PFAS Developmental Meta-Analysis

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Contents

Background

The purpose of this analysis is to investigate the relationship between PFNA exposure during pregnancy and birth weight. Meta-analytic techniques were used to summarize epidemiological findings from 27 studies.

Overall Meta-Analysis

A random effects model was used to estimate the pooled effect of PFNA exposure on birth weight, capturing any between-study heterogeneity. The model employs weighted estimation with inverse-variance weights.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Overall	27	-32.9	7.2	-47	-18.7	0	35.93	0.05

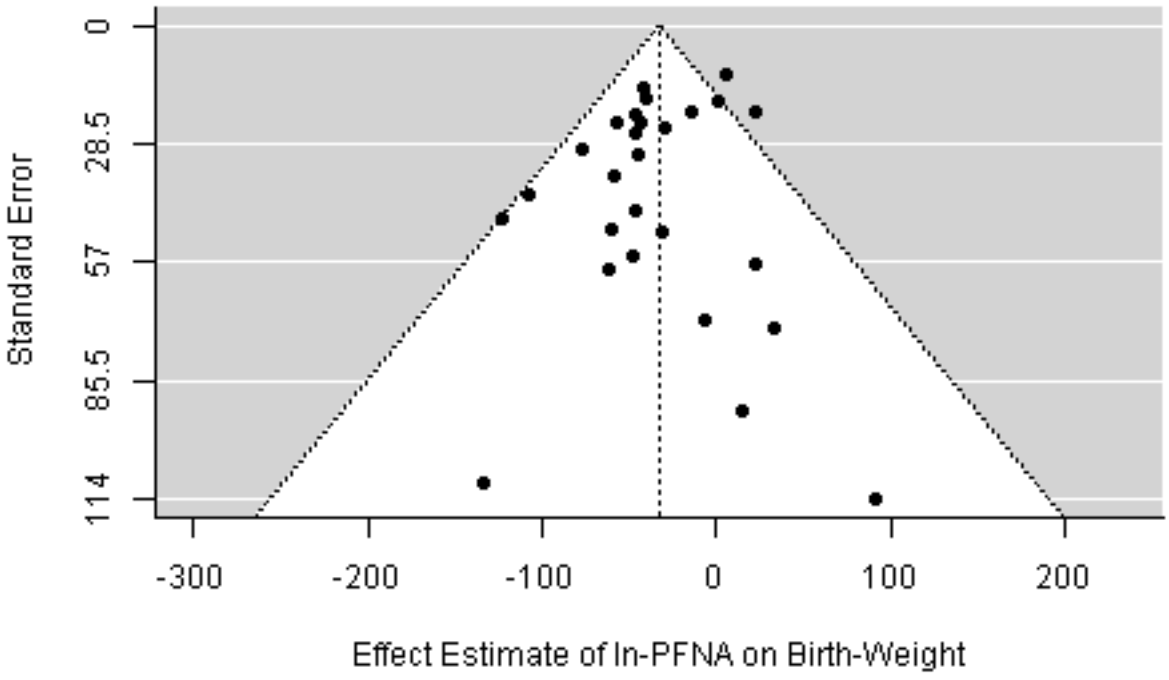
Leave-One-Out Analyis: Assessing heterogeneity

Results indicate that dropping Chen, 2012 leads to the lowest I2, 20.72%. Sensitivity analysis pertaining to dropping Chen, 2012 are carried out in the sections below.

Study	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
Bach, 2016	-35.80	7.04	-5.08	0e+00	-49.60	-21.99	32.54	0.14	309.67	28.97	1.41
Buck Louis, 2018	-35.30	7.46	-4.73	0e+00	-49.93	-20.68	36.22	0.07	403.28	34.28	1.52
Manzano-Salgado, 2017	-34.37	7.64	-4.50	1e-05	-49.34	-19.40	38.20	0.04	456.96	37.56	1.60
Sagiv, 2018	-32.66	7.71	-4.23	2e-05	-47.78	-17.54	37.91	0.05	466.22	37.37	1.60
Shoaff, 2018	-33.20	7.30	-4.54	1e-05	-47.51	-18.88	38.49	0.04	422.86	37.27	1.59
Starling, 2017	-31.48	7.43	-4.23	2e-05	-46.05	-16.91	36.79	0.06	412.91	35.61	1.55
Valvi, 2017	-32.39	7.32	-4.42	1e-05	-46.75	-18.04	38.08	0.05	419.10	36.90	1.58
Chen, 2012	-36.20	6.85	-5.28	0e+00	-49.63	-22.77	28.54	0.28	226.33	20.72	1.26
Gyllenhammar, 2018	-30.64	7.11	-4.31	2e-05	-44.58	-16.71	34.57	0.10	359.73	33.30	1.50
Kwon, 2016	-30.78	7.23	-4.26	2e-05	-44.94	-16.62	35.63	0.08	374.26	33.82	1.51
Lenters, 2016	-32.51	7.57	-4.29	2e-05	-47.35	-17.66	38.04	0.05	448.57	37.51	1.60
Meng, 2018	-33.36	7.61	-4.38	1e-05	-48.27	-18.44	38.55	0.04	460.42	38.21	1.62
Callan, 2016	-33.20	7.28	-4.56	1e-05	-47.46	-18.93	38.37	0.04	419.43	37.14	1.59
Li, 2017	-32.53	7.46	-4.36	1e-05	-47.16	-17.90	38.20	0.04	436.87	37.45	1.60
Shi, 2017	-33.76	7.32	-4.61	0e+00	-48.11	-19.40	37.81	0.05	423.74	37.24	1.59
Xu, 2019	-32.44	7.23	-4.49	1e-05	-46.61	-18.27	37.63	0.05	409.15	36.58	1.58
Hjermitslev, 2020	-32.09	7.37	-4.35	1e-05	-46.54	-17.65	37.74	0.05	419.72	36.69	1.58
Kashino, 2020	-32.46	7.74	-4.19	3e-05	-47.63	-17.29	37.49	0.05	465.69	36.75	1.58
Wikstrm, 2020	-32.27	7.58	-4.26	2e-05	-47.13	-17.41	37.74	0.05	445.43	37.13	1.59
Chen, 2021	-32.72	7.32	-4.47	1e-05	-47.08	-18.36	38.43	0.04	422.84	37.17	1.59
Lind, 2017	-33.55	7.30	-4.60	0e+00	-47.85	-19.25	37.88	0.05	421.43	37.20	1.59
Robledo, 2015	-33.40	7.26	-4.60	0e+00	-47.64	-19.16	37.49	0.05	417.59	37.06	1.59
Wang, 2016	-33.02	7.36	-4.49	1e-05	-47.44	-18.59	38.56	0.04	428.95	37.46	1.60
Luo, 2021	-30.69	7.09	-4.33	2e-05	-44.59	-16.79	34.15	0.10	359.40	33.37	1.50
Yao, 2021	-32.68	7.37	-4.44	1e-05	-47.12	-18.24	38.38	0.04	427.38	37.30	1.59
Workman, 2019	-32.51	7.30	-4.45	1e-05	-46.82	-18.20	38.20	0.04	417.80	36.92	1.59
Chang, 2022	-32.38	7.52	-4.30	2e-05	-47.13	-17.64	37.98	0.05	441.25	37.34	1.60

Publication Bias

The Egger's regression test did not detect a statistically significant relationship between the observed effect sizes and their standard errors ($p = 0.3042$), indicating no evidence of funnel plot asymmetry due to publication bias. The funnel plot is displayed below.



Stratified Analyses

In addition to the overall meta-analysis, the studies are also examined according to the following stratification: study confidence, sample timing.

Study Confidence

In this section, the studies are examined by confidence levels - low, medium, high, or medium and high combined. Pooled effects are calculated and statistical differences across strata are considered.

```
## The following objects are masked from betas (pos = 3):
##
##     BetaLnNgml, BetaLnNgmlLCL, BetaLnNgmlSE, BetaLnNgmlUCL, BetaNgml,
##     BetaNgmlLCL, BetaNgmlSE, BetaNgmlUCL, BetaOrig, BetaOrigLCL,
##     BetaOrigUCL, BetaUnit, Bin, Confidence, GA, Population,
##     Sample.Size, Sampling_1, Sampling_2, Sampling_3, Study
```

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	High	12	-28.0	10.8	-49.0	-6.9	0.01	38.80	0.11
intrcpt1	Medium	10	-39.0	11.6	-61.8	-16.3	0.00	48.09	0.03
intrcpt2	Low	5	-36.9	23.5	-82.9	9.1	0.12	0.00	0.66

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt3	High+Medium	22	-32.9	7.7	-48.0	-17.8	0.00	42.22	0.02

Results from the hypothesis test results for any significant differences across strata:

- For all three levels, High, Medium and Low: p = 0.7733.
- For High + Medium and Low: p = 0.8718.

Sample Timing

In this approach, the strata have the following definitions:

- Early: first trimester only, mixture of first and second trimester.
- Late: second trimester only, mixture of second and third trimester, third trimester only.
- Post: at or after birth.

Pooled effects are calculated and statistical differences across strata are considered.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Early	11	-22.0	9.2	-40.1	-4.0	0.02	25.91	0.26
intrcpt1	Late	10	-48.4	9.9	-67.7	-29.0	0.00	0.00	0.91
intrcpt2	Post	6	-42.9	23.0	-88.0	2.2	0.06	63.08	0.01

Results from the hypothesis test for any differences across strata: p = 0.1407.

Meta-Regression

To further examine the impact of sampling on the relationship between PFNA and birth weight, a continuous approach for the analysis of sample timing is employed. A meta-regression on a measure of centrality of sample timing is carried out and a pooled effect is presented. Measures of centrality include mean, median, range midpoints, weighted mean of means/medians/midpoints and exact numbers. The results estimate that the effect of PFNA on birth weight changes by -0.8642 g per unit increase in the measure of centrality of gestational age at sample timing (95% CI: -2.05, 0.32).

Sensitivity Analyses

Leave-One-Out Sensitivity Analysis

In this section, the robustness of the overall, confidence and sampling timing meta-analyses is examined with regards to dropping the study identified by the Leave-One-Out analysis above. Each analysis is run without the study, Chen, 2012.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Overall	26	-36.2	6.9	-49.6	-22.8	0	20.72	0.28
intrcpt1	Medium	9	-47.8	9.1	-65.6	-30.1	0	0.00	0.71

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt2	High+Medium	21	-36.5	7.3	-50.9	-22.1	0	27.03	0.16
intrcpt3	post	5	-64.5	17.9	-99.5	-29.5	0	0.00	0.36

Two-Strata Approach for the Analysis of Sample Timing

In this section, the three-strata approach is compared to a two-strata approach, wherein the "late" and "post" strata are collapsed into a single "late+post" strata. Pooled effects are calculated and statistical differences across strata are considered.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Late+Post	16	-44.5	10.9	-65.9	-23	0	40.02	0.05

Results from the hypothesis test for any differences between "early" and "late+post" strata: p = 0.1171.

Log-based studies only

This analysis examines the sensitivity of the overall pooled estimate to using only the 24 log-based studies, excluding those needed re-expression, i.e., Bach, 2016, Sagiv, 2018, Shoaff, 2018.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Overall	24	-36.2	7.6	-51.2	-21.3	0	31.78	0.1

Random vs. fixed effect analyses

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Random	27	-32.9	7.2	-47.0	-18.7	0	35.93	0.05
intrcpt1	Fixed	27	-26.8	5.1	-36.8	-16.8	0	32.58	0.05

Re-expression to Natural Scale

In this section, each model is re-run using data re-expressed to the natural scale as a sensitivity test to the findings on the log-scale.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Overall	27	-37.0	10.2	-56.9	-17.0	0.00	50.74	0.00
intrcpt1	High	12	-37.7	15.9	-69.0	-6.5	0.02	44.04	0.04
intrcpt2	Medium	10	-35.1	13.9	-62.4	-7.9	0.01	60.94	0.00
intrcpt3	Low	5	-163.5	104.2	-367.8	40.8	0.12	0.00	0.66
intrcpt4	High+Medium	22	-35.4	10.1	-55.1	-15.7	0.00	54.56	0.00
intrcpt5	Early	11	-25.7	12.6	-50.4	-1.1	0.04	29.39	0.13
intrcpt6	Late	10	-49.0	13.7	-75.9	-22.1	0.00	10.82	0.30
intrcpt7	Post	6	-186.3	95.4	-373.2	0.6	0.05	66.25	0.00
intrcpt8	Late+Post	16	-72.7	22.6	-117.1	-28.3	0.00	77.96	0.00

Additional Sensitivity Analyses

For PFNA, sensitivity testing was required regarding the study, Kwon, 2016, which did not report the log base of their estimates. Firstly, the medium confidence strata is examined for sensitively to including Kwon. Estimates are provided below.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	Medium w/o Kwon, 2016	9	-34.6	11.8	-57.8	-11.5	0	45.92	0.04

Additionally, sensitivity was explored with regards to different log bases of the Kwon, 2016 study. Estimates are provided below.

	Model	N	Estimate	SE	LCL	UCL	PVal	I2	Q_PVal
intrcpt	log_e	27	-32.9	7.2	-47.0	-18.7	0	35.93	0.05
intrcpt1	log_2	27	-33.0	7.4	-47.5	-18.6	0	36.50	0.04
intrcpt2	log_10	27	-30.6	6.6	-43.6	-17.6	0	32.29	0.09

Supplemental