

Supplementary Online Content

Ji Y, Azuine RE, Zhang Y, et al. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry*. Published online October 30, 2019. doi:10.1001/jamapsychiatry.2019.3259

eFigure 1. Flowchart of the Sample Inclusion and Exclusion

eFigure 2. Distribution of Maternal and Cord Plasma Acetaminophen Metabolites

eTable 1. Maternal and Child Characteristics Between Mother-Infant Dyads Included and Excluded in the Analyses

eTable 2. Adjusted Associations Between Cord Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood, Using Inverse Probability Weighting

eTable 3. Adjusted Associations Between Cord Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood, With Further Adjustment for Maternal Diagnoses of ADHD, Depression, and Anxiety

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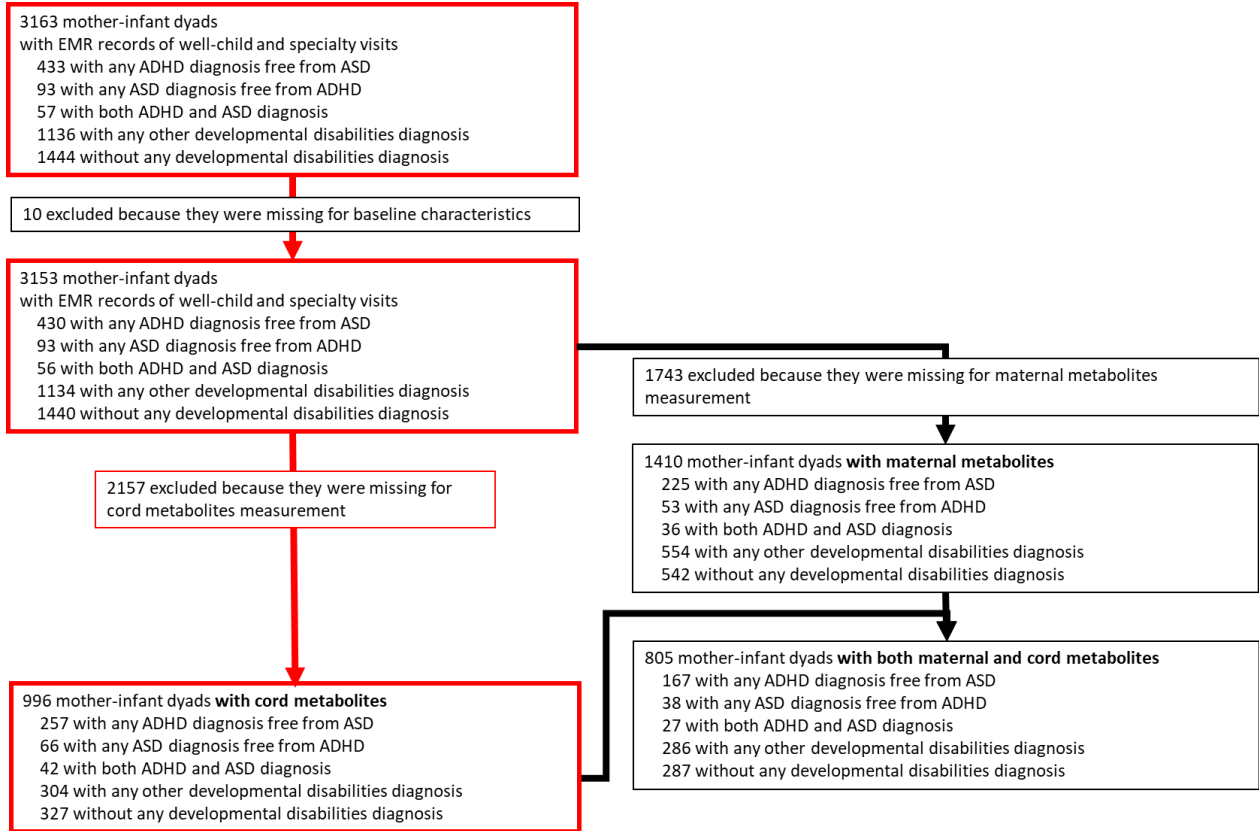
eTable 5. Adjusted Associations Between Cord Plasma Acetaminophen Burden (Alternative Calculation) and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood

eTable 6. Correlation Between Maternal and Cord Plasma Acetaminophen Metabolites

eTable 7. Adjusted Associations Between Maternal Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood

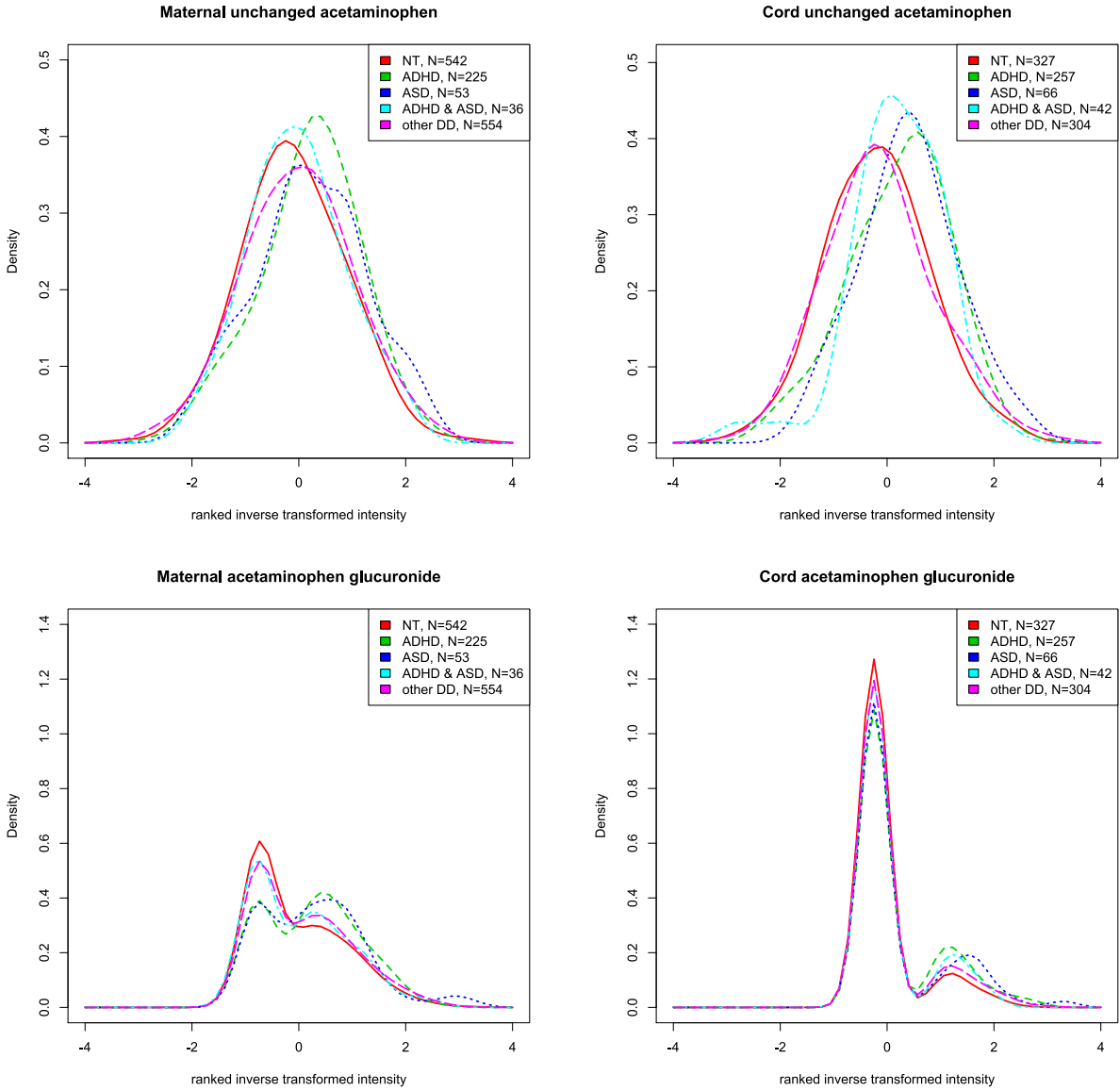
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flowchart of the Sample Inclusion and Exclusion

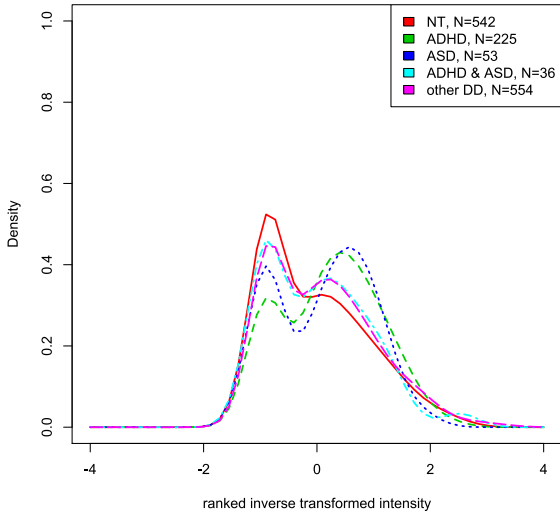


eFigure 2. Distribution of Maternal and Cord Plasma Acetaminophen Metabolites

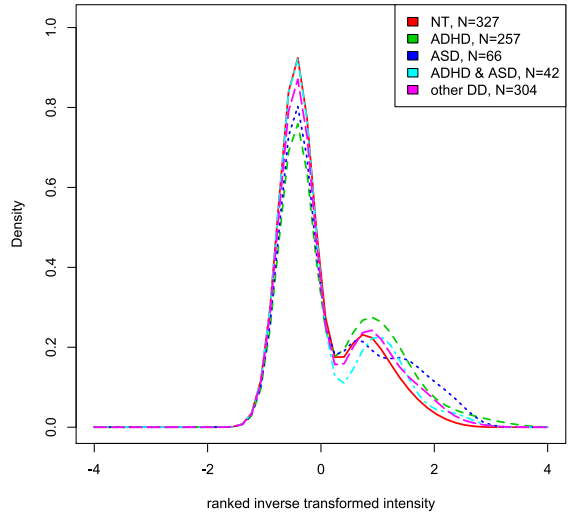
Legend: Distribution of maternal (left) and cord (right) plasma acetaminophen metabolites by child physician-diagnosed conditions (mutually exclusive): neurotypical development (NT), attention deficit and hyperactive disorder (ADHD), autism spectrum disorder (ASD), both ADHD & ASD, and developmental disabilities (other DD).



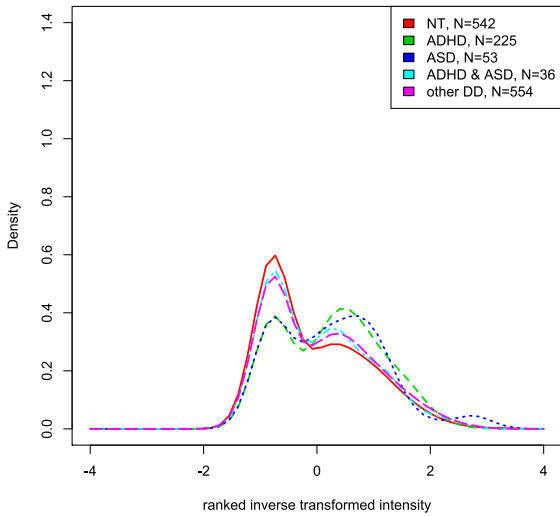
Maternal 3-(N-acetyl-L-cystein-S-yl) acetaminophen



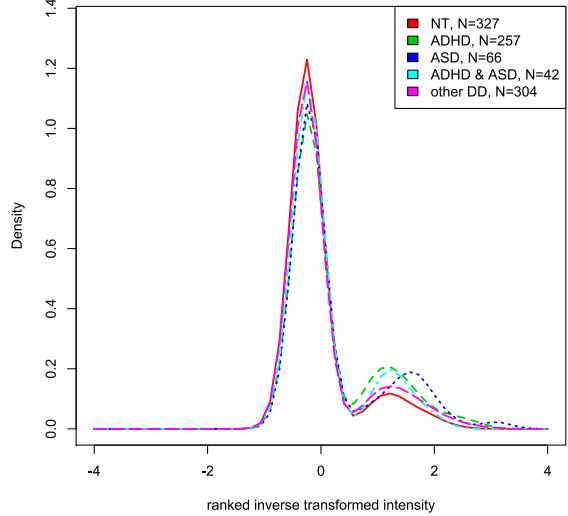
Cord 3-(N-acetyl-L-cystein-S-yl) acetaminophen



Maternal acetaminophen burden



Cord acetaminophen burden



eTable 1. Maternal and Child Characteristics Between Mother-Infant Dyads Included and Excluded in the Analyses

Variables	Subgroups	Included	Excluded	P-value
n		996	2157	
Maternal age (%)	<20	85 (8.5)	210 (9.7)	0.53
	20-34	728 (73.1)	1566 (72.6)	
	>=35	183 (18.4)	381 (17.7)	
Maternal BMI (SD)		26.64 (6.29)	26.59 (6.82)	0.85
Parity (%)	Nulliparous	411 (41.3)	932 (43.2)	0.32
	Multiparous	585 (58.7)	1225 (56.8)	
Income (%)	<\$30,000	475 (47.7)	1044 (48.4)	0.83
	>=\$30,000	143 (14.4)	293 (13.6)	
	Unknown	378 (38.0)	820 (38.0)	
Race/ethnicity (%)	Non-Hispanic Black	632 (63.5)	1379 (63.9)	0.02
	Non-Hispanic White	53 (5.3)	175 (8.1)	
	Hispanic	237 (23.8)	465 (21.6)	
	Others	74 (7.4)	138 (6.4)	
Marital status (%)	Married	347 (34.8)	692 (32.1)	0.14
	Not Married	649 (65.2)	1465 (67.9)	
Maternal education (%)	Below college	659 (66.2)	1368 (63.4)	0.15
	Above college	337 (33.8)	789 (36.6)	
Maternal stress during pregnancy (%)	Not stressful	386 (38.8)	793 (36.8)	0.30
	Stressful	610 (61.2)	1364 (63.2)	
Maternal smoking during pregnancy (%)	Never smoke	824 (82.7)	1744 (80.9)	0.42
	Quitter	98 (9.8)	242 (11.2)	
	Continuous	74 (7.4)	171 (7.9)	
Maternal drinking during pregnancy (%)	No	926 (93.0)	1969 (91.3)	0.12
	Yes	70 (7.0)	188 (8.7)	
Child age by last visit (SD)		9.52 (3.83)	8.62 (4.72)	<0.01
Child's gender (%)	Female	448 (45.0)	1116 (51.7)	<0.01
	Male	548 (55.0)	1041 (48.3)	
Delivery type (%)	C-section	334 (33.5)	797 (36.9)	0.07
	Vaginal	662 (66.5)	1360 (63.1)	
Preterm birth (%)	No	818 (82.1)	1430 (66.3)	<0.01
	Yes	178 (17.9)	727 (33.7)	
Low birthweight (%)	No	825 (82.8)	1460 (67.7)	<0.01
	Yes	171 (17.2)	697 (32.3)	

Note: The p-values were obtained using Pearson's chi-squared test (or Fisher's exact test for small cells) for categorical variables and Student's t-test for continuous variables, respectively.

eTable 2. Adjusted Associations Between Cord Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood, Using Inverse Probability Weighting

Model	Total	NT, N=327	ADHD only, N=257				ASD only, N=66				ADHD & ASD, N=42				Other DD, N=304			
			N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value
Cord unchanged acetaminophen*																		
First tertile	332	132	62 (18.7)	Ref			12 (3.6)	Ref			8 (2.4)	Ref			118 (35.5)	Ref		
Second tertile	332	112	75 (22.6)	1.54	[1.17, 2.04]	<0.01	21 (6.3)	1.32	[0.83, 2.13]	0.25	17 (5.1)	2.25	[1.27, 4.08]	<0.01	107 (32.2)	0.97	[0.78, 1.20]	0.77
Third tertile	332	83	120 (36.1)	2.97	[2.26, 3.91]	<0.01	33 (9.9)	3.29	[2.11, 5.19]	<0.01	17 (5.1)	3.46	[1.94, 6.33]	<0.01	79 (23.8)	0.92	[0.73, 1.17]	0.51
Cord acetaminophen glucuronide*																		
No detection	804	283	190 (23.6)	Ref			50 (6.2)	Ref			34 (4.2)	Ref			247 (30.7)	Ref		
Any detection	192	44	67 (34.9)	2.35	[1.78, 3.10]	<0.01	16 (8.3)	2.29	[1.48, 3.51]	<0.01	8 (4.2)	1.88	[1.06, 3.30]	0.03	57 (29.7)	1.31	[1.01, 1.69]	0.04
Cord 3-(N-Acetyl-L-cystein-S-yl) acetaminophen*																		
No detection	661	234	151 (22.8)	Ref			41 (6.2)	Ref			30 (4.5)	Ref			205 (31.0)	Ref		
Any detection	335	93	106 (31.6)	1.48	[1.17, 1.86]	<0.01	25 (7.5)	1.00	[0.69, 1.44]	1.00	12 (3.6)	0.68	[0.41, 1.10]	0.12	99 (29.6)	0.91	[0.74, 1.11]	0.34
Cord acetaminophen burden**																		
First tertile	332	133	57 (17.2)	Ref			11 (3.3)	Ref			9 (2.7)	Ref			122 (36.7)	Ref		
Second tertile	332	105	89 (26.8)	2.22	[1.67, 2.95]	<0.01	26 (7.8)	1.90	[1.19, 3.05]	<0.01	17 (5.1)	1.82	[1.03, 3.26]	0.04	95 (28.6)	0.92	[0.73, 1.14]	0.44
Third tertile	332	89	111 (33.4)	2.84	[2.15, 3.77]	<0.01	29 (8.7)	2.68	[1.71, 4.28]	<0.01	16 (4.8)	2.41	[1.38, 4.31]	<0.01	87 (26.2)	0.82	[0.65, 1.04]	0.10

Note: All adjusted models were compared to the neurotypical group with adjustment for maternal age at delivery, maternal race/ethnicity, maternal education, marital status, stress during pregnancy, smoking before or during pregnancy, drinking before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and low birthweight.

* Inverse normal transformed intensity ** Sum of all the acetaminophen metabolites.

Unchanged acetaminophen and acetaminophen burden: first tertile as reference; For other acetaminophen metabolites: no detection as reference.

eTable 3. Adjusted Associations Between Cord Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood, With Further Adjustment for Maternal Diagnoses of ADHD, Depression, and Anxiety

Model	NT, N=277		ADHD only, N=178				ASD only, N=57				ADHD & ASD, N=31				Other DD, N=262			
	Total		N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value
Cord unchanged acetaminophen*																		
First tertile	249	102	40 (16.1)	Ref			8 (3.2)	Ref			5 (2.0)	Ref			94 (37.8)	Ref		
Second tertile	272	94	51 (18.8)	1.38	[0.78, 2.46]	0.27	20 (7.4)	1.45	[0.55, 4.08]	0.46	12 (4.4)	1.96	[0.54, 8.00]	0.32	95 (34.9)	0.94	[0.61, 1.45]	0.79
Third tertile	284	81	87 (30.6)	2.72	[1.56, 4.81]	<0.01	29 (10.2)	3.33	[1.33, 9.09]	0.01	14 (4.9)	4.43	[1.27, 18.44]	0.03	73 (25.7)	0.79	[0.50, 1.25]	0.31
Cord acetaminophen glucuronide*																		
No detection	642	236	128 (19.9)	Ref			43 (6.7)	Ref			26 (4.0)	Ref			209 (32.6)	Ref		
Any detection	163	41	50 (30.7)	2.40	[1.38, 4.23]	<0.01	14 (8.6)	1.75	[0.74, 4.03]	0.19	5 (3.1)	1.30	[0.34, 4.24]	0.68	53 (32.5)	1.26	[0.78, 2.06]	0.34
Cord 3-(N-Acetyl-L-cystein-S-yl) acetaminophen*																		
No detection	526	194	95 (18.1)	Ref			37 (7.0)	Ref			24 (4.6)	Ref			176 (33.5)	Ref		
Any detection	279	83	83 (29.7)	2.10	[1.32, 3.36]	<0.01	20 (7.2)	1.07	[0.51, 2.19]	0.85	7 (2.5)	0.50	[0.16, 1.39]	0.21	86 (30.8)	0.96	[0.65, 1.43]	0.85
Cord acetaminophen burden**																		
First tertile	254	102	35 (13.8)	Ref			9 (3.5)	Ref			6 (2.4)	Ref			102 (40.2)	Ref		
Second tertile	273	93	61 (22.3)	2.10	[1.18, 3.78]	0.01	23 (8.4)	1.76	[0.69, 4.72]	0.25	14 (5.1)	2.43	[0.76, 8.70]	0.15	82 (30.0)	0.79	[0.51, 1.21]	0.28
Third tertile	278	82	82 (29.5)	2.89	[1.64, 5.17]	<0.01	25 (9.0)	2.48	[1.00, 6.57]	0.06	11 (4.0)	2.02	[0.60, 7.33]	0.26	78 (28.1)	0.74	[0.47, 1.16]	0.19

Note: All adjusted models were compared to the neurotypical group with adjustment for maternal age at delivery, maternal race/ethnicity, maternal education, marital status, stress during pregnancy, smoking before or during pregnancy, drinking before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, low birthweight, maternal ADHD, maternal depression, and maternal anxiety.

* Inverse normal transformed intensity ** Sum of all the acetaminophen metabolites.

Unchanged acetaminophen and acetaminophen burden: first tertile as reference; For other acetaminophen metabolites: no detection as reference.

eTable 4. Adjusted Associations Between Cord Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood, With Further Adjustment for Maternal Intrauterine Infection/Inflammation

Model	NT, N=327		ADHD only, N=257				ASD only, N=65				ADHD & ASD, N=42				Other DD, N=304			
	Total	N (%)	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value
Cord unchanged acetaminophen*																		
First tertile	332	132 (39.8)	62 (18.7)	Ref			12 (3.6)	Ref			8 (2.4)	Ref			118 (35.5)	Ref		
Second tertile	332	112 (33.7)	75 (22.6)	1.48	[0.92, 2.39]	0.11	21 (6.3)	1.32	[0.56, 3.14]	0.53	17 (5.1)	2.03	[0.75, 5.82]	0.17	107 (32.2)	0.94	[0.64, 1.37]	0.73
Third tertile	331	83 (25.1)	120 (36.3)	2.89	[1.80, 4.67]	<0.01	32 (9.7)	3.54	[1.62, 8.18]	<0.01	17 (5.1)	3.46	[1.28, 10.15]	0.02	79 (23.9)	0.86	[0.56, 1.32]	0.49
Cord acetaminophen glucuronide*																		
No detection	804	283 (35.2)	190 (23.6)	Ref			50 (6.2)	Ref			34 (4.2)	Ref			247 (30.7)	Ref		
Any detection	191	44 (23.0)	67 (35.1)	2.25	[1.38, 3.69]	<0.01	15 (7.9)	2.15	[0.98, 4.60]	0.05	8 (4.2)	1.53	[0.53, 4.10]	0.41	57 (29.8)	1.28	[0.81, 2.03]	0.29
Cord 3-(N-Acetyl-L-cystein-S-yl) acetaminophen*																		
No detection	661	234 (35.4)	151 (22.8)	Ref			41 (6.2)	Ref			30 (4.5)	Ref			205 (31.0)	Ref		
Any detection	334	93 (27.8)	106 (31.7)	1.69	[1.13, 2.53]	0.01	24 (7.2)	1.31	[0.68, 2.52]	0.41	12 (3.6)	0.71	[0.28, 1.65]	0.44	99 (29.6)	1.02	[0.71, 1.47]	0.92
Cord acetaminophen burden**																		
First tertile	332	133 (40.1)	57 (17.2)	Ref			11 (3.3)	Ref			9 (2.7)	Ref			122 (36.7)	Ref		
Second tertile	332	105 (31.6)	89 (26.8)	2.26	[1.40, 3.69]	<0.01	26 (7.8)	2.11	[0.92, 5.07]	0.09	17 (5.1)	2.12	[0.81, 5.82]	0.13	95 (28.6)	0.92	[0.62, 1.36]	0.67
Third tertile	331	89 (26.9)	111 (33.5)	2.86	[1.77, 4.68]	<0.01	28 (8.5)	3.49	[1.55, 8.32]	<0.01	16 (4.8)	2.46	[0.92, 6.87]	0.08	87 (26.3)	0.84	[0.55, 1.26]	0.40

Note: All adjusted models were compared to the neurotypical group with adjustment for maternal age at delivery, maternal race/ethnicity, maternal education, marital status, stress during pregnancy, smoking before or during pregnancy, drinking before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, low birthweight, and maternal intrauterine infection/inflammation.

* Inverse normal transformed intensity ** Sum of all the acetaminophen metabolites.

Unchanged acetaminophen and acetaminophen burden: first tertile as reference; For other acetaminophen metabolites: no detection as reference.

eTable 5. Adjusted Associations Between Cord Plasma Acetaminophen Burden (Alternative Calculation) and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood

Model	Total	NT, N=327	ADHD only, N=257				ASD only, N=66				ADHD & ASD, N=42				Other DD, N=304				
			N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	
Cord acetaminophen burden**																			
First tertile	332	133	57 (17.2)	Ref			11 (3.3)	Ref				9 (2.7)	Ref			122 (36.7)	Ref		
Second tertile	332	105	89 (26.8)	1.64	[1.02, 2.66]	0.04	26 (7.8)	1.88	[0.82, 4.48]	0.14		17 (5.1)	2.24	[0.85, 6.34]	0.11	95 (28.6)	0.91	[0.62, 1.34]	0.64
Third tertile	332	89	111 (33.4)	3.05	[1.90, 4.93]	<0.01	29 (8.7)	3.88	[1.72, 9.26]	<0.01		16 (4.8)	3.47	[1.26, 10.26]	0.02	87 (26.2)	0.94	[0.61, 1.42]	0.75

Cord acetaminophen burden** was based on pediatric percentages (acetaminophen sulfate: 72%, acetaminophen glucuronide: 14%, unchanged acetaminophen: 14%)

eTable 6. Correlation Between Maternal and Cord Plasma Acetaminophen Metabolites

	Maternal unchanged acetaminophen		
Cord unchanged acetaminophen	First tertile	Second tertile	Third tertile
First tertile	112 (41.6%)	94 (35.1%)	63 (23.5%)
Second tertile	77 (28.6%)	83 (31.0%)	108 (40.3%)
Third tertile	80 (29.8%)	91 (33.9%)	97 (36.2%)

Pearson's chi-squared test p-value = 0.0002623

	Maternal acetaminophen glucuronide	
Cord acetaminophen glucuronide	No detection	Any detection
No detection	333 (51.4%)	21 (13.3%)
Any detection	315 (48.6%)	136 (86.7%)

Pearson's chi-squared test p-value < 2.2e-16

	Maternal 3-(N-Acetyl-L-cystein-S-yl) acetaminophen	
Cord 3-(N-Acetyl-L-cystein-S-yl) acetaminophen	No detection	Any detection
No detection	257 (47.9%)	45 (16.7%)
Any detection	279 (52.1%)	224 (83.3%)

Pearson's chi-squared test p-value < 2.2e-16

	Maternal acetaminophen burden		
Cord acetaminophen burden	First tertile	Second tertile	Third tertile
First tertile	122 (45.4%)	99 (36.9%)	48 (17.9%)
Second tertile	65 (24.2%)	90 (33.6%)	113 (42.2%)
Third tertile	82 (30.5%)	79 (29.5%)	107 (39.9%)

Pearson's chi-squared test p-value= 3.318e-10

eTable 7. Adjusted Associations Between Maternal Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions (Mutually Exclusive): Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Both ADHD and ASD, and Developmental Disabilities (Other DD) in Childhood

Model	NT, N=542		ADHD, N=225				ASD, N=53				ADHD & ASD, N=36				Other DD, N=554			
	Total		N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value	N (%)	aOR	95% CI	P-value
Unchanged acetaminophen*																		
First tertile	471	202	51 (10.8)	Ref			13 (2.8)	Ref			12 (2.5)	Ref			193 (41.0)	Ref		
Second tertile	470	178	84 (17.9)	1.83	[1.17, 2.87]	<0.01	18 (3.8)	1.35	[0.61, 3.04]	0.45	14 (3.0)	1.49	[0.61, 3.71]	0.39	176 (37.4)	0.95	[0.70, 1.28]	0.72
Third tertile	470	162	90 (19.1)	2.06	[1.26, 3.38]	<0.01	22 (4.7)	1.26	[0.53, 3.08]	0.60	10 (2.1)	0.88	[0.30, 2.53]	0.82	186 (39.6)	1.02	[0.73, 1.41]	0.91
Acetaminophen glucuronide*																		
No detection	610	268	71 (11.6)	Ref			16 (2.6)	Ref			16 (2.6)	Ref			239 (39.2)	Ref		
Any detection	801	274	154 (19.2)	2.09	[1.42, 3.11]	<0.01	37 (4.6)	1.71	[0.85, 3.52]	0.14	20 (2.5)	1.38	[0.61, 3.15]	0.44	316 (39.5)	1.15	[0.89, 1.50]	0.29
3-(N-Acetyl-L-cystein-S-yl) acetaminophen*																		
No detection	510	227	56 (11.0)	Ref			17 (3.3)	Ref			13 (2.5)	Ref			197 (38.6)	Ref		
Any detection	901	315	169 (18.8)	2.02	[1.36, 3.03]	<0.01	36 (4.0)	1.09	[0.55, 2.21]	0.80	23 (2.6)	1.38	[0.62, 3.19]	0.43	358 (39.7)	1.14	[0.87, 1.49]	0.33
Acetaminophen burden**																		
First tertile	471	205	50 (10.6)	Ref			14 (3.0)	Ref			11 (2.3)	Ref			191 (40.6)	Ref		
Second tertile	470	181	81 (17.2)	1.75	[1.12, 2.76]	0.01	16 (3.4)	1.15	[0.52, 2.57]	0.73	15 (3.2)	1.87	[0.76, 4.79]	0.18	177 (37.7)	0.94	[0.69, 1.26]	0.66
Third tertile	470	156	94 (20.0)	2.45	[1.50, 4.03]	<0.01	23 (4.9)	1.37	[0.59, 3.24]	0.47	10 (2.1)	1.24	[0.42, 3.71]	0.69	187 (39.8)	1.08	[0.78, 1.51]	0.64

Note: All adjusted models were compared to the neurotypical group with adjustment for maternal age at delivery, maternal race/ethnicity, maternal education, marital status, stress during pregnancy, smoking before or during pregnancy, drinking before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and low birthweight.

* Inverse normal transformed intensity ** Sum of all the acetaminophen metabolites.

Unchanged acetaminophen and acetaminophen burden: first tertile as reference; For other acetaminophen metabolites: no detection as reference