

Supplementary Materials

Prenatal exposure to metabolism-disrupting chemicals, cord blood transcriptome perturbations, and birth weight in a Belgian birth cohort

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Figure S2. DAG of authors' conception of the associations between prenatal MDC exposures, covariates, and (a) cord blood transcriptome and (b) birth weight among infants born at term.

Table S1. The concentrations of MDCs measured in cord blood among 193 newborns.

	Missing, <i>n</i> (%)	LOQ (ng/L)	> LOQ (%)	Median (P25-P75) (ng/L)	Median ^a (P25-P75) (ng/g lipid)
<i>p,p'</i> -DDE	2 (1)	20	100	157 (91-255)	75.0 (45.8-134.0)
PCB-153	2 (1)	20	97	54 (40-85)	28.7 (18.7-39.4)
PFOA	25 (13)	300	100	1600 (1100-2100)	
PFOS	25 (13)	300	100	2700 (1700-3700)	

^a Lipophilic chemicals *p,p'*-DDE and PCB-153 were lipid-standardized and expressed in ng/g lipid.

Abbreviations: MDCs, metabolism-disrupting chemicals; *p,p'*-DDE, dichlorodiphenyldichloroethylene; PCB-153, polychlorinated biphenyl 153; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; LOQ, limit of quantification; P, percentile.

Table S2. Number of features associated with MDCs at different significance levels (sensitivity analysis: gestational age-unadjusted).

	FDR < 0.05	FDR < 0.20	<i>p</i>-value < 0.01	<i>p</i>-value < 0.05
<i>p,p'</i> -DDE	0	0	146	837
PCB-153	0	0	78	634
PFOA	0	0	33	375
PFOS	0	0	79	631

Abbreviations: MDCs, metabolism-disrupting chemicals; *p,p'*-DDE, dichlorodiphenyldichloroethylene; PCB-153, polychlorinated biphenyl 153; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; FDR, false discovery rate.

Table S3. The individual associations of gene expression with MDCs or birth weight, β (p -value).

ProbeID	GeneSymbol	p,p' -DDE ^a	PCB-153 ^a	PFOA ^a	PFOS ^a	Birth weight ^b
A_23_P90163	BCAT2	-0.07 (0.04)				128.82 (0.04)
A_23_P129322	IVD		-0.17 (0.04)			-98.48 (0.01)
A_32_P74075	SLC25A16		-0.10 (0.02)			208.48 (0.01)
A_23_P357229	HAS3			0.04 (0.23)		79.70 (0.04)
A_24_P114255	MBOAT2				0.08 (0.03)	-153.87 (0.04)

^a The effect estimate β refers to log₂-fold change in gene expression per unit increase in log(MDC).

^b The effect estimate β refers to birth weight change (g) per log₂-fold increase in gene expression.

Abbreviations: MDCs, metabolism-disrupting chemicals; p,p' -DDE, dichlorodiphenyldichloroethylene; PCB-153, polychlorinated biphenyl 153; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; FDR, false discovery rate.

Table S4. Enriched KEGG pathways associated with MDCs and birth weight at FDR < 0.05.

<i>p,p'</i> -DDE					
Rank	Pathway	Category	NES	FDR	Effective/total gene size
1	Ribosome	GIP (Translation)	2.18	0.00	76/126
2	Allograft rejection	HD (Immune disease)	2.08	0.01	21/34
3	RNA degradation	GIP (Folding, sorting and degradation)	2.05	0.01	44/74
4	Intestinal immune network for IgA production	OS (Immune system)	1.93	0.02	15/38
5	T cell receptor signaling pathway	OS (Immune system)	1.93	0.02	71/91
6	RNA transport	GIP (Translation)	1.92	0.02	74/149
7	Th1 and Th2 cell differentiation	OS (Immune system)	1.92	0.02	34/81
8	Th17 cell differentiation	OS (Immune system)	1.89	0.02	38/101
9	Hematopoietic cell lineage	OS (Immune system)	1.86	0.02	28/87
10	Glycosaminoglycan biosynthesis	Metabolism (Glycan biosynthesis and metabolism)	1.81	0.04	7/21
11	Inflammatory bowel disease (IBD)	HD (Immune disease)	1.80	0.04	22/59
12	Platelet activation	OS (Immune system)	1.80	0.03	32/109
13	Autoimmune thyroid disease	HD (Immune disease)	1.79	0.03	20/40
14	Antigen processing and presentation	OS (Immune system)	1.79	0.03	41/71
15	Ribosome biogenesis in eukaryotes	GIP (Translation)	1.75	0.04	35/72
1	Olfactory transduction	OS (Sensory system)	-2.17	0.00	61/143
2	Taste transduction	OS (Sensory system)	-1.95	0.03	33/59
PCB-153					
Rank	Pathway	Category	NES	FDR	Effective/total gene size
1	Ribosome	GIP (Translation)	-2.33	< 2.2e-16	85/126
2	Mismatch repair	GIP (Replication and repair)	-2.01	0.01	12/22
3	Fanconi anemia pathway	GIP (Replication and repair)	-1.84	0.04	23/46
PFOA					
Rank	Pathway	Category	NES	FDR	Effective/total gene size
1	Metabolism of xenobiotics by cytochrome P450	Metabolism (Xenobiotics biodegradation and metabolism)	2.22	< 2.2e-16	25/51
2	Drug metabolism	Metabolism (Xenobiotics biodegradation and metabolism)	2.16	< 2.2e-16	23/47
3	Olfactory transduction	OS (Sensory system)	1.88	0.02	64/143
4	Neuroactive ligand-receptor interaction	EIP (Signaling molecules and interaction)	1.83	0.03	79/219

1	Antigen processing and presentation	OS (Immune system)	-2.57	< 2.2e-16	38/71
2	Natural killer cell mediated cytotoxicity	OS (Immune system)	-2.53	< 2.2e-16	32/107
3	Graft-versus-host disease	HD (Immune disease)	-2.43	< 2.2e-16	17/36
4	Th1 and Th2 cell differentiation	OS (Immune system)	-2.3	< 2.2e-16	27/81
5	Spliceosome	GIP (Transcription)	-2.06	0.00	66/124
6	Viral myocarditis	HD (Cardiovascular disease)	-2.04	0.00	19/53
7	Type I diabetes mellitus	HD (Endocrine and metabolic disease)	-2.02	0.00	16/38
8	Human immunodeficiency virus 1 infection	HD (Infectious disease: viral)	-1.97	0.00	47/188
9	Colorectal cancer	HD (Cancer: specific types)	-1.95	0.01	35/80
10	Cellular senescence	CP (Cell growth and death)	-1.94	0.01	57/148
11	Apoptosis	CP (Cell growth and death)	-1.92	0.01	44/125
12	Th17 cell differentiation	OS (Immune system)	-1.89	0.01	28/101
13	Measles	HD (Infectious disease: viral)	-1.86	0.01	39/111
14	Allograft rejection	HD (Immune disease)	-1.84	0.02	14/34
15	Herpes simplex infection	HD (Infectious disease: viral)	-1.81	0.02	59/164
16	Salmonella infection	HD (Infectious disease: viral)	-1.80	0.02	36/74
17	B cell receptor signaling pathway	OS (Immune system)	-1.76	0.03	28/69
18	Autophagy	CP (Transport and catabolism)	-1.75	0.03	48/121
19	FoxO signaling pathway	EIP (Signal transduction)	-1.73	0.04	44/115
20	Epstein-Barr virus infection	HD (Infectious disease: viral)	-1.72	0.04	86/183
21	Protein processing in endoplasmic reticulum	GIP (Folding, sorting and degradation)	-1.70	0.04	54/156
22	Proteasome	GIP (Folding, sorting and degradation)	-1.69	0.04	28/43
23	Pathogenic Escherichia coli infection	HD (Infectious disease: bacterial)	-1.69	0.04	20/47

PFOS

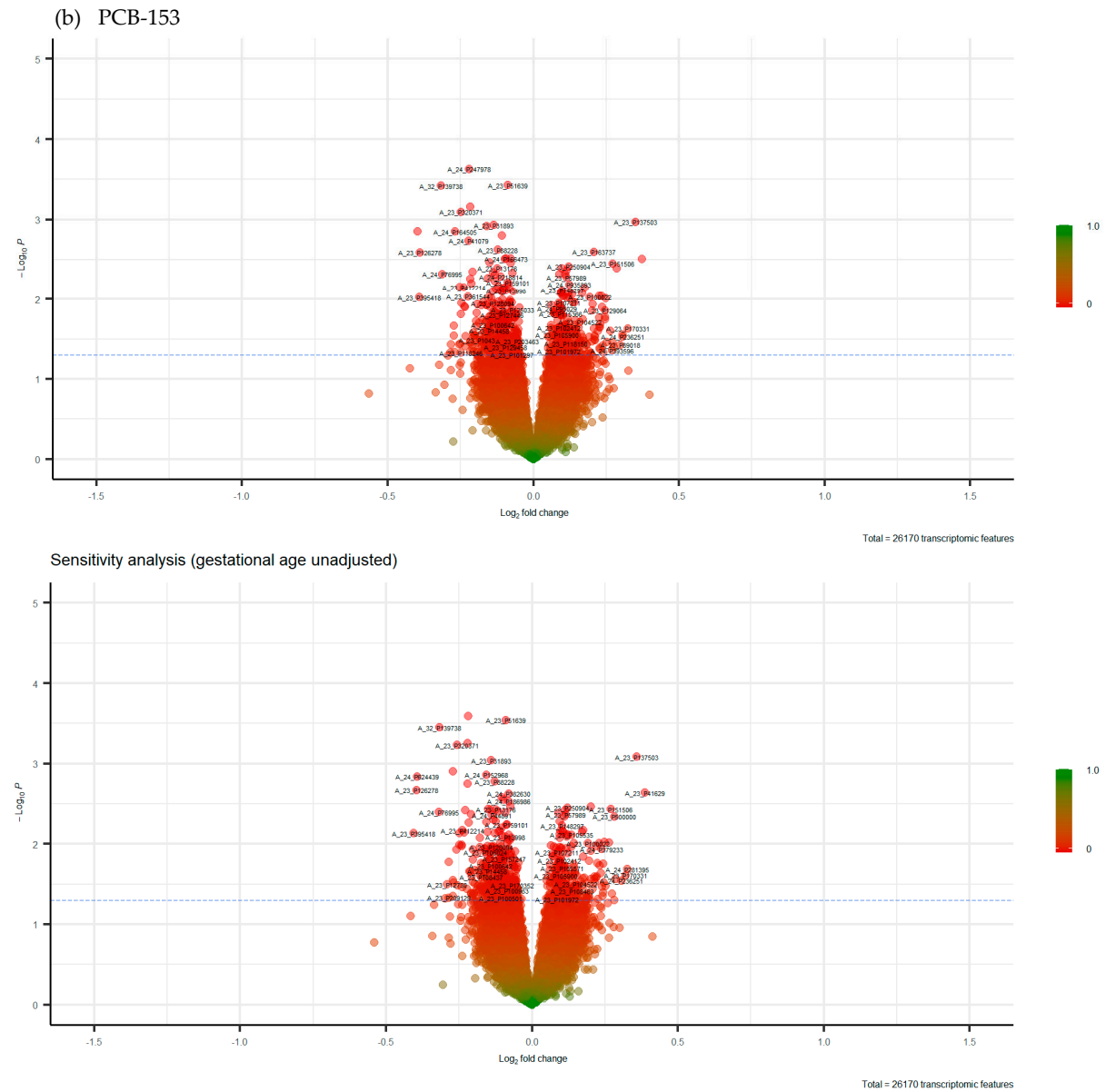
Rank	Pathway	Category	NES	FDR	Effective/total gene size
1	Leishmaniasis	HD (Infectious disease: parasitic)	-2.16	0.01	41/68
2	Natural killer cell mediated cytotoxicity	OS (Immune system)	-2.04	0.03	49/107
3	Antigen processing and presentation	OS (Immune system)	-2.02	0.02	34/71
4	Spliceosome	GIP (Transcription)	-2.02	0.02	70/124
5	B cell receptor signaling pathway	OS (Immune system)	-1.97	0.02	33/69
6	NOD-like receptor signaling pathway	OS (Immune system)	-1.97	0.02	59/145

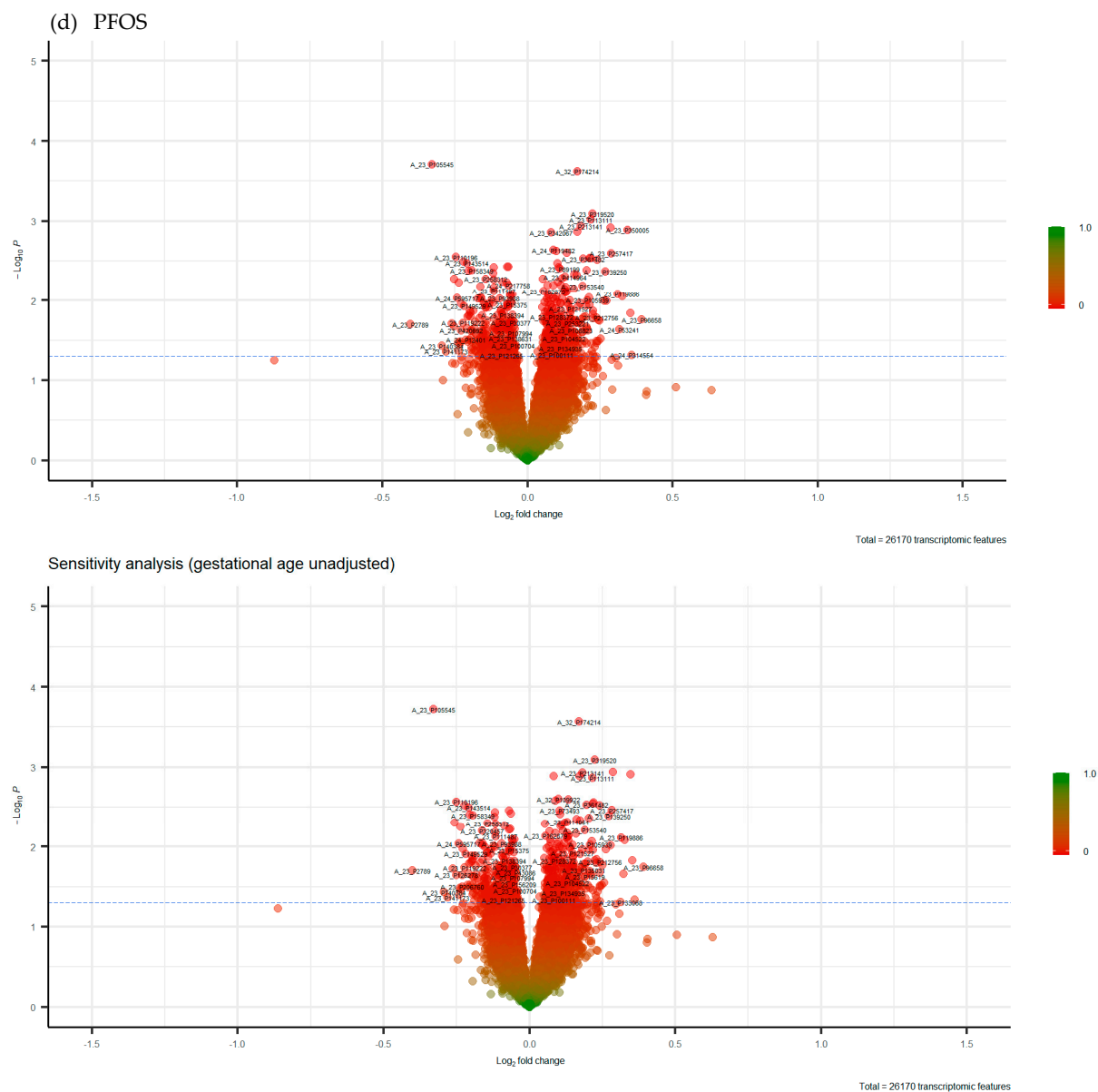
7	Salmonella infection	HD (Infectious disease: viral)	-1.96	0.02	36/74
8	Graft-versus-host disease	HD (Immune disease)	-1.92	0.02	12/36
9	Phagosome	CP (Transport and catabolism)	-1.89	0.02	34/137
10	Amino sugar and nucleotide sugar metabolism	Metabolism (Carbohydrate metabolism)	-1.88	0.02	14/42
11	Osteoclast differentiation	OS (Development and regeneration)	-1.83	0.03	46/115
12	Acute myeloid leukemia	HD (Cancer: specific types)	-1.82	0.03	23/61
13	Influenza A	HD (Infectious disease: viral)	-1.81	0.03	52/147
14	Fanconi anemia pathway	GIP (Replication and repair)	-1.79	0.04	16/46
15	Viral myocarditis	HD (Cardiovascular disease)	-1.78	0.04	14/53
16	Mismatch repair	GIP (Replication and repair)	-1.77	0.04	11/22
17	Pancreatic cancer	HD (Cancer: specific types)	-1.77	0.04	26/69
18	Type I diabetes mellitus	HD (Endocrine and metabolic disease)	-1.75	0.04	22/38
19	Kaposi sarcoma-associated herpesvirus infection	HD (Infectious disease: viral)	-1.72	0.04	58/165
20	Pathogenic Escherichia coli infection	HD (Infectious disease: bacterial)	-1.70	0.04	22/47

Birth weight					
Rank	Pathway	Category	NES	FDR	Effective/total gene size
1	Olfactory transduction	OS (Sensory system)	2.75	< 2.2e-16	82/143
2	Neuroactive ligand-receptor interaction	EIP (Signaling molecules and interaction)	2.24	0.00	115/219
3	Nicotine addiction	HD (Substance dependence)	2.10	0.00	17/32
4	Taste transduction	OS (Sensory system)	2.04	0.00	25/59
5	Cytokine-cytokine receptor interaction	EIP (Signaling molecules and interaction)	1.95	0.01	95/221
6	Dilated cardiomyopathy (DCM)	HD (Cardiovascular disease)	1.85	0.02	23/83
1	Ribosome	GIP (Translation)	-2.78	< 2.2e-16	91/126
2	Spliceosome	GIP (Transcription)	-2.62	< 2.2e-16	75/124
3	Oxidative phosphorylation	Metabolism (Energy metabolism)	-2.43	< 2.2e-16	52/110
4	Proteasome	GIP (Folding, sorting and degradation)	-2.39	< 2.2e-16	31/43
5	Cell cycle	CP (Cell growth and death)	-2.30	< 2.2e-16	70/117
6	Fanconi anemia pathway	GIP (Replication and repair)	-2.28	< 2.2e-16	22/46
7	DNA replication	GIP (Replication and repair)	-2.14	0.00	18/35
8	Non-alcoholic fatty liver disease (NAFLD)	HD (Endocrine and metabolic disease)	-2.14	0.00	54/131
9	Nucleotide excision repair	GIP (Replication and repair)	-2.13	0.00	22/42

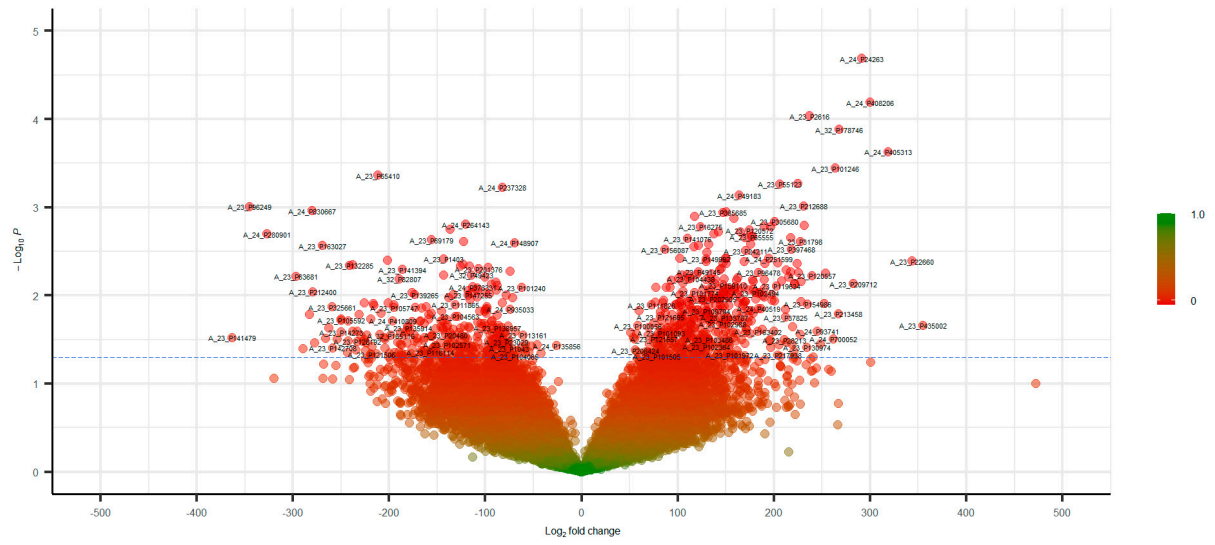
10	Huntington disease	HD (Neurodegenerative disease)	-2.09	0.00	80/166
11	Mismatch repair	GIP (Replication and repair)	-2.05	0.00	15/22
12	Parkinson disease	HD (Neurodegenerative disease)	-2.01	0.00	49/116
13	RNA transport	GIP (Translation)	-2.00	0.00	65/149
14	Autophagy	CP (Transport and catabolism)	-1.91	0.01	13/31
15	Homologous recombination	GIP (Replication and repair)	-1.91	0.01	23/36
16	Autophagy_1	CP (Transport and catabolism)	-1.85	0.01	32/121
17	Thermogenesis	OS (Environmental adaptation)	-1.85	0.01	88/196
18	Alzheimer disease	HD (Neurodegenerative disease)	-1.85	0.01	50/152
19	Protein processing in endoplasmic reticulum	GIP (Folding, sorting and degradation)	-1.83	0.01	73/156
20	RNA polymerase	GIP (Transcription)	-1.78	0.02	14/27
21	mRNA surveillance pathway	GIP (Translation)	-1.77	0.02	34/84
22	Cysteine and methionine metabolism	Metabolism (Amino acid metabolism)	-1.77	0.02	13/40
23	Protein export	GIP (Folding, sorting and degradation)	-1.72	0.03	15/23
24	Sulfur metabolism	Metabolism (Energy metabolism)	-1.70	0.03	8/12
25	Valine, leucine and isoleucine degradation	Metabolism (Energy metabolism)	-1.69	0.04	16/43
26	Ubiquitin mediated proteolysis	GIP (Folding, sorting and degradation)	-1.68	0.04	50/126
27	Fatty acid biosynthesis	Metabolism (Lipid metabolism)	-1.67	0.04	16/35

The highlighted cells in ranks columns refer to positive (blue) and inverse (orange) associations and the red font in pathway columns denote metabolism-related pathways. Abbreviations: MDCs, metabolism-disrupting chemicals; *p,p'*-DDE, dichlorodiphenyldichloroethylene; PCB-153, polychlorinated biphenyl 153; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; KEGG, Kyoto Encyclopedia of Genes and Genomes; NES, normalized enrichment score; FDR, false discovery rate; GIP, Genetic Information Processing; OS, Organismal Systems; EIP, Environmental Information Processing; CP, Cellular Processes; HD, Human Diseases.





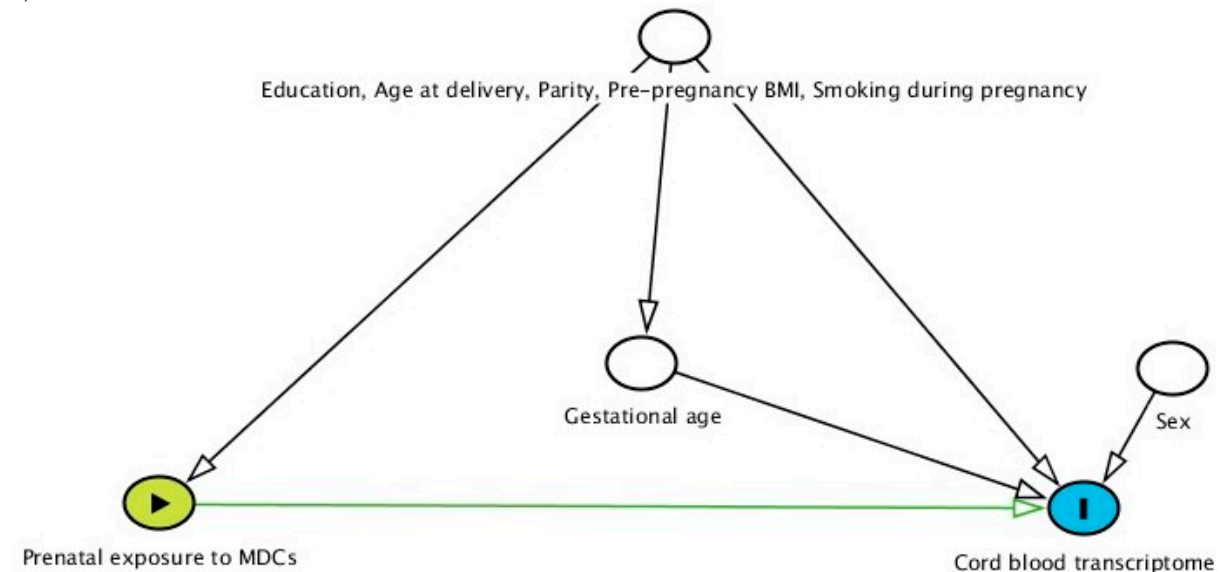
(e) Birth weight



Total = 26170 transcriptomic features

Figure S1 continued

a)



b)

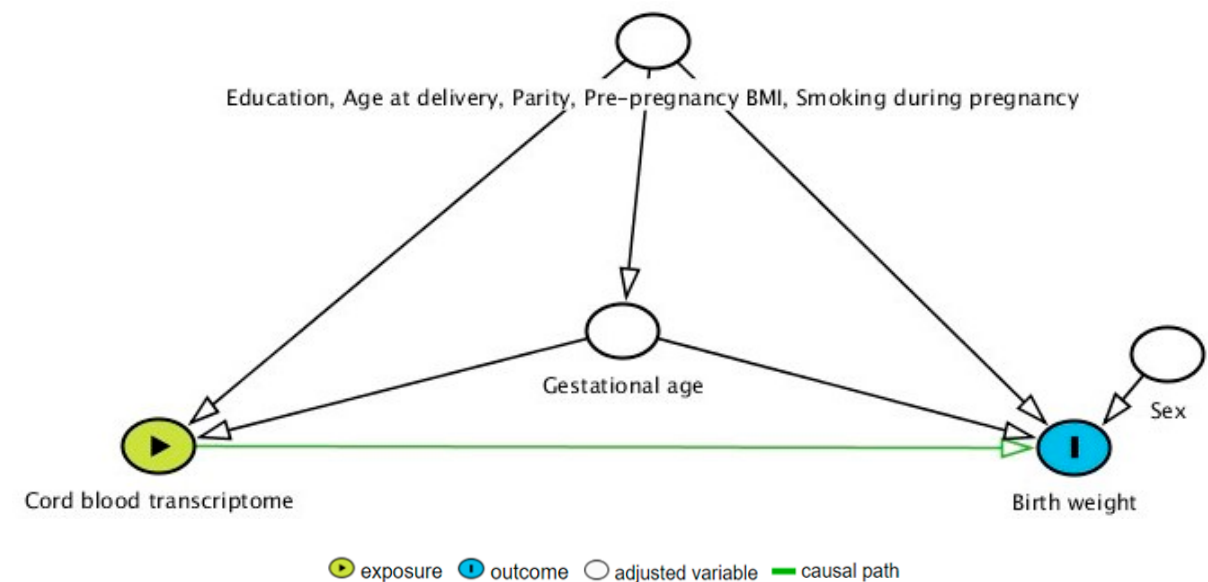


Figure S2. DAG of authors' conception of the associations between prenatal MDC exposures, covariates, and (a) cord blood transcriptome and (b) birth weight among infants born at term.

Abbreviations: DAG, Directed acyclic graphs; MDC, metabolism-disrupting chemical; *p,p'*-DDE, dichlorodiphenyldichloroethylene; PCB-153, polychlorinated biphenyl 153; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid.