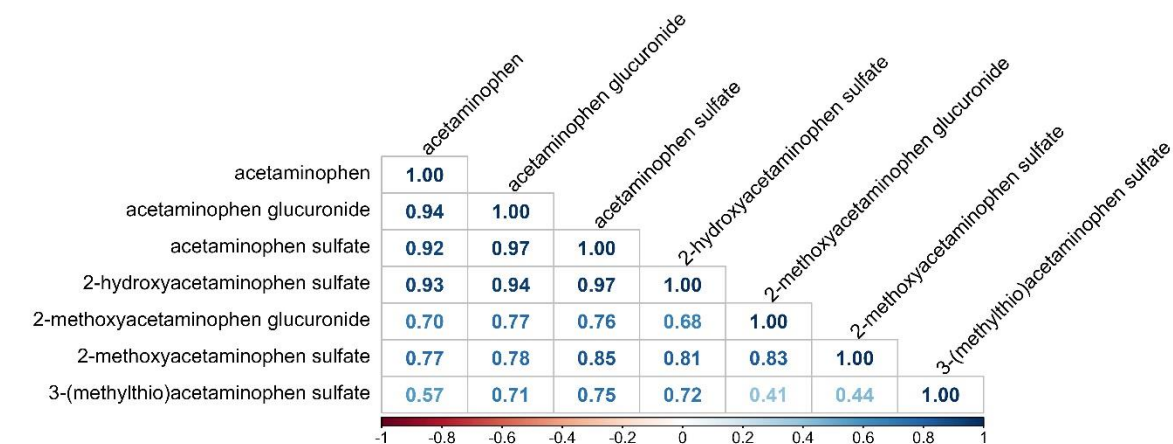


Associations of maternal blood biomarkers of prenatal APAP exposure with placental gene expression and child attention deficit hyperactivity disorder

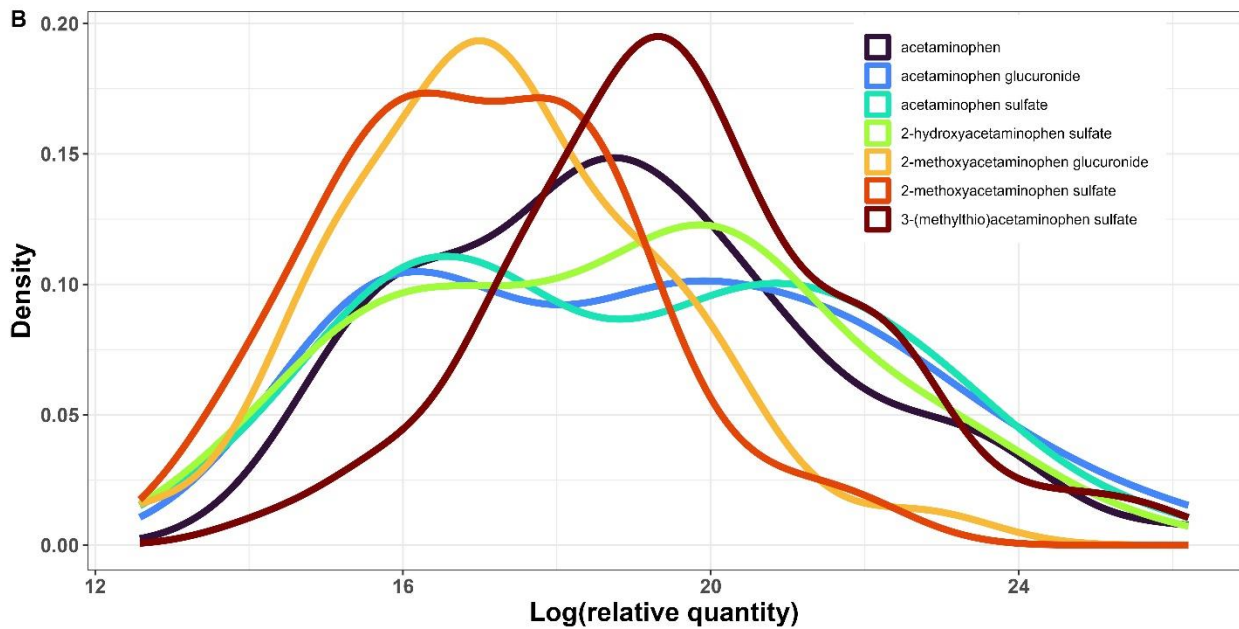
In the format provided by the
authors and unedited

Supplemental Figure 1: Acetaminophen Analyte Pair-wise Pearson Correlations and Distributions

A

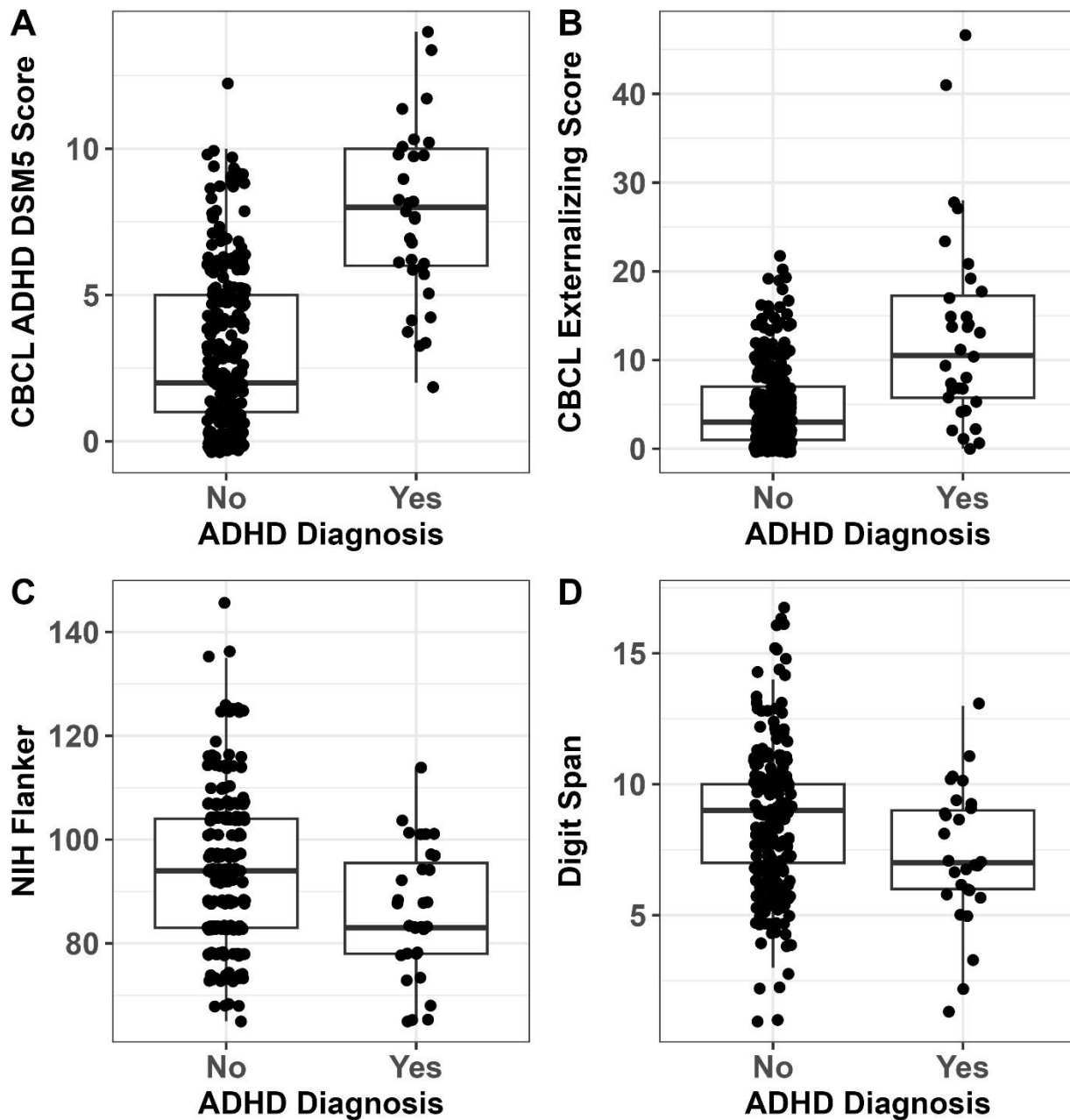


B



Legend: Pearson correlation coefficients for all possible pairs of acetaminophen analytes (A). Non-detect values were dropped within pairs, and all pair-wise correlation P-values <0.05. Acetaminophen analyte distributions among individuals with analytes detected (B). Metabolomics analysis of maternal plasma samples collected in the second trimester was performed using the Metabolon Discovery HD4TM Platform (Metabolon Inc., Morrisville, NC). Metabolomics were relative quantitative, so absolute concentrations are not shown.

Supplemental Figure 2: CBCL and Task Related Outcomes According to Child ADHD Diagnosis



Legend: Boxplots depict median (center line), 25th percentile (minima), and 75th percentile (maxima), while whiskers extend to the highest and lowest values that are within 1.5 times the inter-quartile range of the box. One point per individual depicts scores on CBCL and task related outcomes according to child ADHD diagnosis. Unadjusted analysis of variance two-sided p-values for associations with ADHD were 9.62×10^{-14} (A), $<2 \times 10^{-16}$ (B), 0.005307 (C), and 0.01739 (D). P-values are not adjusted for multiple comparisons.

Supplemental Table 1: Contingency Tables for Prenatal Acetaminophen and Binary Outcomes

Outcome: ADHD diagnosis											
Female				Male				Both Sexes			
		ADHD				ADHD				ADHD	
		Yes	No			Yes	No			Yes	No
Prenatal acetaminophen	Yes	6	25	Prenatal acetaminophen	Yes	5	26	Prenatal acetaminophen	Yes	11	51
	No	6	120		No	15	104		No	21	224
Outcome: prescription ADHD medications											
Female				Male				Both Sexes			
		ADHD medications				ADHD medications				ADHD medications	
		Yes	No			Yes	No			Yes	No
Prenatal acetaminophen	Yes	4	27	Prenatal acetaminophen	Yes	4	27	Prenatal acetaminophen	Yes	8	54
	No	3	123		No	10	109		No	13	232

Supplemental Table 2: Associations of Prenatal Acetaminophen with Child ADHD-Related Outcomes

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Primary analysis results pooled with rubins' rules across 100 imputed datasets							
Acetaminophen (yes vs no) among females	1.819	0.695	2.618	0.009	6.16 (1.58 - 24.05)	ADHD Diagnosis	Female
Acetaminophen (yes vs no) among females	2.328	0.915	2.544	0.011	10.26 (1.71 - 61.68)	Taking ADHD Medications	Female
Acetaminophen (yes vs no) among females	1.028	0.648	1.586	0.113	1.03 (-0.24 - 2.3)	CBCL ADHD-DSM5 Score	Female
Acetaminophen (yes vs no) among females	2.605	1.233	2.112	0.035	2.6 (0.19 - 5.02)	CBCL Externalizing Score	Female
Acetaminophen (yes vs no) among females	-0.109	3.021	-0.036	0.971	-0.11 (-6.03 - 5.81)	NIH Flanker	Female
Acetaminophen (yes vs no) among females	0.452	0.593	0.762	0.447	0.45 (-0.71 - 1.61)	Digit Span	Female
Interaction: acetaminophen yes * sex male	-1.290	0.962	-1.341	0.181	0.28 (0.04 - 1.81)	ADHD Diagnosis	Female
Interaction: acetaminophen yes * sex male	-1.286	1.216	-1.057	0.291	0.28 (0.03 - 3)	Taking ADHD Medications	Female
Interaction: acetaminophen yes * sex male	-1.046	0.829	-1.263	0.207	-1.05 (-2.67 - 0.58)	CBCL ADHD-DSM5 Score	Female
Interaction: acetaminophen yes * sex male	-2.195	1.599	-1.373	0.170	-2.19 (-5.33 - 0.94)	CBCL Externalizing Score	Female
Interaction: acetaminophen yes * sex male	-3.507	4.286	-0.818	0.414	-3.51 (-11.91 - 4.89)	NIH Flanker	Female
Interaction: acetaminophen yes * sex male	-0.721	0.840	-0.859	0.391	-0.72 (-2.37 - 0.92)	Digit Span	Female
Acetaminophen (yes vs no) among males	0.529	0.694	0.762	0.447	1.7 (0.44 - 6.61)	ADHD Diagnosis	Male
Acetaminophen (yes vs no) among males	1.043	0.867	1.203	0.230	2.84 (0.52 - 15.51)	Taking ADHD Medications	Male

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Acetaminophen (yes vs no) among males	-0.019	0.578	-0.032	0.974	-0.02 (-1.15 - 1.11)	CBCL ADHD-DSM5 Score	Male
Acetaminophen (yes vs no) among males	0.410	1.113	0.368	0.713	0.41 (-1.77 - 2.59)	CBCL Externalizing Score	Male
Acetaminophen (yes vs no) among males	-3.617	3.043	-1.189	0.236	-3.62 (-9.58 - 2.35)	NIH Flanker	Male
Acetaminophen (yes vs no) among males	-0.269	0.593	-0.454	0.650	-0.27 (-1.43 - 0.89)	Digit Span	Male
Interaction: acetaminophen yes * sex female	1.290	0.962	1.341	0.181	3.63 (0.55 - 23.94)	ADHD Diagnosis	Male
Interaction: acetaminophen yes * sex female	1.286	1.216	1.057	0.291	3.62 (0.33 - 39.21)	Taking ADHD Medications	Male
Interaction: acetaminophen yes * sex female	1.046	0.829	1.263	0.207	1.05 (-0.58 - 2.67)	CBCL ADHD-DSM5 Score	Male
Interaction: acetaminophen yes * sex female	2.195	1.599	1.373	0.170	2.19 (-0.94 - 5.33)	CBCL Externalizing Score	Male
Interaction: acetaminophen yes * sex female	3.507	4.286	0.818	0.414	3.51 (-4.89 - 11.91)	NIH Flanker	Male
Interaction: acetaminophen yes * sex female	0.721	0.840	0.859	0.391	0.72 (-0.92 - 2.37)	Digit Span	Male
Acetaminophen (yes vs no) among both sexes	1.148	0.494	2.326	0.021	3.15 (1.2 - 8.29)	ADHD Diagnosis	NA
Acetaminophen (yes vs no) among both sexes	1.648	0.642	2.569	0.011	5.2 (1.48 - 18.28)	Taking ADHD Medications	NA
Acetaminophen (yes vs no) among both sexes	0.510	0.456	1.119	0.263	0.51 (-0.38 - 1.4)	CBCL ADHD-DSM5 Score	NA
Acetaminophen (yes vs no) among both sexes	1.527	0.861	1.773	0.076	1.53 (-0.16 - 3.22)	CBCL Externalizing Score	NA
Acetaminophen (yes vs no) among both sexes	-1.868	2.142	-0.872	0.384	-1.87 (-6.07 - 2.33)	NIH Flanker	NA

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Acetaminophen (yes vs no) among both sexes	0.094	0.418	0.224	0.823	0.09 (-0.73 - 0.91)	Digit Span	NA
Results additionally adjusted for birthweight and gestational age							
Acetaminophen (yes vs no) among females	1.855	0.749	2.476	0.014	6.39 (1.47 - 27.77)	ADHD Diagnosis	Female
Acetaminophen (yes vs no) among females	2.474	1.002	2.469	0.014	11.87 (1.67 - 84.56)	Taking ADHD Medications	Female
Acetaminophen (yes vs no) among females	1.005	0.656	1.533	0.125	1.01 (-0.28 - 2.29)	CBCL ADHD-DSM5 Score	Female
Acetaminophen (yes vs no) among females	2.398	1.222	1.963	0.050	2.4 (0 - 4.79)	CBCL Externalizing Score	Female
Acetaminophen (yes vs no) among females	-0.011	3.040	-0.004	0.997	-0.01 (-5.97 - 5.95)	NIH Flanker	Female
Acetaminophen (yes vs no) among females	0.446	0.596	0.747	0.456	0.45 (-0.72 - 1.61)	Digit Span	Female
Interaction: acetaminophen yes * sex male	-1.559	1.029	-1.515	0.131	0.21 (0.03 - 1.58)	ADHD Diagnosis	Female
Interaction: acetaminophen yes * sex male	-1.558	1.302	-1.196	0.233	0.21 (0.02 - 2.7)	Taking ADHD Medications	Female
Interaction: acetaminophen yes * sex male	-1.050	0.826	-1.272	0.203	-1.05 (-2.67 - 0.57)	CBCL ADHD-DSM5 Score	Female
Interaction: acetaminophen yes * sex male	-2.199	1.568	-1.402	0.161	-2.2 (-5.27 - 0.88)	CBCL Externalizing Score	Female
Interaction: acetaminophen yes * sex male	-3.555	4.298	-0.827	0.409	-3.55 (-11.98 - 4.87)	NIH Flanker	Female
Interaction: acetaminophen yes * sex male	-0.735	0.841	-0.874	0.383	-0.73 (-2.38 - 0.91)	Digit Span	Female
Acetaminophen (yes vs no) among males	0.296	0.735	0.403	0.687	1.34 (0.32 - 5.67)	ADHD Diagnosis	Male

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Acetaminophen (yes vs no) among males	0.916	0.921	0.995	0.321	2.5 (0.41 - 15.2)	Taking ADHD Medications	Male
Acetaminophen (yes vs no) among males	-0.045	0.580	-0.078	0.938	-0.05 (-1.18 - 1.09)	CBCL ADHD-DSM5 Score	Male
Acetaminophen (yes vs no) among males	0.199	1.108	0.180	0.857	0.2 (-1.97 - 2.37)	CBCL Externalizing Score	Male
Acetaminophen (yes vs no) among males	-3.566	3.069	-1.162	0.246	-3.57 (-9.58 - 2.45)	NIH Flanker	Male
Acetaminophen (yes vs no) among males	-0.289	0.599	-0.482	0.630	-0.29 (-1.46 - 0.88)	Digit Span	Male
Interaction: acetaminophen yes * sex female	1.559	1.029	1.515	0.131	4.76 (0.63 - 35.74)	ADHD Diagnosis	Male
Interaction: acetaminophen yes * sex female	1.558	1.302	1.196	0.233	4.75 (0.37 - 60.96)	Taking ADHD Medications	Male
Interaction: acetaminophen yes * sex female	1.050	0.826	1.272	0.203	1.05 (-0.57 - 2.67)	CBCL ADHD-DSM5 Score	Male
Interaction: acetaminophen yes * sex female	2.199	1.568	1.402	0.161	2.2 (-0.88 - 5.27)	CBCL Externalizing Score	Male
Interaction: acetaminophen yes * sex female	3.555	4.298	0.827	0.409	3.55 (-4.87 - 11.98)	NIH Flanker	Male
Interaction: acetaminophen yes * sex female	0.735	0.841	0.874	0.383	0.73 (-0.91 - 2.38)	Digit Span	Male
Acetaminophen (yes vs no) among both sexes	1.021	0.528	1.935	0.054	2.78 (0.99 - 7.81)	ADHD Diagnosis	NA
Acetaminophen (yes vs no) among both sexes	1.625	0.694	2.342	0.020	5.08 (1.3 - 19.8)	Taking ADHD Medications	NA
Acetaminophen (yes vs no) among both sexes	0.486	0.464	1.048	0.294	0.49 (-0.42 - 1.39)	CBCL ADHD-DSM5 Score	NA
Acetaminophen (yes vs no) among both sexes	1.319	0.865	1.524	0.127	1.32 (-0.38 - 3.01)	CBCL Externalizing Score	NA

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Acetaminophen (yes vs no) among both sexes	-1.786	2.168	-0.824	0.411	-1.79 (-6.04 - 2.46)	NIH Flanker	NA
Acetaminophen (yes vs no) among both sexes	0.083	0.424	0.195	0.845	0.08 (-0.75 - 0.91)	Digit Span	NA
Unadjusted model results							
Acetaminophen (yes vs no) among females	1.569	0.618	2.539	0.011	4.8 (1.4 - 16.56)	ADHD Diagnosis	Female
Acetaminophen (yes vs no) among females	1.804	0.793	2.276	0.023	6.07 (1.27 - 32.35)	Taking ADHD Medications	Female
Acetaminophen (yes vs no) among females	1.043	0.682	1.530	0.127	1.04 (-0.29 - 2.38)	CBCL ADHD-DSM5 Score	Female
Acetaminophen (yes vs no) among females	2.451	1.317	1.861	0.064	2.45 (-0.13 - 5.03)	CBCL Externalizing Score	Female
Acetaminophen (yes vs no) among females	-0.130	2.949	-0.044	0.965	-0.13 (-5.94 - 5.68)	NIH Flanker	Female
Acetaminophen (yes vs no) among females	0.838	0.593	1.414	0.158	0.84 (-0.33 - 2.01)	Digit Span	Female
Interaction: acetaminophen yes * sex male	-1.281	0.834	-1.535	0.125	0.28 (0.05 - 1.4)	ADHD Diagnosis	Female
Interaction: acetaminophen yes * sex male	-1.325	1.012	-1.309	0.191	0.27 (0.03 - 1.89)	Taking ADHD Medications	Female
Interaction: acetaminophen yes * sex male	-1.562	0.935	-1.671	0.096	-1.56 (-3.39 - 0.27)	CBCL ADHD-DSM5 Score	Female
Interaction: acetaminophen yes * sex male	-3.120	1.928	-1.618	0.107	-3.12 (-6.9 - 0.66)	CBCL Externalizing Score	Female
Interaction: acetaminophen yes * sex male	-1.838	4.131	-0.445	0.657	-1.84 (-9.97 - 6.29)	NIH Flanker	Female
Interaction: acetaminophen yes * sex male	-1.340	0.823	-1.629	0.104	-1.34 (-2.96 - 0.28)	Digit Span	Female

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Acetaminophen (yes vs no) among males	0.288	0.561	0.513	0.608	1.33 (0.4 - 3.8)	ADHD Diagnosis	Male
Acetaminophen (yes vs no) among males	0.479	0.629	0.761	0.446	1.61 (0.42 - 5.25)	Taking ADHD Medications	Male
Acetaminophen (yes vs no) among males	-0.519	0.640	-0.812	0.418	-0.52 (-1.77 - 0.73)	CBCL ADHD-DSM5 Score	Male
Acetaminophen (yes vs no) among males	-0.669	1.408	-0.475	0.635	-0.67 (-3.43 - 2.09)	CBCL Externalizing Score	Male
Acetaminophen (yes vs no) among males	-1.968	2.892	-0.680	0.497	-1.97 (-7.66 - 3.73)	NIH Flanker	Male
Acetaminophen (yes vs no) among males	-0.502	0.570	-0.880	0.380	-0.5 (-1.63 - 0.62)	Digit Span	Male
Interaction: acetaminophen yes * sex female	1.281	0.834	1.535	0.125	3.6 (0.71 - 19.45)	ADHD Diagnosis	Male
Interaction: acetaminophen yes * sex female	1.325	1.012	1.309	0.191	3.76 (0.53 - 30.33)	Taking ADHD Medications	Male
Interaction: acetaminophen yes * sex female	1.562	0.935	1.671	0.096	1.56 (-0.27 - 3.39)	CBCL ADHD-DSM5 Score	Male
Interaction: acetaminophen yes * sex female	3.120	1.928	1.618	0.107	3.12 (-0.66 - 6.9)	CBCL Externalizing Score	Male
Interaction: acetaminophen yes * sex female	1.838	4.131	0.445	0.657	1.84 (-6.29 - 9.97)	NIH Flanker	Male
Interaction: acetaminophen yes * sex female	1.340	0.823	1.629	0.104	1.34 (-0.28 - 2.96)	Digit Span	Male
Acetaminophen (yes vs no) among both sexes	0.833	0.403	2.066	0.039	2.3 (1.01 - 4.99)	ADHD Diagnosis	NA
Acetaminophen (yes vs no) among both sexes	0.972	0.474	2.051	0.040	2.64 (1 - 6.6)	Taking ADHD Medications	NA
Acetaminophen (yes vs no) among both sexes	0.290	0.463	0.627	0.531	0.29 (-0.62 - 1.2)	CBCL ADHD-DSM5 Score	NA

Model Term	Estimate	Standard error	Statistic	P-value ¹	Odds ratio or regression coefficient (95% confidence interval)	Outcome	Sex reference level
Acetaminophen (yes vs no) among both sexes	0.942	0.952	0.990	0.323	0.94 (-0.92 - 2.81)	CBCL Externalizing Score	NA
Acetaminophen (yes vs no) among both sexes	-0.988	2.065	-0.479	0.633	-0.99 (-5.05 - 3.08)	NIH Flanker	NA
Acetaminophen (yes vs no) among both sexes	0.145	0.411	0.353	0.725	0.15 (-0.66 - 0.96)	Digit Span	NA

¹Two-sided P-values come from logistic regressions for binary outcomes (child ADHD and ADHD medications) and linear regressions for continuous outcomes (CBCL, NIH Flanker, and Digit Span). P-values are not adjusted for multiple comparisons.

Supplemental Table 3: Descriptive Statistics of the Study Sample Stratified by RNA-Sequencing Data Availability

	No RNA-seq (N=133)	RNA-seq sample (N=174)	Total (N=307)	P-value ¹
Prenatal acetaminophen				0.744
No	105 (78.9%)	140 (80.5%)	245 (79.8%)	
Yes	28 (21.1%)	34 (19.5%)	62 (20.2%)	
Child ADHD Diagnosis (n (%))				0.482
No	121 (91.0%)	154 (88.5%)	275 (89.6%)	
Yes	12 (9.0%)	20 (11.5%)	32 (10.4%)	
Prescription medications for ADHD (n (%))				0.681
No	123 (92.5%)	163 (93.7%)	286 (93.2%)	
Yes	10 (7.5%)	11 (6.3%)	21 (6.8%)	
CBCL ADHD DSM5-oriented scale (raw score)				0.897
N-Miss	0	2	2	
Mean (SD)	3.436 (3.154)	3.483 (3.064)	3.462 (3.098)	
Range	0.000 - 12.000	0.000 - 14.000	0.000 - 14.000	
CBCL externalizing (raw score)				0.588
N-Miss	0	2	2	
Mean (SD)	5.699 (6.686)	5.302 (6.058)	5.475 (6.332)	
Range	0.000 - 41.000	0.000 - 47.000	0.000 - 47.000	
NIH Flanker (uncorrected standard score)				0.388
N-Miss	9	17	26	
Mean (SD)	93.516 (14.559)	92.045 (13.860)	92.694 (14.166)	
Range	65.000 - 146.000	65.000 - 136.000	65.000 - 146.000	
Digit Span (scaled score)				0.738
N-Miss	18	23	41	
Mean (SD)	8.383 (2.885)	8.497 (2.648)	8.447 (2.748)	
Range	1.000 - 17.000	1.000 - 16.000	1.000 - 17.000	
Child sex (n (%))				0.821
Female	69 (51.9%)	88 (50.6%)	157 (51.1%)	
Male	64 (48.1%)	86 (49.4%)	150 (48.9%)	
Maternal age (years)				0.394

	No RNA-seq (N=133)	RNA-seq sample (N=174)	Total (N=307)	P-value ¹
Mean (SD)	24.511 (5.090)	25.029 (5.397)	24.805 (5.264)	
Range	16.000 - 40.000	16.000 - 40.000	16.000 - 40.000	
Pre-pregnancy BMI (kg/m²)				0.403
N-Miss	2	0	2	
Mean (SD)	28.290 (8.257)	29.098 (8.383)	28.751 (8.325)	
Range	15.000 - 56.000	16.000 - 62.000	15.000 - 62.000	
Maternal tobacco (n (%))				0.467
No	114 (85.7%)	154 (88.5%)	268 (87.3%)	
Yes	19 (14.3%)	20 (11.5%)	39 (12.7%)	
Maternal alcohol (n (%))				0.533
No	123 (92.5%)	164 (94.3%)	287 (93.5%)	
Yes	10 (7.5%)	10 (5.7%)	20 (6.5%)	
Prenatal stressful life experiences (number)				0.415
Mean (SD)	2.023 (2.017)	1.839 (1.898)	1.919 (1.949)	
Range	0.000 - 8.000	0.000 - 9.000	0.000 - 9.000	
Gravidity (number of pregnancies)				0.905
Mean (SD)	2.812 (1.810)	2.787 (1.769)	2.798 (1.784)	
Range	1.000 - 9.000	1.000 - 9.000	1.000 - 9.000	
Maternal ethnicity (n (%))				0.618
Not Hispanic/Latino	131 (98.5%)	170 (97.7%)	301 (98.0%)	
Hispanic/Latino	<5 (<4%)	<5 (<3%)	6 (2.0%)	
Maternal education (n (%))				0.847
High School completion	79 (59.4%)	101 (58.0%)	180 (58.6%)	
<High School	22 (16.5%)	27 (15.5%)	49 (16.0%)	
Graduated college or technical school	29 (21.8%)	39 (22.4%)	68 (22.1%)	
Some graduate work or graduate/professional degree	<5 (<4%)	7 (4.0%)	10 (3.3%)	
Family income adjusted (USD)				0.325
N-Miss	15	12	27	
Mean (SD)	23463 (21928)	26111 (22352)	24995 (22173)	

	No RNA-seq (N=133)	RNA-seq sample (N=174)	Total (N=307)	P-value ¹
Range	2493 - 82637	2545 - 83437	2493 – 83437	
Neighborhood deprivation index (standardized score)				0.217
N-Miss	0	1	1	
Mean (SD)	0.760 (0.747)	0.654 (0.737)	0.700 (0.742)	
Range	-3.271	-3.683	-3.683	
Mental health disorders in immediate family (n (%))				0.992
N-Miss	8	4	12	
No	103 (82.4%)	140 (82.4%)	243 (82.4%)	
Yes	22 (17.6%)	30 (17.6%)	52 (17.6%)	
NSAIDs during pregnancy (n (%))				0.451
N-Miss	3	3	6	
No	126 (96.9%)	168 (98.2%)	294 (97.7%)	
Yes	<5 (<4%)	<5 (<3%)	7 (2.3%)	
Antibiotics during pregnancy (n (%))				0.051
N-Miss	3	3	6	
No	109 (83.8%)	156 (91.2%)	265 (88.0%)	
Yes	21 (16.2%)	15 (8.8%)	36 (12.0%)	
Delivery method (n (%))				0.092
Vaginal	89 (66.9%)	100 (57.5%)	189 (61.6%)	
C-section	44 (33.1%)	74 (42.5%)	118 (38.4%)	
Labor type (n (%))				0.029
Spontaneous, augmented	41 (30.8%)	62 (35.6%)	103 (33.6%)	
Spontaneous	45 (33.8%)	33 (19.0%)	78 (25.4%)	
Induced	28 (21.1%)	45 (25.9%)	73 (23.8%)	
No Labor	19 (14.3%)	34 (19.5%)	53 (17.3%)	
Birthweight (g)				0.028
Mean (SD)	3007.060 (624.333)	3159.845 (579.980)	3093.655 (603.382)	
Range	780.000 - 4450.000	757.000 - 4640.000	757.000 - 4640.000	
Gestational age at birth (weeks)				0.303
Mean (SD)	38.377 (2.902)	38.670 (2.072)	38.543 (2.466)	
Range	25.857 - 41.714	26.857 - 41.857	25.857 - 41.857	
Child age at study visit (years)				0.787

	No RNA-seq (N=133)	RNA-seq sample (N=174)	Total (N=307)	P-value ¹
Mean (SD)	9.087 (0.809)	9.113 (0.869)	9.102 (0.843)	
Range	8.010 - 10.970	8.010 - 10.980	8.010 - 10.980	

¹ Two-sided P-values calculated from analysis of variance and chi-square goodness of fit tests for continuous and categorical variables, respectively. P-values are not adjusted for multiple comparisons.