

Figure S1. Flowchart of sample included in the analysis.

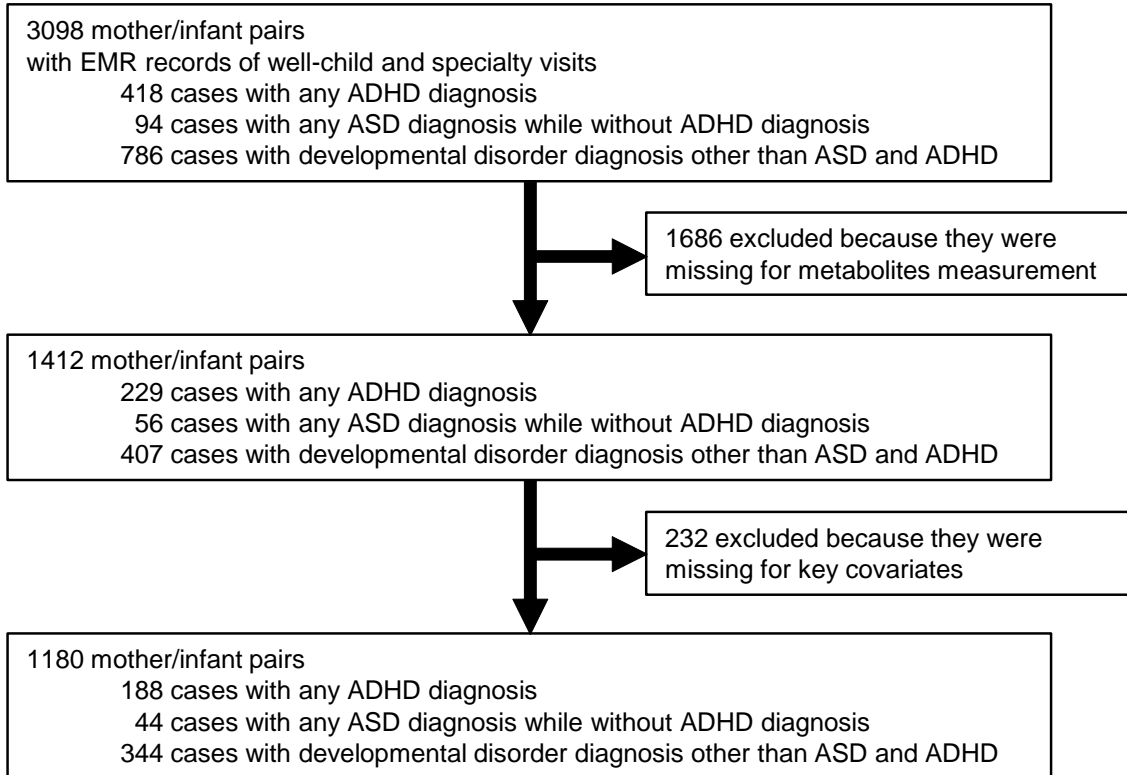


Table S1. Maternal and child characteristics for participants excluded and included in the analysis.

Variable	Total, N (%)	Excluded, N (%)	Included, N (%)	P-value[‡]
Total	3098 (100)	1918 (61.91)	1180 (38.09)	
Maternal Age				0.796
	2534			
<35	(81.79)	1569 (81.80)	965 (81.78)	
≥35	556 (17.95)	341 (17.78)	215 (18.22)	
Education level				0.109
	2642			
Below college degree	(85.28)	1609 (83.89)	1033 (87.54)	
College degree or above	420 (13.56)	273 (14.23)	147 (12.46)	
Maternal race/ethnicity				<0.001
	1965			
Black	(63.43)	1156 (60.27)	809 (68.56)	
White	227 (7.33)	179 (9.33)	48 (4.07)	
Hispanic	682 (22.01)	426 (22.21)	256 (21.69)	
Other	209 (6.75)	142 (7.40)	67 (5.68)	
Smoking before or during pregnancy				0.222
	2496			
Never	(80.57)	1519 (79.20)	977 (82.80)	
Quitter	238 (7.68)	148 (7.72)	90 (7.63)	
Continuous	330 (10.65)	217 (11.31)	113 (9.58)	
Drinking before or during pregnancy				0.627
	2740			
No	(88.44)	1654 (86.24)	1086 (92.03)	
Yes	247 (7.97)	153 (7.98)	94 (7.97)	
Child's sex				0.617
	1529			
Female	(49.35)	953 (49.69)	576 (48.81)	
	1567			
Male	(50.58)	963 (50.21)	604 (51.19)	
Delivery type				0.930
	1116			
C-section	(36.02)	690 (35.97)	426 (36.10)	
	1967			
Vaginal	(63.49)	1213 (63.24)	754 (63.90)	
Gestational age, week				0.003
Mean (SD)	37.6(3.5)	37.5(3.6)	37.9(3.3)	
Birthweight, g				<0.001
	2898.3(819.			
Mean (SD)	7)	2856.5(834.9)	2966.2(789.9)	

Note: [‡]The p-values were obtained from χ^2 tests or t-tests between children included in and excluded from the main analysis.

Table S2. List of ICD-9 and ICD-10 codes for the diagnosis of each developmental disorder.

Developmental disorder	ICD-9 codes	ICD-10 codes
ASD	299.0, 299.00, 299.01, 299.8, 299.80, 299.81, 299.9, 299.90, 299.91	F84.0, F84.8, F84.9
ADHD	314.0, 314.00, 314.01, 314.1, 314.2, 314.8, 314.9	F90, F90.0, F90.1, F90.2, F90.8, F90.9
Developmental delays	315.0-315.9	F81.0, R48.0, F81.81, F81.2, F81.89, F80.1, F80.2, H93.25, F80.4, F80.81, F80.0, F80.82, F80.89, F82, F88, F81.9, F89
Intellectual disabilities	317-319	F70, F71, F72, F73, F78, F79

Table S3. The association between maternal acetaminophen metabolites and the risk of ADHD diagnosis only, ASD diagnosis only, and diagnoses of both ADHD and ASD in offspring.

Model	ADHD only, N=166			ASD only, N=44			ADHD and ASD, N=22		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Unchanged acetaminophen*									
Model 1	Second tertile	1.92 (1.22,3.01)	0.005	1.09 (0.49,2.45)	0.832	0.79 (0.28,2.25)	0.657		
	Third tertile	2.29 (1.47,3.57)	<0.001	1.79 (0.86,3.73)	0.118	0.95 (0.35,2.61)	0.928		
Model 2	Second tertile	1.96 (1.20,3.20)	0.007	0.96 (0.41,2.25)	0.932	0.85 (0.28,2.64)	0.785		
	Third tertile	2.32 (1.38,3.89)	0.001	1.32 (0.57,3.07)	0.523	0.92 (0.27,3.20)	0.901		
Model 3	Second tertile	1.96 (1.20,3.20)	0.007	0.97 (0.41,2.28)	0.947	0.91 (0.29,2.83)	0.868		
	Third tertile	2.32 (1.38,3.89)	0.001	1.32 (0.57,3.08)	0.516	0.92 (0.26,3.21)	0.891		
Model 4	Second tertile	1.95 (1.19,3.18)	0.008	0.96 (0.41,2.25)	0.926	0.85 (0.27,2.63)	0.778		
	Third tertile	2.30 (1.37,3.86)	0.002	1.31 (0.56,3.05)	0.534	0.91 (0.26,3.14)	0.884		
Model 5	Second tertile	1.97 (1.21,3.22)	0.007	0.96 (0.41,2.24)	0.920	0.85 (0.28,2.64)	0.783		
	Third tertile	2.29 (1.37,3.85)	0.002	1.33 (0.57,3.10)	0.509	0.93 (0.27,3.24)	0.912		
Model 6	Second tertile	2.01 (1.22,3.29)	0.006	0.98 (0.42,2.29)	0.958	0.91 (0.29,2.85)	0.872		
	Third tertile	2.28 (1.36,3.84)	0.002	1.33 (0.57,3.10)	0.516	0.92 (0.26,3.22)	0.892		
3-(N-Acetyl-L-cystein-S-yl) acetaminophen*									
Model 1	Below median	1.82 (1.17,2.83)	0.008	0.91 (0.40,2.07)	0.819	0.91 (0.32,2.60)	0.858		
	Above median	2.31 (1.50,3.55)	<0.001	1.81 (0.89,3.65)	0.100	1.11 (0.41,3.03)	0.841		
Model 2	Below median	1.90 (1.18,3.05)	0.008	0.77 (0.33,1.82)	0.557	0.98 (0.32,2.99)	0.974		
	Above median	2.28 (1.37,3.80)	0.002	1.19 (0.52,2.73)	0.688	0.90 (0.26,3.13)	0.868		
Model 3	Below median	1.91 (1.18,3.08)	0.008	0.78 (0.33,1.86)	0.576	1.12 (0.37,3.43)	0.843		
	Above median	2.28 (1.37,3.81)	0.002	1.19 (0.52,2.75)	0.680	0.91 (0.26,3.18)	0.888		
Model 4	Below median	1.87 (1.16,3.01)	0.010	0.76 (0.32,1.80)	0.537	1.00 (0.33,3.07)	0.996		
	Above median	2.25 (1.34,3.76)	0.002	1.17 (0.51,2.70)	0.717	0.89 (0.26,3.08)	0.860		
Model 5	Below median	1.88 (1.17,3.03)	0.009	0.78 (0.33,1.85)	0.576	1.00 (0.33,3.05)	0.994		
	Above median	2.25 (1.35,3.75)	0.002	1.21 (0.52,2.78)	0.660	0.91 (0.26,3.18)	0.882		
Model 6	Below median	1.93 (1.19,3.11)	0.008	0.80 (0.33,1.89)	0.604	1.15 (0.37,3.53)	0.812		
	Above median	2.24 (1.34,3.76)	0.002	1.20 (0.52,2.78)	0.676	0.91 (0.26,3.20)	0.889		
Acetaminophen glucuronide*									
Model 1	Below median	1.69 (1.09,2.60)	0.018	1.97 (0.94,4.13)	0.074	0.66 (0.21,2.07)	0.471		
	Above median	2.16 (1.44,3.26)	<0.001	1.82 (0.86,3.88)	0.118	0.98 (0.36,2.65)	0.964		
Model 2	Below median	1.67 (1.04,2.68)	0.033	1.39 (0.63,3.07)	0.411	0.51 (0.15,1.79)	0.293		
	Above median	2.30 (1.40,3.78)	0.001	1.20 (0.50,2.88)	0.680	0.88 (0.24,3.20)	0.845		
Model 3	Below median	1.67 (1.04,2.69)	0.034	1.42 (0.64,3.15)	0.390	0.56 (0.16,2.00)	0.373		
	Above median	2.30 (1.40,3.78)	0.001	1.22 (0.51,2.92)	0.663	0.88 (0.24,3.22)	0.851		
Model 4	Below median	1.66 (1.04,2.66)	0.035	1.38 (0.63,3.05)	0.422	0.51 (0.14,1.79)	0.293		
	Above median	2.26 (1.37,3.72)	0.001	1.19 (0.49,2.86)	0.702	0.88 (0.24,3.17)	0.845		
Model 5	Below median	1.68 (1.05,2.69)	0.032	1.39 (0.63,3.06)	0.418	0.51 (0.15,1.78)	0.290		
	Above median	2.28 (1.38,3.75)	0.001	1.21 (0.50,2.91)	0.668	0.89 (0.24,3.25)	0.858		
Model 6	Below median	1.74 (1.08,2.81)	0.023	1.44 (0.65,3.20)	0.373	0.56 (0.16,2.02)	0.378		
	Above median	2.26 (1.37,3.73)	0.001	1.21 (0.50,2.92)	0.675	0.88 (0.24,3.24)	0.852		

Model	ADHD only, N=166			ASD only, N=44			ADHD and ASD, N=22		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Acetaminophen burden**									
Model 1	Below median	1.77 (1.15,2.71)	0.009	1.85 (0.87,3.93)	0.110	0.66 (0.21,2.08)	0.478		
	Above median	2.08 (1.38,3.14)	0.001	1.94 (0.92,4.08)	0.080	0.97 (0.36,2.64)	0.954		
Model 2	Below median	1.76 (1.10,2.80)	0.018	1.32 (0.59,2.95)	0.495	0.52 (0.15,1.81)	0.303		
	Above median	2.16 (1.31,3.55)	0.003	1.30 (0.55,3.08)	0.553	0.86 (0.24,3.12)	0.819		
Model 3	Below median	1.76 (1.10,2.82)	0.019	1.35 (0.60,3.02)	0.471	0.57 (0.16,2.03)	0.387		
	Above median	2.16 (1.31,3.55)	0.003	1.31 (0.55,3.12)	0.539	0.86 (0.24,3.14)	0.822		
Model 4	Below median	1.74 (1.09,2.79)	0.020	1.31 (0.59,2.93)	0.506	0.52 (0.15,1.82)	0.303		
	Above median	2.12 (1.28,3.50)	0.003	1.28 (0.54,3.06)	0.572	0.86 (0.24,3.09)	0.819		
Model 5	Below median	1.77 (1.11,2.82)	0.017	1.31 (0.59,2.93)	0.505	0.52 (0.15,1.80)	0.299		
	Above median	2.13 (1.29,3.52)	0.003	1.31 (0.55,3.12)	0.539	0.87 (0.24,3.17)	0.832		
Model 6	Below median	1.84 (1.14,2.96)	0.012	1.37 (0.61,3.07)	0.452	0.57 (0.16,2.05)	0.392		
	Above median	2.11 (1.27,3.49)	0.004	1.30 (0.55,3.12)	0.550	0.86 (0.24,3.15)	0.823		

Note: NT was defined as free of any developmental disorder diagnosis; ADHD only was defined as any ADHD diagnosis without having an ASD diagnosis; ASD only was defined as any ASD diagnosis without having an ADHD diagnosis; ADHD and ASD was defined as having both ADHD and ASD diagnosis;

Model 1: Multinomial logistic regression without adjustment;

Model 2: Model 1 further adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking before or during pregnancy, drinking before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and birthweight;

Model 3: Model 2 further adjusted for maternal fever during pregnancy;

Model 4: Model 2 further adjusted for maternal intrauterine infection/inflammation during pregnancy;

Model 5: Model 2 further adjusted for breastfeeding;

Model 6: Model 2 further adjusted for maternal fever, maternal intrauterine infection/inflammation during pregnancy, and breastfeeding.

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

Unchanged acetaminophen: first tertile as reference; For other exposures: no detection as reference

Table S4. The association between maternal acetaminophen metabolites and the risk of ADHD diagnosis, ASD diagnosis (excluding ADHD), and other DD diagnosis in offspring using propensity score weighted multinomial logistic regression models.

Model	ADHD,188(15.9%)			ASD,44(3.7%)			otherDD,344(29.2%)		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Unchanged acetaminophen*									
Model 1	Second tertile	2.48 (1.56,3.96)	<0.001	1.14 (0.56,2.32)	0.712	0.94 (0.69,1.26)	0.665		
	Third tertile	3.75 (2.38,5.89)	<0.001	1.67 (0.85,3.26)	0.136	1.10 (0.81,1.48)	0.547		
Model 2	Second tertile	3.02 (1.83,4.97)	<0.001	1.58 (0.74,3.35)	0.238	1.16 (0.83,1.60)	0.389		
	Third tertile	4.14 (2.56,6.71)	<0.001	1.72 (0.85,3.47)	0.130	1.05 (0.76,1.46)	0.770		
Model 3	Second tertile	3.05 (1.85,5.03)	<0.001	1.68 (0.78,3.60)	0.183	1.13 (0.81,1.58)	0.456		
	Third tertile	4.14 (2.55,6.70)	<0.001	1.79 (0.88,3.61)	0.106	1.05 (0.75,1.45)	0.790		
Model 4	Second tertile	2.99 (1.81,4.94)	<0.001	1.64 (0.77,3.52)	0.201	1.14 (0.82,1.59)	0.421		
	Third tertile	4.12 (2.54,6.67)	<0.001	1.80 (0.89,3.64)	0.103	1.04 (0.75,1.45)	0.804		
Model 5	Second tertile	2.98 (1.80,4.91)	<0.001	1.57 (0.74,3.34)	0.240	1.15 (0.83,1.60)	0.401		
	Third tertile	4.05 (2.50,6.57)	<0.001	1.71 (0.85,3.46)	0.134	1.04 (0.75,1.44)	0.824		
Model 6	Second tertile	3.00 (1.81,4.95)	<0.001	1.68 (0.78,3.60)	0.183	1.13 (0.81,1.57)	0.467		
	Third tertile	3.96 (2.44,6.44)	<0.001	1.78 (0.87,3.61)	0.112	1.03 (0.74,1.43)	0.857		
3-(N-Acetyl-L-cystein-S-yl) acetaminophen*									
Model 1	Below median	2.98 (1.87,4.77)	<0.001	1.85 (0.91,3.75)	0.088	2.06 (1.53,2.76)	<0.001		
	Above median	4.35 (2.75,6.88)	<0.001	2.28 (1.13,4.60)	0.021	1.65 (1.20,2.27)	0.002		
Model 2	Below median	3.45 (2.11,5.64)	<0.001	2.19 (1.05,4.55)	0.037	2.19 (1.59,3.02)	<0.001		
	Above median	4.60 (2.81,7.54)	<0.001	2.20 (1.05,4.62)	0.037	1.44 (1.02,2.03)	0.041		
Model 3	Below median	3.52 (2.15,5.78)	<0.001	2.38 (1.14,4.97)	0.022	2.18 (1.58,3.01)	<0.001		
	Above median	4.61 (2.82,7.55)	<0.001	2.32 (1.11,4.87)	0.026	1.43 (1.01,2.03)	0.043		
Model 4	Below median	3.43 (2.09,5.61)	<0.001	2.30 (1.10,4.82)	0.027	2.18 (1.58,3.01)	<0.001		
	Above median	4.58 (2.79,7.50)	<0.001	2.34 (1.11,4.92)	0.025	1.43 (1.01,2.03)	0.044		
Model 5	Below median	3.38 (2.06,5.54)	<0.001	2.19 (1.05,4.56)	0.037	2.17 (1.58,2.99)	<0.001		
	Above median	4.50 (2.75,7.38)	<0.001	2.20 (1.05,4.61)	0.037	1.42 (1.00,2.01)	0.047		
Model 6	Below median	3.46 (2.11,5.69)	<0.001	2.39 (1.14,5.00)	0.021	2.17 (1.57,2.99)	<0.001		
	Above median	4.41 (2.68,7.25)	<0.001	2.31 (1.10,4.88)	0.028	1.41 (1.00,2.01)	0.052		
Acetaminophen glucuronide*									
Model 1	Below median	2.86 (1.85,4.44)	<0.001	1.65 (0.84,3.25)	0.146	1.25 (0.92,1.70)	0.160		
	Above median	3.72 (2.45,5.65)	<0.001	1.53 (0.77,3.05)	0.226	1.28 (0.94,1.73)	0.117		
Model 2	Below median	3.01 (1.89,4.79)	<0.001	2.06 (1.01,4.18)	0.046	1.30 (0.93,1.81)	0.121		
	Above median	3.77 (2.40,5.91)	<0.001	1.40 (0.68,2.89)	0.357	1.12 (0.80,1.56)	0.520		
Model 3	Below median	3.04 (1.91,4.84)	<0.001	2.16 (1.06,4.40)	0.035	1.28 (0.92,1.79)	0.140		
	Above median	3.77 (2.40,5.91)	<0.001	1.46 (0.71,3.01)	0.308	1.11 (0.80,1.55)	0.531		
Model 4	Below median	2.99 (1.88,4.76)	<0.001	2.16 (1.06,4.42)	0.034	1.29 (0.93,1.80)	0.133		
	Above median	3.74 (2.38,5.88)	<0.001	1.48 (0.71,3.05)	0.294	1.11 (0.79,1.55)	0.552		
Model 5	Below median	3.01 (1.90,4.79)	<0.001	2.07 (1.02,4.20)	0.045	1.30 (0.93,1.81)	0.121		

	Above median	3.71	(2.37,5.83)	<0.001	1.40	(0.68,2.89)	0.362	1.11	(0.79,1.55)	0.547
Model 6	Below median	3.02	(1.89,4.81)	<0.001	2.17	(1.06,4.44)	0.034	1.28	(0.92,1.79)	0.139
	Above median	3.61	(2.29,5.68)	<0.001	1.45	(0.70,3.01)	0.316	1.10	(0.79,1.54)	0.566
Acetaminophen burden**										
Model 1	Below median	2.99	(1.94,4.63)	<0.001	1.55	(0.78,3.10)	0.212	1.26	(0.92,1.71)	0.149
	Above median	3.59	(2.36,5.46)	<0.001	1.63	(0.83,3.21)	0.157	1.27	(0.93,1.72)	0.126
Model 2	Below median	3.18	(2.00,5.04)	<0.001	1.91	(0.93,3.93)	0.079	1.30	(0.93,1.81)	0.120
	Above median	3.59	(2.29,5.64)	<0.001	1.52	(0.75,3.08)	0.250	1.11	(0.80,1.55)	0.523
Model 3	Below median	3.21	(2.02,5.10)	<0.001	2.00	(0.97,4.14)	0.061	1.28	(0.92,1.79)	0.140
	Above median	3.59	(2.29,5.63)	<0.001	1.57	(0.77,3.20)	0.213	1.11	(0.80,1.55)	0.533
Model 4	Below median	3.15	(1.99,5.01)	<0.001	2.01	(0.97,4.16)	0.061	1.29	(0.93,1.80)	0.132
	Above median	3.57	(2.27,5.60)	<0.001	1.59	(0.78,3.25)	0.201	1.11	(0.79,1.54)	0.556
Model 5	Below median	3.19	(2.01,5.06)	<0.001	1.92	(0.93,3.95)	0.077	1.30	(0.94,1.82)	0.118
	Above median	3.53	(2.25,5.55)	<0.001	1.51	(0.74,3.07)	0.255	1.11	(0.79,1.54)	0.556
Model 6	Below median	3.20	(2.01,5.08)	<0.001	2.02	(0.97,4.18)	0.060	1.29	(0.92,1.80)	0.136
	Above median	3.42	(2.17,5.40)	<0.001	1.56	(0.76,3.20)	0.222	1.10	(0.79,1.54)	0.576

Note: NT was defined as free of any developmental disorder diagnosis; ADHD only was defined as any ADHD diagnosis without having an ASD diagnosis; ASD only was defined as any ASD diagnosis without having an ADHD diagnosis; ADHD and ASD was defined as having both ADHD and ASD diagnosis;

Model 1: Multinomial logistic regression without adjustment;

Model 2: Model 1 further adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking before or during pregnancy, drinking before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and birthweight;

Model 3: Model 2 further adjusted for maternal fever during pregnancy;

Model 4: Model 2 further adjusted for maternal intrauterine infection/inflammation during pregnancy;

Model 5: Model 2 further adjusted for breastfeeding;

Model 6: Model 2 further adjusted for maternal fever, maternal intrauterine infection/inflammation during pregnancy, and breastfeeding.

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

Unchanged acetaminophen: first tertile as reference; For other exposures: no detection as reference