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THE GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER

WASHINGTON DC

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Baltimore THREE Study

Methods



The Baltimore THREE study is designed to investigate prenatal exposure to environmental chemicals and how this may affect newborn growth and development.

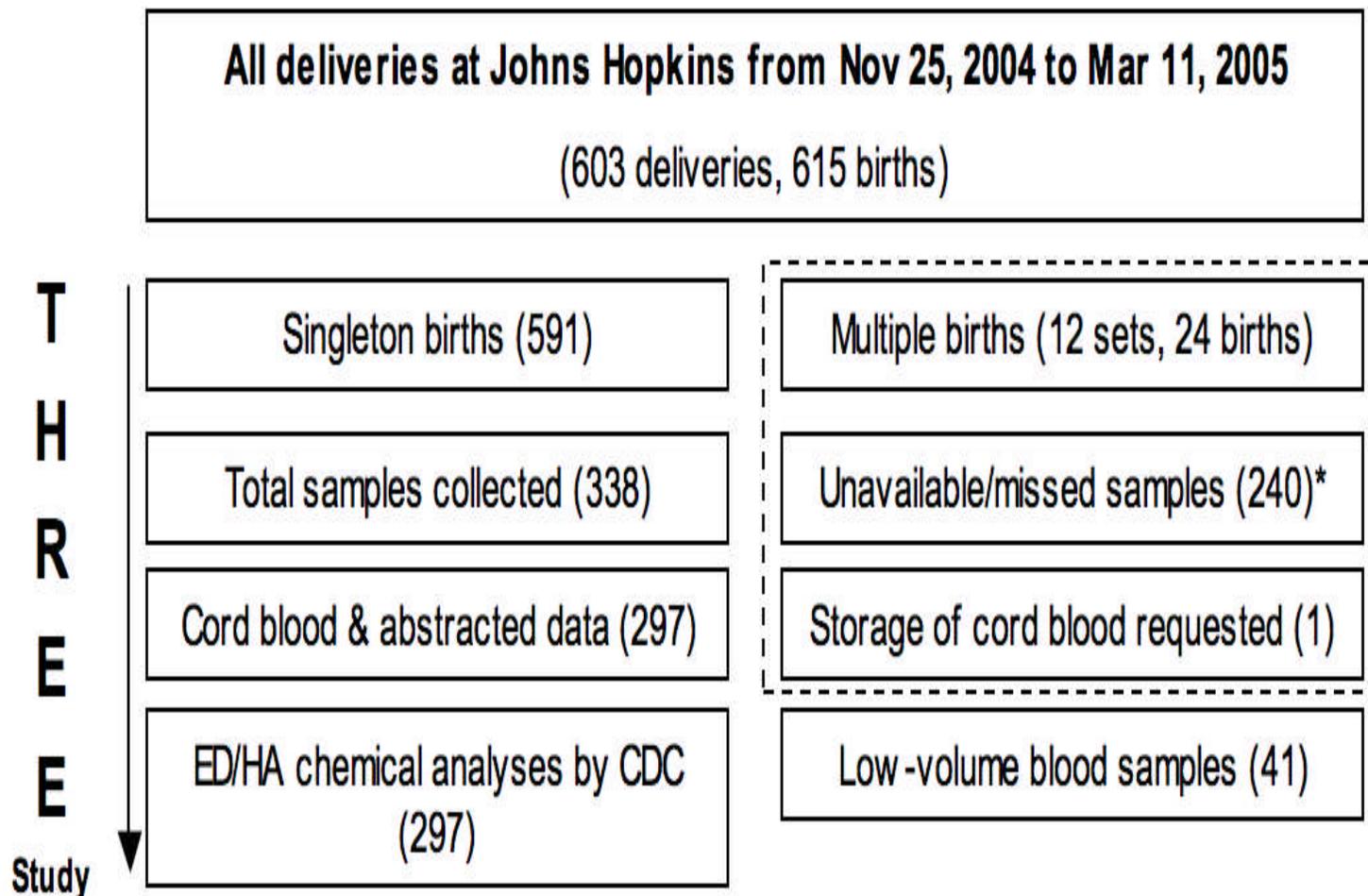
- Cord blood was collected from a cohort of babies delivered at the Johns Hopkins Hospital
- Eligibility: All singleton births
- Collection period: 11/26/04 to 3/17/05
 - Until 300 samples with sufficient quantity and quality were obtained
- Cord blood collected by nursing and house medical staff and processed by THREE study staff.
 - JHSoM Institutional Review Board
 - JHH Maternal and Fetal Research Committee
 - Maryland DHMH Institutional Review Board
- Medical records were abstracted
- Cord blood was analyzed:
 - Quest: Thyroids
 - CDC: chemicals and cotinine
 - Hopkins: epigenetics



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Three Study Population



Apelberg, Goldman, Halden, Herbstman, Witter



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Study Population Characteristics

Characteristic	Value	N (%)
Maternal Age	<18 years	24 (8.2)
	18-35 years	246 (84.0)
	>35 years	23 (7.8)
Race/Ethnicity	White	60 (20.5)
	Asian	25 (8.5)
	Black	208 (71.0)
Education	<HS diploma	86 (29.8)
	HS diploma	96 (33.2)
	1-4 years college	65 (22.5)
	5+ years college	42 (14.5)
Body Mass Index	Underweight (<18.5)	16 (5.6)
	Normal (18.5-24.9)	132 (46.6)
	Overweight (25-29.9)	64 (22.6)
	Obese (30+)	71 (25.1)
Primiparous	Yes	171 (58.4)
Marital Status	Unmarried	196 (66.9)
Smoker	Active	55 (18.8)
Delivery Mode	Vaginal	228 (77.8)
Infant Gender	Male	162 (55.3)



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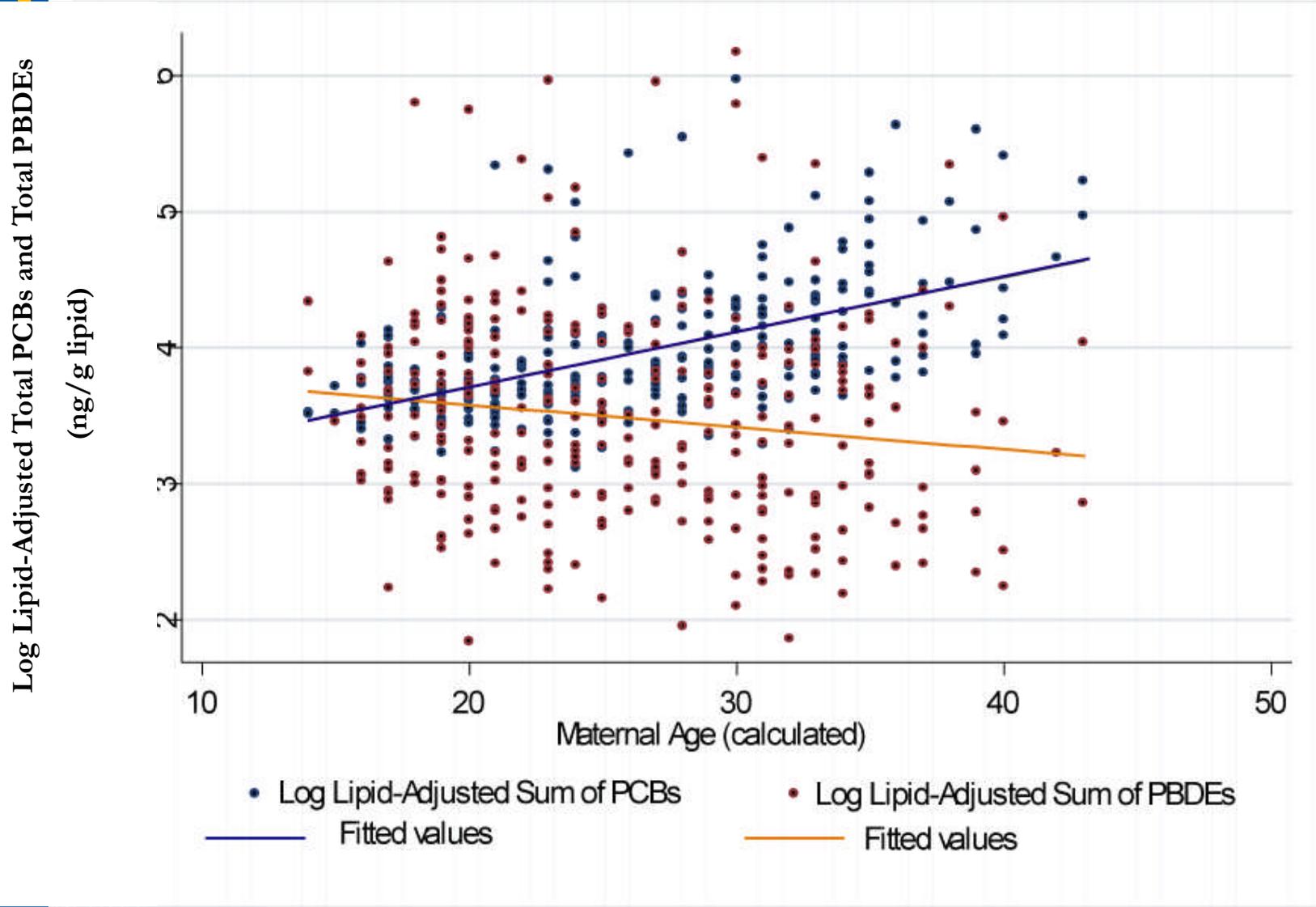
Biomarkers Analyzed

“EMERGING” BIOMARKERS	“TRADITIONAL” COMPOUNDS
Flame retardants	Organochlorine Pesticides
9 of 209 Polybrominated diphenyl ether (PBDE) congeners	DDT, DDE, Dieldrin, Oxychlordane, Dieldrin, trans-Nonachlor, Heptachlor, Hexachlorobenzene, (β - and γ -Hexachlorocyclohexane
Perfluorinated Compounds (PFCs)	Polychlorinated Biphenyls
Perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA) and 8 other PFCs	35 of 209 PCB congeners
Biomarkers	Metals
Cytokines, thyroid hormones, lipids (including n-3's), epigenetic marks	Lead, mercury (total and speciated), copper, selenium, cadmium



PCBs and PBDEs by Maternal Age

Sc





Determinants of PBDE Exposure

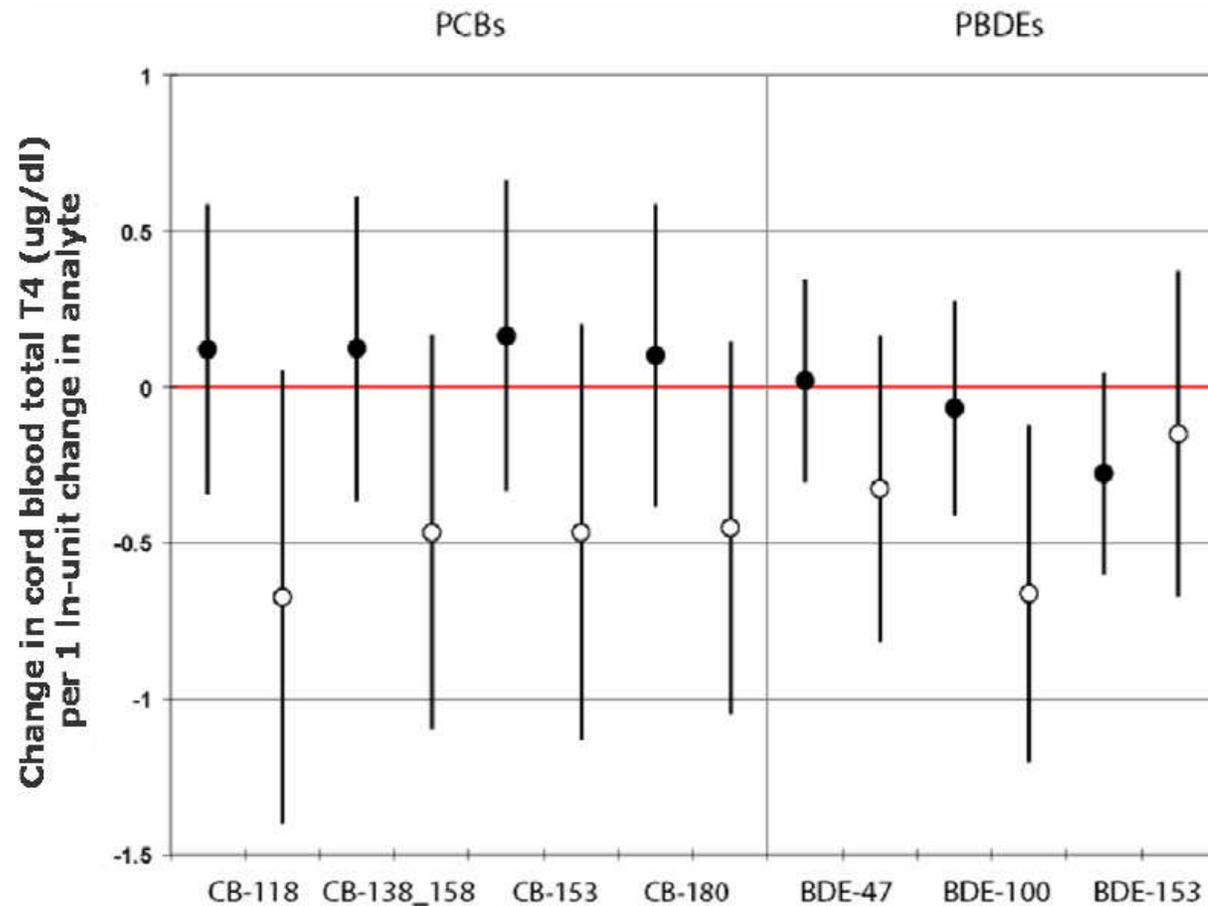
- **Cord blood levels of PBDE in Baltimore are similar to Indiana; much higher than Sweden**
- **Low correlation between PCBs and PBDEs**
- **Patterns and determinants of PCBs and PBDEs differ**
- **PBDEs were associated with:**
 - Maternal age*
 - Number of prior live births*
 - Maternal race*†
 - Maternal education*
 - Smoking during pregnancy†
 - Weight gain during pregnancy†
 - BMI*



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PCBs and PBDEs in relation to newborn thyroid levels

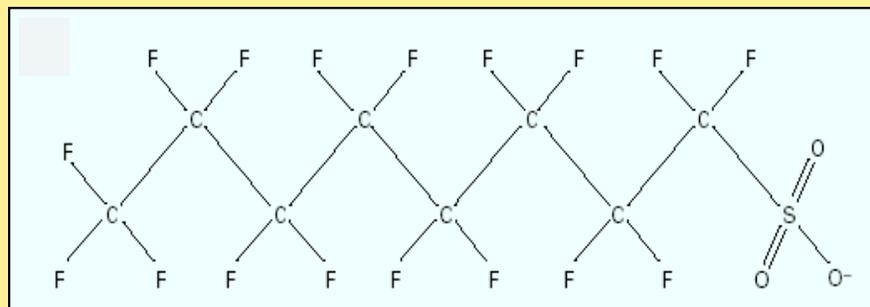




PFOS and PFOA

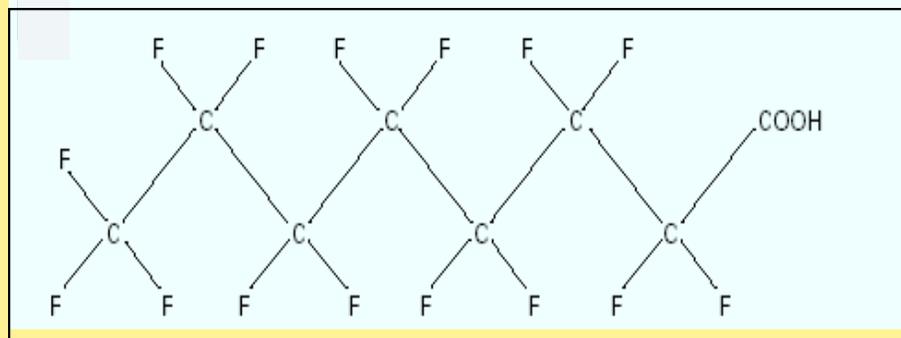
Perfluorooctane sulfonate (PFOS)

- Found in oil and water repellents for fabrics, apparel, carpets; paper coatings.
- Performance chemicals



Perfluorooctanoic acid (PFOA, C8)

- Used as processing aid for fluoropolymer production
- Breakdown from fluorotelomers

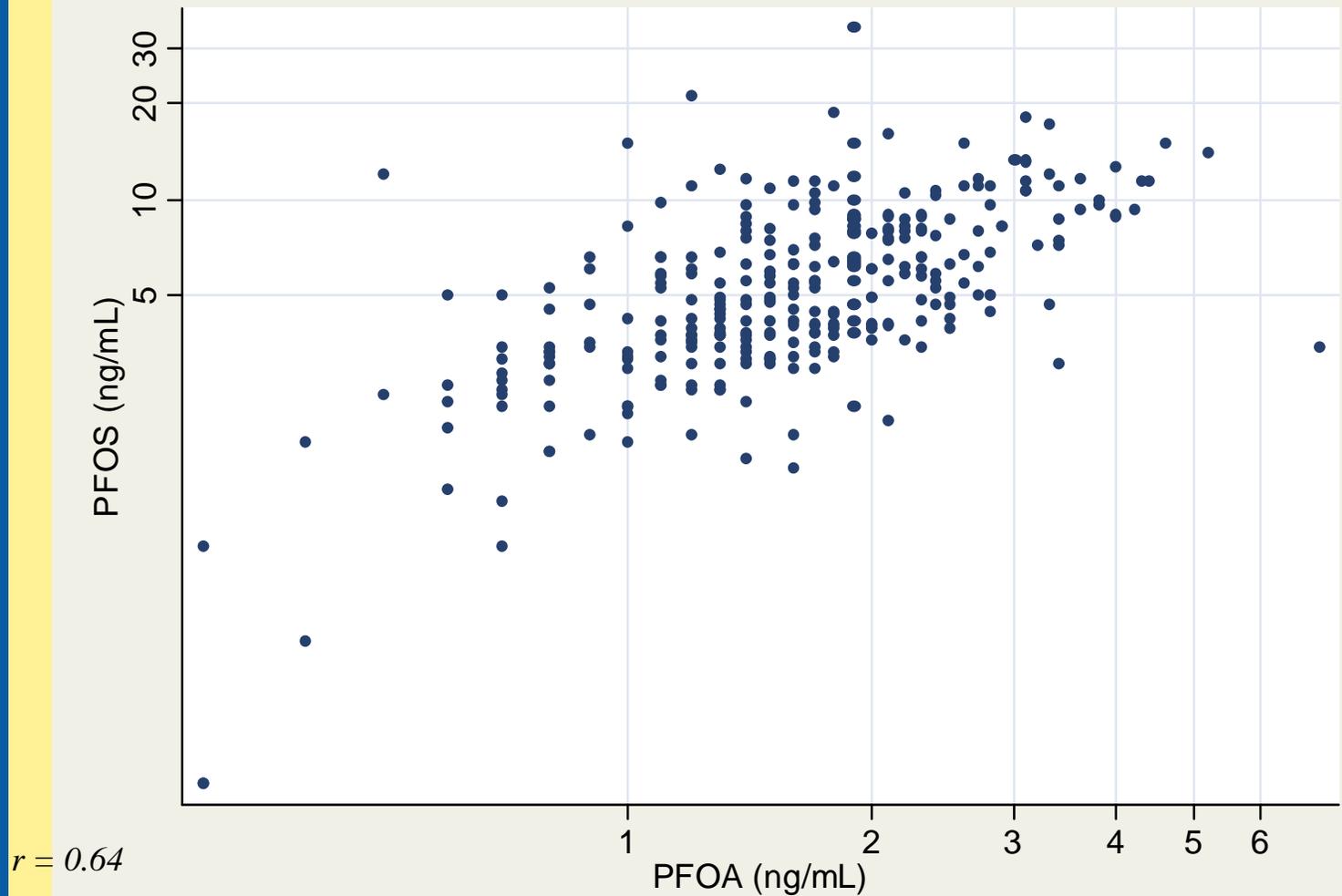




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Correlation between PFOS and PFOA concentrations in cord blood serum





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Conclusions: PFOS and PFOA Distribution

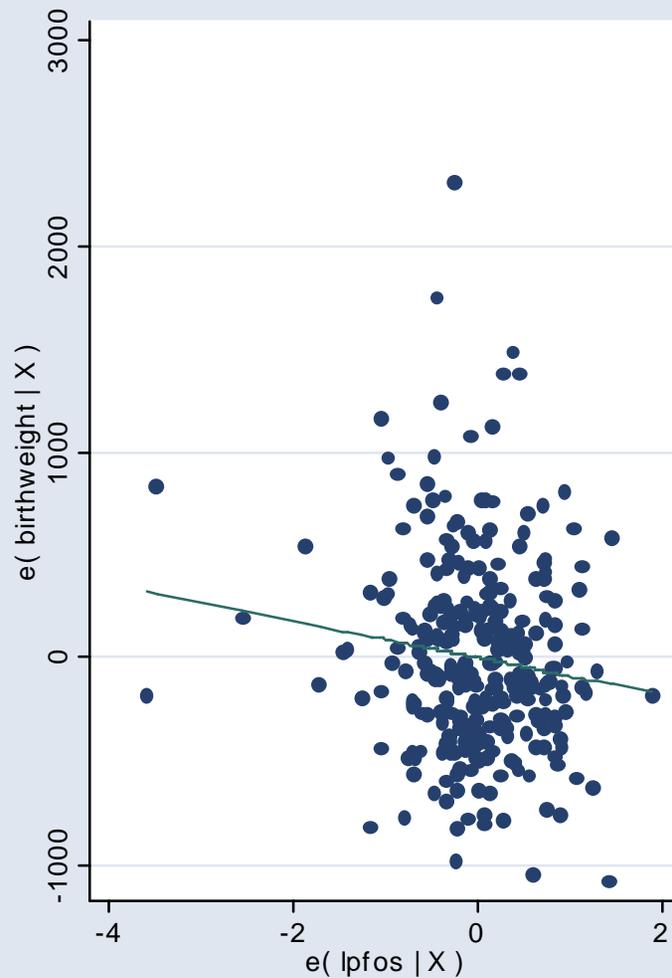
- **Widespread *in utero* exposure to PFCs at low levels in the Baltimore area**
- **PFOS and PFOA concentrations highly correlated**
 - May suggest similar pathways of exposure
- **Concentrations lower than typically reported among adults and children**
 - Consistent with incomplete transfer across the placenta, likely due to surfactant properties, large size, affinity for protein-binding
- **Only demographic factor predictive of cord serum concentrations is race/ethnicity**
 - Asians had the highest geometric mean PFOS concentrations
 - Some Asian countries report high PFOS serum concentrations
- **Socioeconomic status (e.g. education, marital status, city living) not predictive of *in utero* exposure**



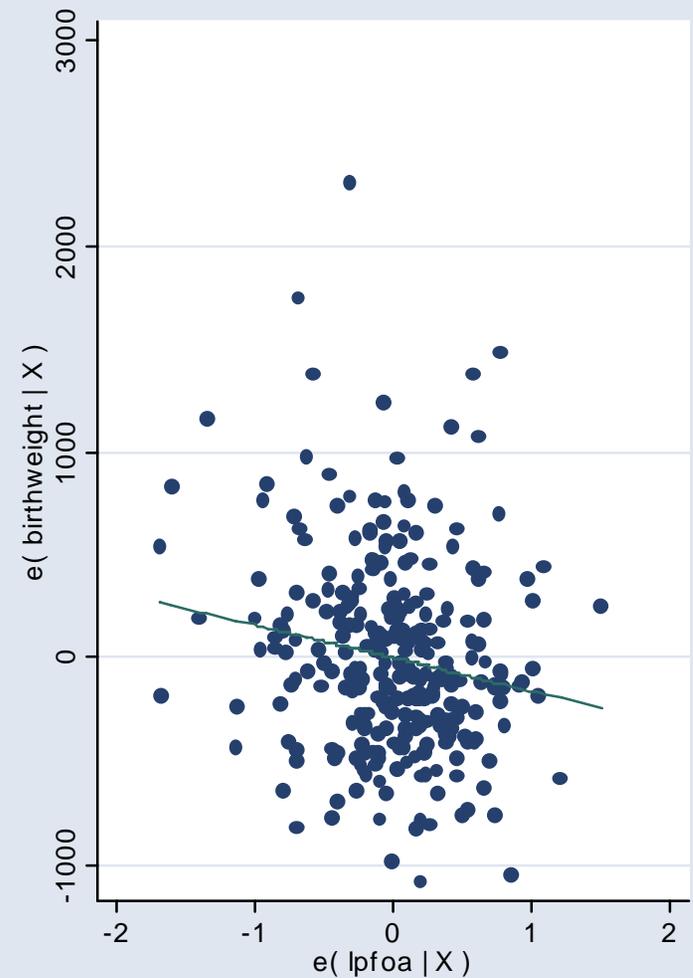
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PFOS/PFOA and Birthweight (Adjusted for GA)



coef = -88.916596, se = 41.15576, t = -2.16



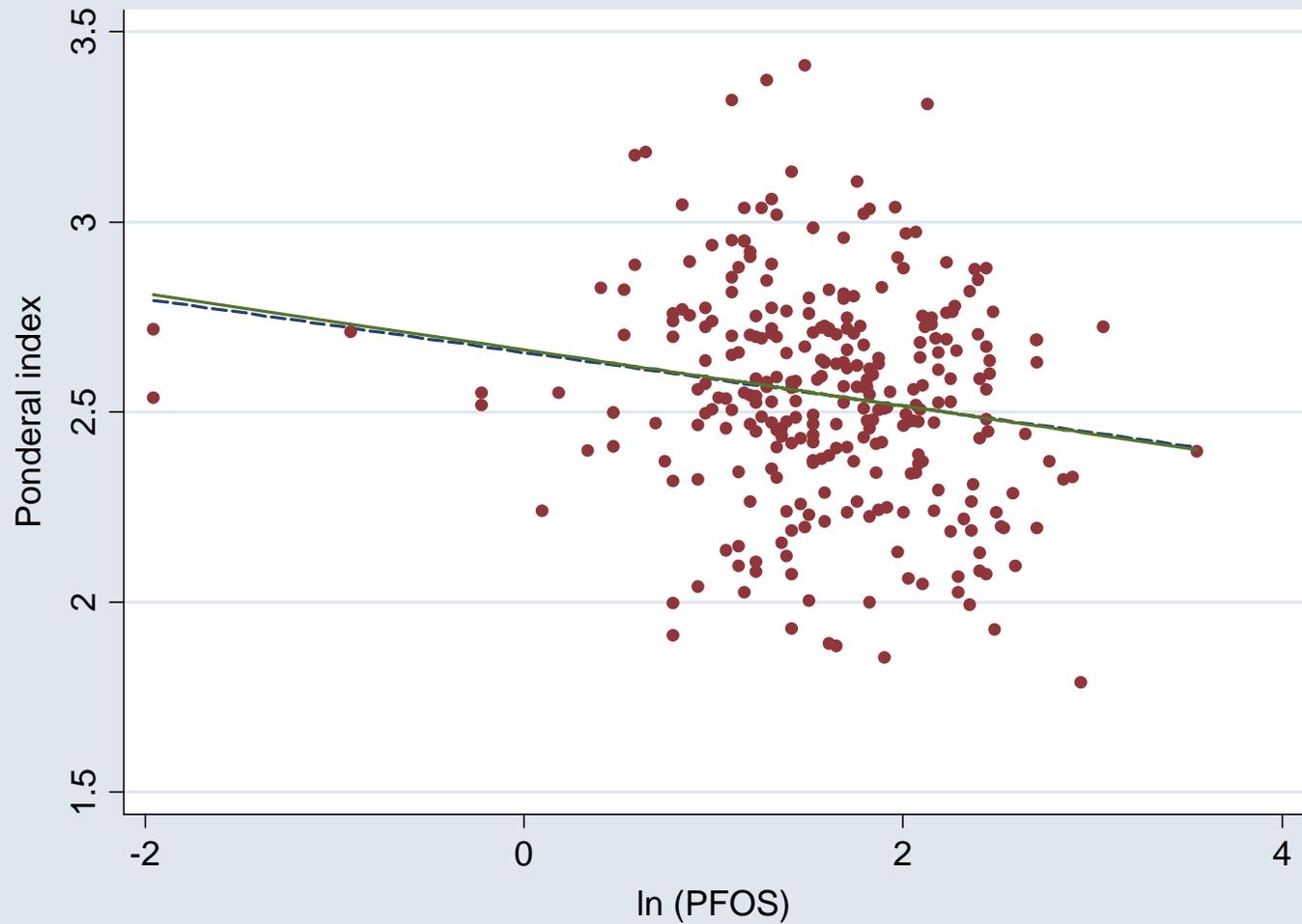
coef = -160.96464, se = 55.393742, t = -2.91



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PFOS and Ponderal Index (PFOA not shown)

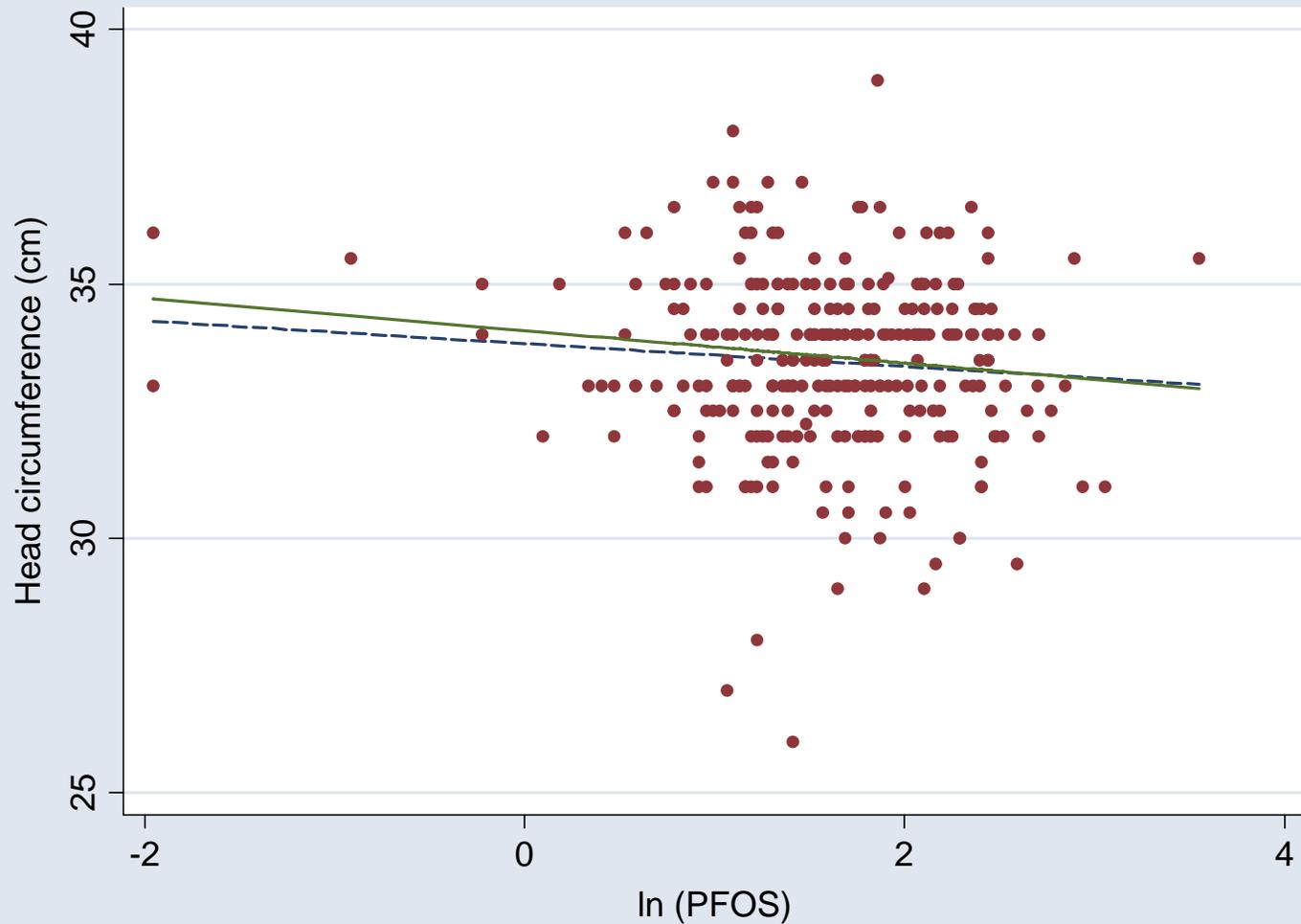


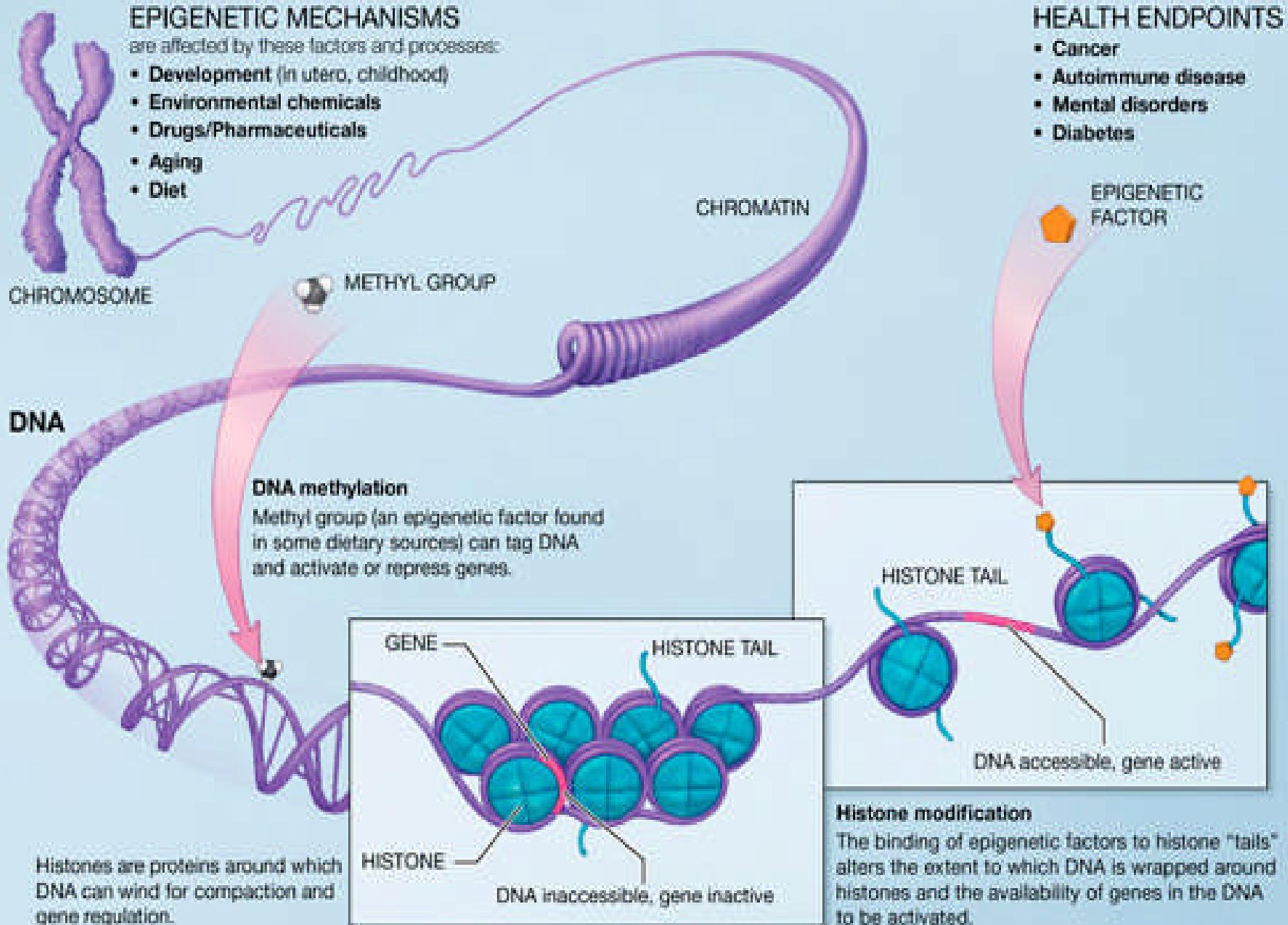


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PFOS and Head Circumference (PFOA not shown)







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Objectives

We hypothesized that in utero exposures to maternal smoking and PFCs are associated with global DNA hypomethylation in umbilical cord serum.



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Methods

Global DNA methylation assay

ELISA based commercial kit (MDQ1, Imprint® Methylated DNA Quantification Kit, Sigma Aldrich)

Y Chromosome quantification

The Quantifiler Y Human Male DNA Quantification Kit (Applied Biosystems) and Quantifiler Human DNA Quantification Kit (Applied Biosystems) were used on 8 cord blood DNA samples obtained from male infants

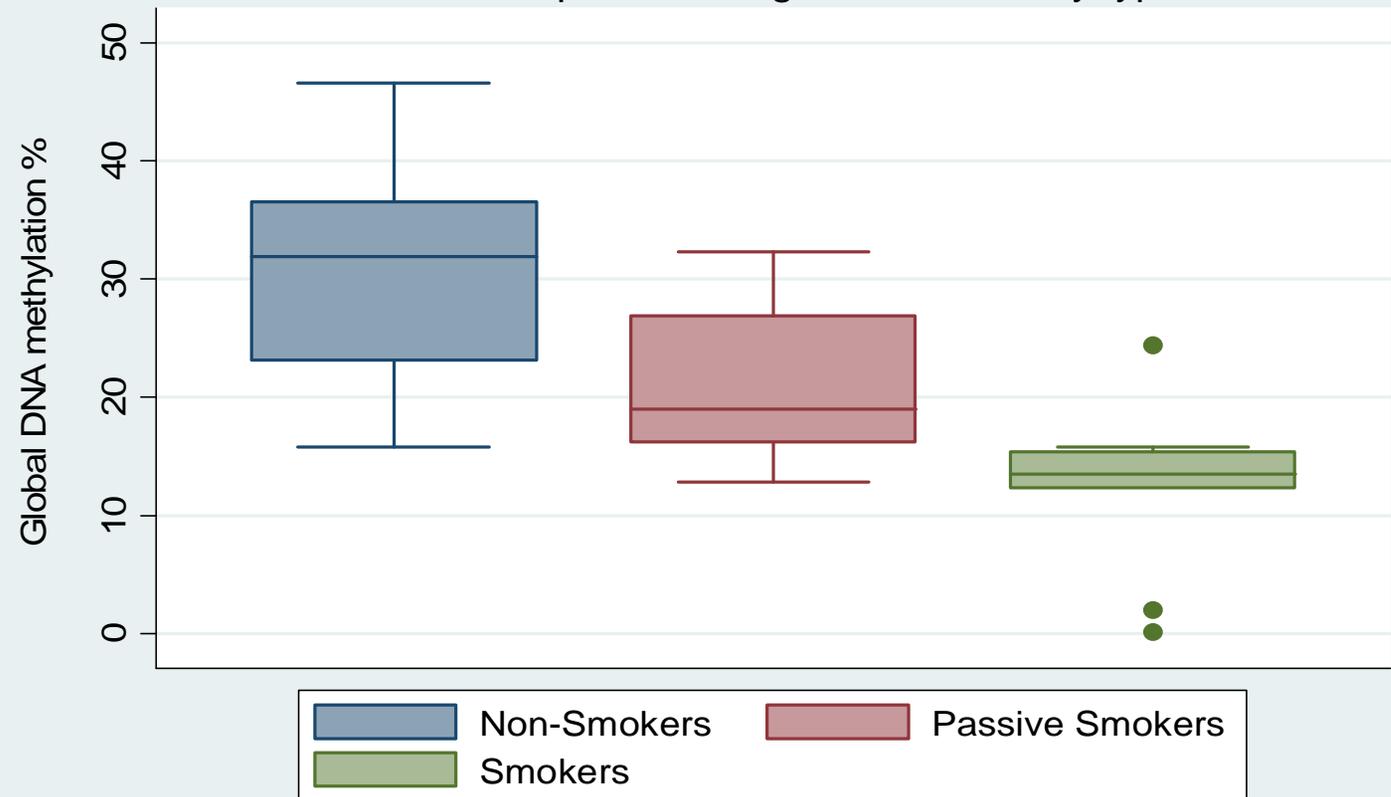


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In-utero exposure to nicotine from 11 maternal smokers, 11 passive smokers, and 8 non-smokers

Global DNA methylation in cord blood serum
In-utero exposure to cigarette smoke by type

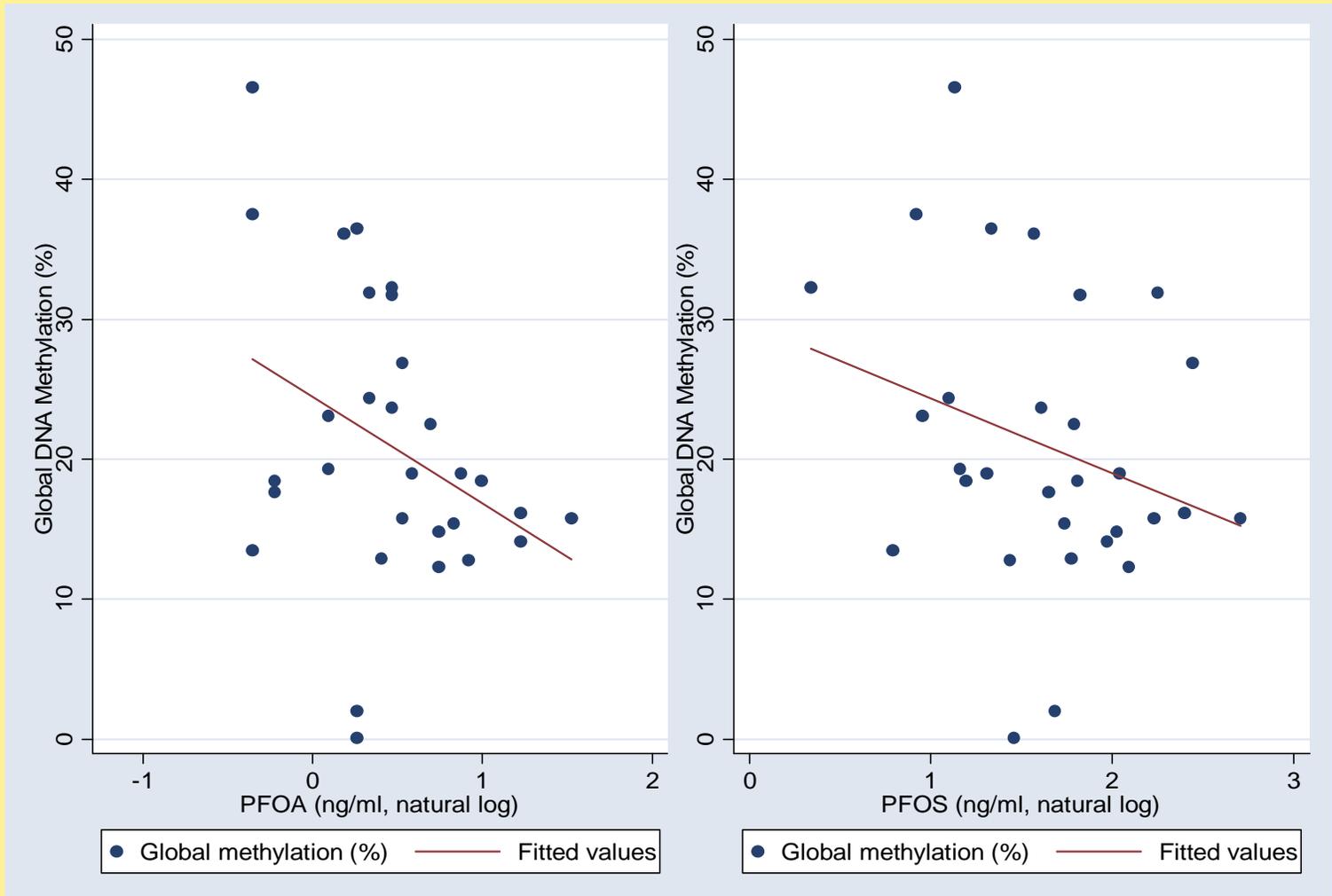




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Global DNA methylation and In PFOA (ng/ml) and In PFOS (ng/ml) (n=30)





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Epigenetics Summary

- Global DNA hypomethylation in fetal DNA was inversely correlated with cotinine and possibly also with PFOA and maternal age.
- This study supports the use of global DNA methylation status as a biomarker of in utero exposure to cigarette smoke and PFCs and suggests a possible mechanism for adverse effects on fetal growth.



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Umbilical cord metals

	Mercury µg/L	Lead µg/dL	Selenium µg/L	Copper µg/dL
N	294	294	287	287
Geo. mean	1.37	0.66	69.1	38.6
Lowest	< LOD	< LOD	42.0	12.1
25 th percentile	0.95	0.46	62.0	27.9
50 th (median)	1.40	0.65	69.0	37.8
75th percentile	2.03	0.95	78.0	51.8
Highest	16.48	15.50	114.0	265.0
Reg. level:	5.8	10.0		



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Metal correlations

	Mercury	Lead	Selenium	Copper
Lead	0.09 (0.13)	--		
Selenium	0.02 (0.81)	0.20 (<0.01)	--	
Copper	-0.07 (0.26)	0.07 (0.28)	0.51 (<0.01)	--

Values are Spearman's correlation coefficient (p-value).

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Lead and maternal blood pressure

Admission Blood Pressure

	Systolic	Diastolic
Crude (n=285)	2.06 (-0.08, 4.19)	1.61 (-0.07, 3.29)
Adjusted (n=285)	2.35 (0.07, 4.63)	1.87 (0.09, 3.66)

Maximum Blood Pressure

	Systolic	Diastolic
Crude (n=285)	2.41 (-0.08, 4.90)	4.11 (1.32, 6.90)
Adjusted (n=285)	2.68 (0.12, 5.24)	4.28 (1.22, 7.35)

Results are change in interquartile range (95% confidence interval)

Crude: is unadjusted

Adjusted: adjusts for maternal age, race, median household income, primiparity, maternal smoking, prepregnancy BMI, and anemia



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Persistent pesticides occur in combination

Organochlorines (n = 297)	DDT Component	Chlordane Component
<i>p,p'</i> -DDE	0.49	-0.24
<i>p,p'</i> -DDT	0.44	-0.32
HCB	0.43	0.15
β -HCCH	0.45	-0.33
<i>trans</i> -Nonachlor	0.25	0.63
Oxychlordane	0.32	0.56
Eigenvalue	3.38	1.55
% cumulative variance	0.56	0.82



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Nonpersistent pesticides occur in combination

Non-persistents (n = 185)	Permethrin Component	Carbamate Component
<i>cis</i> -Permethrin	0.59	-0.08
<i>trans</i> -Permethrin	0.60	-0.07
Piperonyl butoxide	0.52	-0.09
Bendiocarb	0.08	0.73
Propoxur	0.12	0.67
Eigenvalue	2.52	1.05
% cumulative variance	0.50	0.71



We manage chemicals one at a time but they occur in mixtures in cord blood

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	PCBs	PBDEs	DDT/DDE	PFCs	PBDE	Chordane	HCBs	Hg	PCBs
lip_pp_ddt	0.017	-0.078	0.509	0.263	0.017	0.065	-0.0897	0.0051	-0.0789
lip_pp_dde	0.036	-0.107	0.515	0.301	0.059	0.031	0.0264	-0.0336	-0.0390
lip_hcb	0.141	-0.167	0.029	0.070	0.211	-0.031	0.2855	-0.1033	0.0921
lip_b_hcch	0.015	-0.103	0.331	0.275	0.073	-0.069	0.2917	-0.1367	0.0601
lip_oxychlor	0.190	-0.082	0.152	0.094	-0.128	0.253	-0.4537	0.0577	-0.0533
lip_t_nona	0.173	-0.049	-0.010	0.016	-0.164	0.229	-0.4831	0.1007	-0.0617
lip_pbde28	0.067	0.336	0.022	0.022	0.345	0.033	-0.0440	0.0677	-0.0259
lip_pbde47	0.083	0.381	0.036	0.030	0.317	0.076	-0.0408	0.0710	-0.0704
lip_pbde99	0.057	0.269	0.001	0.027	0.410	0.136	-0.0666	0.1220	0.0431
lip_pbde100	0.106	0.404	0.038	0.044	0.173	-0.009	-0.0029	0.0225	-0.0418
lip_pbde153	0.038	0.172	-0.025	0.059	0.111	0.043	-0.1621	-0.2706	0.1050
lip_pcb28	0.033	-0.003	0.054	-0.022	-0.009	0.041	0.0214	0.2962	0.8843
lip_pcb74	0.268	0.095	0.039	0.014	-0.184	0.015	0.0006	0.0106	0.1996
lip_pcb105	0.165	0.302	0.064	0.032	-0.291	-0.138	0.1628	-0.0557	-0.0017
lip_pcb118	0.200	0.277	0.056	0.040	-0.299	-0.101	0.1366	-0.0560	-0.0056
lip_pcb156	0.275	-0.015	0.001	-0.119	-0.123	0.045	-0.0629	-0.0120	-0.0037
lip_pcb99	0.223	0.265	0.040	0.024	-0.260	-0.091	0.1193	-0.0389	-0.0242
lip_pcb138+158	0.301	0.056	0.010	-0.036	-0.140	-0.018	0.0428	-0.0297	-0.0312
lip_pcb146	0.300	-0.059	-0.037	-0.031	-0.020	-0.007	-0.0186	0.0020	-0.0659
lip_pcb153	0.307	-0.078	-0.025	-0.046	0.027	-0.007	0.0795	-0.0389	-0.0188
lip_pcb170	0.275	-0.174	-0.028	-0.066	0.140	-0.006	0.1170	-0.0446	0.0074
lip_pcb180	0.265	-0.188	-0.046	-0.053	0.177	-0.019	0.1447	-0.0394	0.0035
lip_pcb187	0.273	-0.155	-0.074	0.002	0.189	-0.014	0.0311	0.0183	-0.0629
lip_pcb196+203	0.252	-0.157	-0.071	-0.064	0.118	0.024	-0.0451	0.0242	0.0262
lip_pcb199	0.235	-0.181	-0.108	-0.024	0.187	0.004	-0.0286	0.0448	-0.0544
lead (blood)	0.008	-0.019	0.151	0.083	0.016	0.107	-0.1002	0.0374	0.0820
mercury (blood)	0.052	-0.016	-0.131	0.288	0.001	-0.288	0.0566	0.3403	-0.2263
me_pfoa_a~h	-0.024	0.033	-0.073	0.051	-0.069	0.591	0.2950	0.1578	-0.0771
pfdea	0.026	-0.027	-0.251	0.472	-0.048	-0.100	-0.0450	0.1609	0.1099
pfoa	0.009	0.032	-0.260	0.306	0.009	0.175	-0.0813	-0.4183	0.1303
pfos	-0.008	0.004	-0.221	0.281	-0.010	0.178	0.0271	-0.5156	0.0782
pfoa	-0.017	0.004	-0.080	0.070	-0.135	0.511	0.3544	0.2605	-0.1320
pfua	0.022	-0.036	-0.260	0.465	-0.019	-0.160	-0.0725	0.2767	-0.0323

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