27(7). |   |   | Wrong exposure (not PFOS) |   |   |   |
| **Conley,​ JM.,​ Lambright,​ CS.,​ Evans,​ N.,​ Strynar,​ MJ.,​ McCord,​ J.,​ McIntyre,​ BS.,​ Travlos,​ GS.,​ Cardon,​ MC.,​ Medlock-Kakaley,​ E.,​ Hartig,​ PC.,​ Wilson,​ VS.,​ Gray,​ LE.** (2019). Adverse Maternal,​ Fetal,​ and Postnatal Effects of Hexafluoropropylene Oxide Dimer Acid (GenX) from Oral Gestational Exposure in Sprague-Dawley Rats. *Environmental health perspectives*,​ 127(3). | Animal/cell |   |   |   |   |   |
| **Coperchini,​ F.,​ Awwad,​ O.,​ Rotondi,​ M.,​ Santini,​ F.,​ Imbriani,​ M.,​ Chiovato,​ L.** (2017). Thyroid disruption by perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). *Journal of endocrinological investigation*,​ 40(2). |   |   |   | Wrong outcome (not birthweight) |   |   |
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eTable 3. Results of fitting random-effects meta-regression models evaluating modification of birth weight-PFOS association by 6 factors

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  | 95% CI |  |
| Model | Covariate | Coefficient | Lower bound | Upper bound | p |
| 1  | Intercept | 1.38 | -1.38 | 4.14 | 0.33 |
|  | Blood draw (w) | -0.23 | -0.36 | -0.11 | 0.0003 |
|  | Adj. for gest age | -2.30 | -5.64 | 1.03 | 0.18 |
| 2 | Intercept | 1.79 | -1.95 | 5.52 | 0.35 |
|  | Blood draw (w) | -0.23 | -0.36 | -0.10 | 0.0005 |
|  | Adj. for parity | -1.72 | -5.70 | 2.26 | 0.40 |
| 3 | Intercept | 0.55 | -3.99 | 5.08 | 0.81 |
|  | Blood draw (w) | -0.24 | -0.38 | -0.11 | 0.0004 |
|  | Median PFOS | 0.01 | -0.20 | 0.22 | 0.94 |
| 4 | Intercept | 1.36 | -1.82 | 4.53 | 0.40 |
|  | Blood draw (w) | -0.24 | -0.38 | -0.11 | 0.0002 |
|  | Spread in Timing | -0.09 | -0.32 | 0.14 | 0.44 |
| 5 | Intercept | 0.62 | -2.97 | 4.20 | 0.73 |
|  | Blood draw (w) | -0.25 | -0.39 | -0.10 | 0.0009 |
|  | Mean birthweight | 0.00 | -0.00 | 0.00 | 0.96 |
| 6 | Intercept | 1.52 | -1.96 | 5.00 | 0.39 |
|  | Blood draw (w) | -0.27 | -0.42 | -0.12 | 0.0004 |
|  | Term Only | -1.73 | -6.49 | 3.04 | 0.48 |
| 7 | Intercept | 0.20 | -3.26 | 3.66 | 0.91 |
|  | Blood draw (w) | -0.24 | -0.38 | -0.11 | 0.0006 |
|  | Re-expressed β | 1.05 | -2.61 | 4.72 | 0.57 |

**Model 1 – Gestational Age:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero -** Q = 15.82, df = 2, p = 0.0004

**Goodness of fit: Test that unexplained variance is zero - T**au² = 5.5717, Tau = 2.3604, I² = 42.36%, Q = 50.31, df = 29, p = 0.0084

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 -** R² analog = 0.42

**Model 2 – Parity:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero -** Q = 14.38, df = 2, p = 0.0008

**Goodness of fit: Test that unexplained variance is zero -** Tau² = 6.1860, Tau = 2.4872, I² = 46.26%, Q = 53.97, df = 29, p = 0.0033

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 -** R² analog = 0.35

**Model 3 – Median PFOS Concentration:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero -** Q = 13.25, df = 2, p = 0.0013

**Goodness of fit: Test that unexplained variance is zero -** Tau² = 7.0729, Tau = 2.6595, I² = 47.28%, Q = 55.00, df = 29, p = 0.0025

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 –** R² analog = 0.26

**Model 4 – Spread in Timing of Blood Draw Used for PFOS Measurement:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero -** Q = 13.95, df = 2, p = 0.0009

**Goodness of fit: Test that unexplained variance is zero -** Tau² = 6.8273, Tau = 2.6129, I² = 47.46%, Q = 55.20, df = 29, p = 0.0024

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 -** R² analog = 0.29

**Model 5 – Mean Birth Weight in Study Population:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero** Q = 13.37, df = 2, p = 0.0012

**Goodness of fit: Test that unexplained variance is zero -** Tau² = 6.8020, Tau = 2.6081, I² = 46.93%, Q = 54.64, df = 29, p = 0.0027

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 -** R² analog = 0.29

**Model 6 – Results of Variation in Analysis Term:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero -** Q = 13.04, df = 2, p = 0.0015

**Goodness of fit: Test that unexplained variance is zero -** Tau² = 8.8058, Tau = 2.9675, I² = 47.46%, Q = 55.19, df = 29, p = 0.0024

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 -** R² analog = 0.08

**Model 7 – Re-expression Needed for Coefficient Relating Birth Weight to log PFOS Concentration:**

**Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero -** Q = 13.07, df = 2, p = 0.0015

**Goodness of fit: Test that unexplained variance is zero -** Tau² = 8.2538, Tau = 2.8729, I² = 47.27%, Q = 54.99, df = 29, p = 0.0025

**Comparison of Model 1 with the null model**

**Total between-study variance (intercept only) -** Tau² = 9.5795, Tau = 3.0951, I² = 58.39%, Q = 74.50, df = 31, p = 0.0000

**Proportion of total between-study variance explained by Model 1 -** R² analog = 0.14

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