

# Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood

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 Supplemental content

**IMPORTANCE** Prior studies have raised concern about maternal acetaminophen use during pregnancy and increased risk of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in their children; however, most studies have relied on maternal self-report.

**OBJECTIVE** To examine the prospective associations between cord plasma acetaminophen metabolites and physician-diagnosed ADHD, ASD, both ADHD and ASD, and developmental disabilities (DDs) in childhood.

**DESIGN, SETTING, AND PARTICIPANTS** This prospective cohort study analyzed 996 mother-infant dyads, a subset of the Boston Birth Cohort, who were enrolled at birth and followed up prospectively at the Boston Medical Center from October 1, 1998, to June 30, 2018.

**EXPOSURES** Three cord acetaminophen metabolites (unchanged acetaminophen, acetaminophen glucuronide, and 3-[N-acetyl-L-cystein-S-yl]-acetaminophen) were measured in archived cord plasma samples collected at birth.

**MAIN OUTCOMES AND MEASURES** Physician-diagnosed ADHD, ASD, and other DDs as documented in the child's medical records.

**RESULTS** Of 996 participants (mean [SD] age, 9.8 [3.9] years; 548 [55.0%] male), the final sample included 257 children (25.8%) with ADHD only, 66 (6.6%) with ASD only, 42 (4.2%) with both ADHD and ASD, 304 (30.5%) with other DDs, and 327 (32.8%) who were neurotypical. Unchanged acetaminophen levels were detectable in all cord plasma samples. Compared with being in the first tertile, being in the second and third tertiles of cord acetaminophen burden was associated with higher odds of ADHD diagnosis (odds ratio [OR] for second tertile, 2.26; 95% CI, 1.40-3.69; OR for third tertile, 2.86; 95% CI, 1.77-4.67) and ASD diagnosis (OR for second tertile, 2.14; 95% CI, 0.93-5.13; OR for third tertile, 3.62; 95% CI, 1.62-8.60). Sensitivity analyses and subgroup analyses found consistent associations between acetaminophen burden and ADHD and acetaminophen burden and ASD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex, for which point estimates for the ORs vary from 2.3 to 3.5 for ADHD and 1.6 to 4.1 for ASD.

**CONCLUSIONS AND RELEVANCE** Cord biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ADHD and ASD in a dose-response fashion. Our findings support previous studies regarding the association between prenatal and perinatal acetaminophen exposure and childhood neurodevelopmental risk and warrant additional investigations.

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Acetaminophen is the most commonly used medication for analgesic and antipyretic purposes among mothers during pregnancy and infants in early life.<sup>1-8</sup> More than 65% of women in the United States and 50% in Europe ever used acetaminophen during pregnancy.<sup>7,9</sup> Despite its widespread use, previous studies in animals and humans have found an association between prenatal acetaminophen exposure and increased risks of adverse childhood outcomes, including asthma,<sup>10,11</sup> cryptorchidism,<sup>12</sup> and neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD)<sup>12-20</sup> and autism spectrum disorder (ASD).<sup>17,21,22</sup>

Studies<sup>23,24</sup> in rodents reported acetaminophen toxicity in cortical neurons and inhibition of fetal testosterone production, which would critically disrupt brain development. In addition, the therapeutic effect of acetaminophen can selectively inhibit cyclooxygenase 2, which may affect multiple brain functions, including long-term potentiation,<sup>25</sup> spatial learning,<sup>26</sup> and cerebellar development.<sup>27</sup>

Human studies<sup>12-22,28-32</sup> have found that acetaminophen could cross the human placental barrier and remain in an infant's blood circulation for a long duration.<sup>28,29</sup> Ecologic and cohort studies have found an association between maternal acetaminophen use and risk of ADHD<sup>12-20</sup> and ASD.<sup>17,21,22</sup> In the past 5 years, an increasing number of large, prospective cohort studies (mostly from Europe) found significant associations between maternal self-reported acetaminophen use during pregnancy and increased risk of ADHD and related symptoms in offspring in later life.<sup>13-17,30</sup> In addition, a longer duration of reported use was also associated with higher risk of ADHD.<sup>13</sup> Two recent meta-analyses<sup>31,32</sup> found significant associations between maternal-reported acetaminophen use during pregnancy and the risk of ADHD.

However, the Society for Maternal-Fetal Medicine (SMFM) and the US Food and Drug Administration (FDA) have refrained from making recommendations regarding use, citing limited evidence and methodologic concerns, including recall bias, lack of dose information, potential residual confounders, and multiple testing.<sup>33,34</sup> Nonetheless, the FDA has called on pregnant women and health care professionals to carefully evaluate the benefits and risks of using acetaminophen during pregnancy.<sup>34</sup> Similarly, the American Academy of Pediatrics (AAP) Grand Rounds concluded that there was no definitive causal link between acetaminophen exposure and ADHD.<sup>35</sup>

For the first time to our knowledge, we examined the prospective association between cord plasma acetaminophen metabolites (a direct evidence of fetal exposure) and childhood ADHD, ASD, and other developmental disabilities (DDs) using data from the Boston Birth Cohort (BBC). This study aimed to address the limitations highlighted by the SMFM, FDA, and AAP in relevant previous studies.<sup>33-35</sup>

## Methods

### Study Design and Setting

For this cohort study, we used data from the BBC, which consist of 3163 mother-infant dyads who enrolled at birth and remained in the follow-up study from October 1, 1998, to June 30, 2018

### Key Points

**Question** What is the association between cord plasma biomarkers of in utero acetaminophen exposure and risk of childhood attention-deficit/hyperactivity disorder and autism spectrum disorder?

**Findings** In this cohort study of 996 mother-infant dyads from the Boston Birth Cohort, cord plasma biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood attention-deficit/hyperactivity disorder and autism spectrum disorder.

**Meaning** These findings suggest in utero exposure to acetaminophen is associated with increased risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in children and warrant additional investigations.

(eFigure 1 in the [Supplement](#)). A detailed description of the BBC can be found in previous studies.<sup>36,37</sup> In brief, mothers who delivered singleton live births at Boston Medical Center (BMC) were invited into the BBC within 1 to 3 days after delivery. Mothers with the following conditions were not eligible for enrollment in the BBC: conception via in vitro fertilization, nonsingleton pregnancies (eg, twins or triplets), deliveries induced by maternal trauma, and/or newborns with major birth defects. Beginning at 6 months of age, enrolled infants who continued to receive pediatric primary or specialty care at the BMC were invited to participate in the postnatal follow-up study up to 21 years of age.<sup>36,38,39</sup> The institutional review boards of BMC and the Johns Hopkins Bloomberg School of Public Health approved the study protocol for the baseline and follow-up studies. Written consent was obtained from all participating mothers. Depending on a child's age, verbal or written consent was also obtained from participating children. All the databases for research do not contain personal identifiers and are accessible only by authored investigators.

Of the 3163 mother-infant dyads enrolled in the BBC postnatal follow-up study, 996 had sufficient cord plasma samples for metabolite assays and met the definitions for ADHD, ASD, other DDs, or neurotypical development (ND) (eFigure 1 in the [Supplement](#)). Of the dyads with cord metabolite data, 805 also had maternal plasma metabolite data collected within 3 days after delivery. eTable 1 in the [Supplement](#) compares the mother-infant dyads included in these analyses with those who were excluded.

### Definition of Diagnosis Groups

We defined 5 mutually exclusive groups based on physician diagnoses as documented in electronic medical records (EMRs) up to June 2018: ADHD only, ASD only, ADHD and ASD, other DDs, and ND. The group with ADHD consisted of children with diagnoses recorded with ADHD-related *International Classification of Diseases, Ninth Revision (ICD-9)* (codes 314.0-314.9) or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* (codes F90.0-F90.9) codes but excluding ASD-related codes (*ICD-9* codes 299.0-299.91 or *ICD-10* codes F84.0-F84.9). The group with ASD consisted of children with diagnoses recorded with ASD-related *ICD* codes but excluding ADHD-related codes. The

group with ADHD and ASD consisted of children with diagnoses recorded with ADHD-related and ASD-related *ICD* codes. The group with other DDs consisted of children diagnosed with mental, behavioral, and neurodevelopmental disorders (*ICD-9* codes 290-319 or *ICD-10* codes F01-F99 but excluding ADHD- and ASD-related *ICD* codes). The group with ND consisted of children without any of the aforementioned codes related to mental, behavioral, and neurodevelopmental disorders in their EMR. All the primary care and subspecialty visits were recorded in the EMRs at the BMC beginning in January 2004. The primary and secondary diagnoses for each visit were documented along with corresponding codes in the *ICD-9* (before October 1, 2015) and *ICD-10* (after October 1, 2015).

### Cord Biomarkers of Acetaminophen Exposure

Cord plasma metabolites of acetaminophen were measured using umbilical cord plasma samples collected at birth. Maternal plasma metabolites of acetaminophen were measured using nonfasting plasma samples obtained within 3 days after delivery.<sup>40</sup> The unchanged acetaminophen, acetaminophen glucuronide, and 3-(*N*-acetyl-L-cystein-S-yl)-acetaminophen levels in cord and maternal plasma samples were measured using liquid chromatography-tandem mass spectrometry techniques at the Broad Institute Metabolite Profiling Laboratory at Massachusetts Institute of Technology.<sup>41-43</sup>

### Definition of Maternal Characteristics

Similar to a previous study<sup>40</sup> on maternal plasma biomarkers of acetaminophen, we included the following maternal and child clinical and demographic variables as potential confounders: maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), parity, breastfeeding, ever use of illicit drugs, stress during pregnancy, maternal fever during pregnancy, early childhood lead levels, child's sex, delivery type, preterm birth, and birthweight. Maternal demographic and nonclinical variables were obtained by BBC trained research staff using standard questionnaire interview. Clinically related variables were extracted from EMRs. The early childhood lead levels in the children (as part of pediatric routine lead screening) were extracted from their EMRs. The first lead levels measured were chosen for this analysis.

### Statistical Analysis

The maternal and child characteristics of the study children by the 5 groups (ND, ADHD, ASD, ADHD and ASD, and other DDs) were compared using the Pearson  $\chi^2$  test (or Fisher exact test for small cells) for categorical variables and the analysis of variance test for continuous variables. The distribution of peak intensities of maternal and cord acetaminophen metabolite exposure was compared across the 5 groups. Next, metabolites of acetaminophen were ranked using inverse normal transformation for all subsequent analyses. The transformed peak intensities of unchanged cord acetaminophen were categorized into tertiles. Because of a high rate of no detection, other acetaminophen metabolites were grouped into binary groups: no detection and any

detection for further analysis. We evaluated the association between maternal and cord acetaminophen groups using the Pearson  $\chi^2$  test. Because of difficulties in accurately assessing fetal metabolic conditions within the maternal system,<sup>44</sup> we borrowed the metabolite proportions from the adult's acetaminophen metabolic pathway to calculate a variable to reflect overall cord acetaminophen burden using the following formula: [cord acetaminophen burden = (unchanged acetaminophen  $\times$  5% + acetaminophen glucuronide  $\times$  50% + 3-(*N*-acetyl-L-cystein-S-yl)-acetaminophen  $\times$  5%)/60%].<sup>45</sup> We also calculated alternative cord acetaminophen burden based on study of the neonate's urine acetaminophen metabolites as follows: [cord acetaminophen burden = (unchanged acetaminophen/14% + acetaminophen glucuronide/14%)/2].<sup>46</sup> Early childhood lead levels were converted into a binary variable (5  $\mu$ g/dL as the cutoff) based on guidelines from the Centers for Disease Control and Prevention.<sup>47</sup>

Missing data for sociodemographic characteristics (<4%) were imputed using multiple imputation by chained equations (MICE) with the Predictive Mean Matching method via *mice* package in R (R Foundation).<sup>48</sup> Adjusted logistic regression was used to examine the associations between cord acetaminophen metabolite categories and the risk of ADHD, ASD, ADHD and ASD, and other DDs using children with ND as the reference group. The final adjusted model included the following maternal and child variables: maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and low birthweight. We also performed stratified analyses by each stratum of covariates (including child's sex, maternal race/ethnicity, preterm birth, breastfeeding, smoking, alcohol use, illicit drug use, early childhood lead exposure, stress, maternal fever, and child age at last visit group) for binary cord acetaminophen burden (second and third tertiles vs first tertile) using univariate logistic regression comparing children with a diagnosis of ADHD only and children with a diagnosis of ASD only with the children with ND. We further calculated the probability of being included in the study based on race/ethnicity, sex, preterm birth, and low birthweight. Then we performed a series of sensitivity analyses by further using inverse probability (probability of being included in the analysis) weighting; further adjusting for maternal diagnoses of ADHD, depression, and anxiety; further adjusting for intrauterine infection or inflammation; and using alternative acetaminophen burden calculation for neonates. We also repeated the analyses on the association between maternal metabolites and child ADHD using the current data set. R software, version 3.4.3 (R Foundation) was used to perform all analyses.<sup>49</sup> The significance threshold is a 2-sided  $P < .05$ .

## Results

Of 996 participants (mean [SD] age, 9.8 [3.9] years; 548 [55.0%] male), the final sample included 257 children (25.8%) with ADHD only, 66 (6.6%) with ASD only, 42 (4.2%) with both ADHD and ASD, 304 (30.5%) with other DDs, and 327 (32.8%) who were neurotypical (eFigure 1 in the Supplement). This visual observation was supported by the data in Table 1. For instance, the third tertile

Table 1. Maternal and Child Characteristics According to Child Physician-Diagnosed Conditions<sup>a</sup>

Variable	ND (n = 327)	ADHD (n = 257)	ASD (n = 66)	ADHD and ASD (n = 42)	Other DDs (n = 304)	P Value <sup>b</sup>
Maternal age, y						
<20	33 (10.1)	26 (10.1)	1 (1.5)	0 (0.0)	25 (8.2)	
20-34	241 (73.7)	181 (70.4)	50 (75.8)	37 (88.1)	219 (72.0)	.09
≥35	53 (16.2)	50 (19.5)	15 (22.7)	5 (11.9)	60 (19.7)	
Maternal BMI, mean (SD)	25.99 (6.05)	27.02 (6.29)	28.66 (7.52)	26.43 (6.61)	26.60 (6.13)	.02
Parity						
Nulliparous	136 (41.6)	107 (41.6)	30 (45.5)	15 (35.7)	123 (40.5)	.89
Multiparous	191 (58.4)	150 (58.4)	36 (54.5)	27 (64.3)	181 (59.5)	
Income, \$						
<30 000	133 (40.7)	125 (48.6)	30 (45.5)	22 (52.4)	165 (54.3)	
≥30 000	53 (16.2)	40 (15.6)	12 (18.2)	6 (14.3)	32 (10.5)	.06
Unknown	141 (43.1)	92 (35.8)	24 (36.4)	14 (33.3)	107 (35.2)	
Race/ethnicity						
Non-Hispanic black	222 (67.9)	161 (62.6)	35 (53.0)	23 (54.8)	191 (62.8)	
Non-Hispanic white	11 (3.4)	22 (8.6)	2 (3.0)	3 (7.1)	15 (4.9)	.049
Hispanic	65 (19.9)	57 (22.2)	22 (33.3)	12 (28.6)	81 (26.6)	
Others	29 (8.9)	17 (6.6)	7 (10.6)	4 (9.5)	17 (5.6)	
Marital status						
Married	127 (38.8)	71 (27.6)	29 (43.9)	12 (28.6)	108 (35.5)	.02
Not married	200 (61.2)	186 (72.4)	37 (56.1)	30 (71.4)	196 (64.5)	
Maternal educational level						
Below college	220 (67.3)	181 (70.4)	34 (51.5)	24 (57.1)	200 (65.8)	.04
Above college	107 (32.7)	76 (29.6)	32 (48.5)	18 (42.9)	104 (34.2)	
Maternal stress during pregnancy						
Not stressful	149 (45.6)	76 (29.6)	23 (34.8)	13 (31.0)	125 (41.1)	<.001
Stressful	178 (54.4)	181 (70.4)	43 (65.2)	29 (69.0)	179 (58.9)	
Maternal smoking before or during pregnancy						
Never smoke	295 (90.2)	202 (78.6)	52 (78.8)	32 (76.2)	243 (79.9)	.01
Quitter	19 (5.8)	32 (12.5)	7 (10.6)	6 (14.3)	34 (11.2)	
Continuous	13 (4.0)	23 (8.9)	7 (10.6)	4 (9.5)	27 (8.9)	
Maternal alcohol use before or during pregnancy						
No	312 (95.4)	238 (92.6)	61 (92.4)	37 (88.1)	278 (91.4)	.23
Yes	15 (4.6)	19 (7.4)	5 (7.6)	5 (11.9)	26 (8.6)	
Child age by last visit, mean (SD), y	8.56 (3.82)	11.47 (3.42)	7.85 (3.25)	10.93 (3.72)	9.08 (3.63)	<.001
Child's sex						
Male	125 (38.2)	196 (76.3)	51 (77.3)	34 (81.0)	142 (46.7)	2.2 × 10 <sup>-16</sup>
Female	202 (61.8)	61 (23.7)	15 (22.7)	8 (19.0)	162 (53.3)	
Delivery type						
Cesarean	97 (29.7)	92 (35.8)	29 (43.9)	15 (35.7)	101 (33.2)	.19
Vaginal	230 (70.3)	165 (64.2)	37 (56.1)	27 (64.3)	203 (66.8)	
Preterm birth						
No	298 (91.1)	204 (79.4)	47 (71.2)	28 (66.7)	241 (79.3)	1.1 × 10 <sup>-06</sup>
Yes	29 (8.9)	53 (20.6)	19 (28.8)	14 (33.3)	63 (20.7)	
Low birthweight						
No	286 (87.5)	210 (81.7)	49 (74.2)	33 (78.6)	247 (81.2)	.047
Yes	41 (12.5)	47 (18.3)	17 (25.8)	9 (21.4)	57 (18.8)	
Cord unchanged acetaminophen						
First tertile	132 (40.4)	62 (24.1)	12 (18.2)	8 (19.0)	118 (38.8)	5.1 × 10 <sup>-09</sup>
Second tertile	112 (34.3)	75 (29.2)	21 (31.8)	17 (40.5)	107 (35.2)	
Third tertile	83 (25.4)	120 (46.7)	33 (50.0)	17 (40.5)	79 (26.0)	

(continued)

**Table 1. Maternal and Child Characteristics According to Child Physician-Diagnosed Conditions<sup>a</sup> (continued)**

Variable	ND (n = 327)	ADHD (n = 257)	ASD (n = 66)	ADHD and ASD (n = 42)	Other DDs (n = 304)	P Value <sup>b</sup>
Cord acetaminophen glucuronide						
No detection	283 (86.5)	190 (73.9)	50 (75.8)	34 (81.0)	247 (81.2)	.01
Below median	24 (7.3)	35 (13.6)	5 (7.6)	5 (11.9)	27 (8.9)	
Above median	20 (6.1)	32 (12.5)	11 (16.7)	3 (7.1)	30 (9.9)	
Cord 3-(N-acetyl-L-cystein-S-yl)-acetaminophen						
No detection	234 (71.6)	151 (58.8)	41 (62.1)	30 (71.4)	205 (67.4)	.04
Below median	54 (16.5)	47 (18.3)	11 (16.7)	5 (11.9)	51 (16.8)	
Above median	39 (11.9)	59 (23.0)	14 (21.2)	7 (16.7)	48 (15.8)	
Cord acetaminophen burden <sup>c</sup>						
First tertile	133 (40.7)	57 (22.2)	11 (16.7)	9 (21.4)	122 (40.1)	5.4 × 10 <sup>-07</sup>
Second tertile	105 (32.1)	89 (34.6)	26 (39.4)	17 (40.5)	95 (31.2)	
Third tertile	89 (27.2)	111 (43.2)	29 (43.9)	16 (38.1)	87 (28.6)	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DDs, developmental disabilities; ND, neurotypical development.

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

<sup>b</sup> The P values were obtained using Pearson  $\chi^2$  test (or Fisher exact test for small cells) for categorical variables and analysis of variance test for continuous variables.

<sup>c</sup> Cord acetaminophen burden was estimated using the sum of all the acetaminophen metabolites.

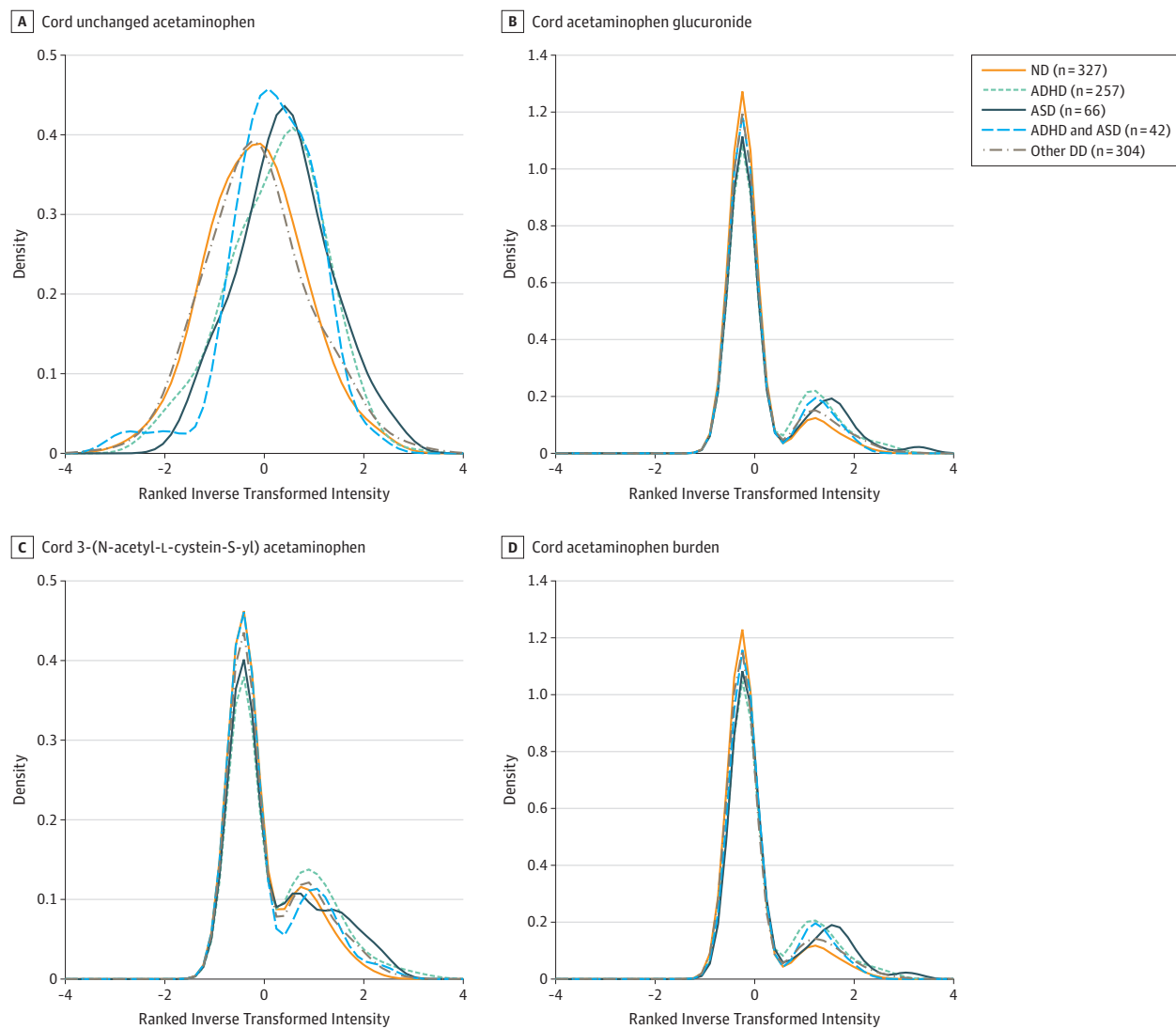
of cord acetaminophen burden was 43.2% for ADHD, 43.9% for ASD, and 27.2% in ND (Figure 1 and eFigure 2 in the Supplement). Table 1 presents the univariate comparisons of maternal and child characteristics among the ND, ADHD, ASD, ADHD and ASD, and other DDs groups. The ADHD and ASD groups had higher exposures of cord unchanged acetaminophen and its metabolites compared with the other DDs and ND groups. Mothers of children in the ADHD only group were also more likely to have higher BMI (27.02 vs 25.99;  $P = .02$ ), be non-Hispanic white (8.6% vs 3.4%;  $P = .049$ ), be unmarried (72.4% vs 61.2%;  $P = .02$ ), feel stressed during pregnancy (70.4% vs 54.4%;  $P = .001$ ), ever smoked before or during pregnancy (quitter: 12.5% vs 5.8%; continuous: 8.9% vs 4.0%;  $P = .01$ ), and ever used alcohol before or during pregnancy (7.4% vs 4.6%;  $P = .23$ ) compared with mothers of children in the ND group. Children in the ADHD only group were more likely to be older (11.47 vs 8.56 years;  $P = .001$ ), be male (76.3% vs 38.2%;  $P = 2.2 \times 10^{-16}$ ), be born preterm (20.6% vs 8.9%;  $P = 1.1 \times 10^{-06}$ ), and have low birthweight (18.3% vs 12.5%;  $P = .047$ ) compared with their counterparts in the ND group. Mothers of children in the ASD group were also more likely to have higher BMI (28.66 vs 25.99;  $P = .02$ ), be Hispanic (33.3% vs 19.9%;  $P = .04$ ), be married (43.9% vs 38.8%;  $P = .02$ ), have an educational level higher than college (48.5% vs 32.7%;  $P = .04$ ), feel stressed during pregnancy (65.2% vs 54.4%;  $P = .001$ ), ever smoked before or during pregnancy (quitter: 10.6% vs 5.8%; continuous: 10.6% vs 4.0%;  $P = .01$ ), and ever used alcohol before or during pregnancy (7.6% vs 4.6%;  $P = .23$ ) compared with mothers of children in the ND group. Children in the ASD group were more likely to be male (77.3% vs 38.2%;  $P = 2.2 \times 10^{-16}$ ), born preterm (28.8% vs 8.9%;  $P = 1.1 \times 10^{-06}$ ), and have low birthweight (25.8% vs 12.5%;  $P = .047$ ) compared with their counterparts in the ND group. Dyads included in these analyses were more likely to have a Hispanic mother (23.8% vs 21.6%,  $P = .02$ ), be older (9.52 vs 8.62 years,  $P < .001$ ), and be male (55.0% vs 48.3%;  $P < .001$ ); and less likely to have had a preterm birth (17.9% vs 33.7%;

$P < .001$ ) and low birthweight (17.2 vs 32.3;  $P < .001$ ) (eTable 1 in the Supplement).

All cord acetaminophen metabolites showed similar significant positive associations with the risk of ADHD diagnosis. The point estimates of the odds ratios (ORs) vary from 1.69 to 2.88 for ADHD and 1.38 to 3.72 for ASD (Table 2). Moreover, we identified dose-response patterns for cord unchanged acetaminophen and cord acetaminophen burden with the risk of ADHD. For instance, compared with being in the first tertile, being in the second tertile of cord acetaminophen burden was associated with 126% higher odds of ADHD diagnosis (OR, 2.26; 95% CI, 1.40-3.69), and being in the third tertile was associated with 186% higher odds of ADHD diagnosis (OR, 2.86; 95% CI, 1.77-4.67). Cord unchanged acetaminophen, cord acetaminophen glucuronide, and cord acetaminophen burden were also significantly associated with increased risk of ASD diagnosis. For instance, the third tertile cord acetaminophen burden was associated with 262% higher odds of ASD diagnosis compared with the first tertile (OR, 3.62; 95% CI, 1.62-8.60). In contrast, only the third tertile cord unchanged acetaminophen was significantly associated with the risk of ADHD and ASD (OR, 3.38; 95% CI, 1.25-9.85). The results of sensitivity analyses by further using inverse probability weighting (eTable 2 in the Supplement); further adjusting for maternal diagnoses of ADHD, depression, and anxiety (eTable 3 in the Supplement); further adjusting for intrauterine infection/inflammation (eTable 4 in the Supplement); and using alternative acetaminophen burden (eTable 5 in the Supplement) are comparable to the results presented in Table 2.

The point estimates of the associations between cord acetaminophen burden and ADHD and cord acetaminophen burden and ASD were in the positive direction across strata of covariates (Figure 2). Sensitivity analyses and subgroup analyses found consistent associations between acetaminophen and ADHD and acetaminophen and ASD across strata of potential confounders, in-

Figure 1. Distribution of Cord Plasma Acetaminophen Metabolites



Distribution of cord plasma acetaminophen metabolites by the following child physician-diagnosed conditions: neurotypical development (ND), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), ADHD and ASD, and other developmental disabilities (DDs).

cluding maternal indication, substance use, preterm birth, and child age and sex, for which point estimates for the ORs vary from 2.3 to 3.5 for ADHD and 1.6 to 4.1 for ASD. A larger difference in the point estimate of the ORs for ADHD only was observed across strata of child's sex (OR within females, 3.3; 95% CI, 1.6-7.2; OR within males, 2.4; 95% CI, 1.5-3.9), breastfeeding (OR within bottle-only group, 4.3; 95% CI, 2.1-9.1; OR within both or breastfed groups, 2.0; 95% CI, 1.3-3.1), and maternal smoking before and during pregnancy (OR within never smokers, 2.2; 95% CI, 1.5-3.3; OR within quitters, 6.9; 95% CI, 1.4-51.8; OR within continuous smokers, 1.1; 95% CI, 0.2-5.4). A larger difference in the point estimate of the ORs for ASD only was observed across strata of child's sex (OR within females, 2.6; 95% CI, 0.8-11.5; OR within males, 4.1; 95% CI, 1.9-10.0), maternal race/ethnicity (OR within black individuals, 2.1; 95% CI, 1.0-4.9; OR within nonblack individuals, 8.9; 95% CI, 2.5-57.1), maternal alcohol use before and

during pregnancy (OR within no alcohol use group, 3.6; 95% CI, 1.8-7.7; OR within alcohol use group, 2.0; 95% CI, 0.2-44.8), maternal ever drug use (OR within no drug use group, 4.1; 95% CI, 2.0-9.7; OR within drug use group, 1.6; 95% CI, 0.4-7.8), stress during pregnancy (OR within those not stressful, 4.6; 95% CI, 1.5-20.2; OR within those stressful, 3.0; 95% CI, 1.4-7.3), and last diagnosis age (OR within those <9 years old, 3.4; 95% CI, 1.8-7.1; OR within those ≥9 years old, 2.1; 95% CI, 0.9-5.7). However, tests of interactions between each covariate and cord acetaminophen burden did not produce significant findings.

eTable 6 in the Supplement gives the association between maternal and cord plasma acetaminophen metabolites. The Pearson  $\chi^2$  tests found a significant association for all forms of acetaminophen metabolites between cord and maternal categories (unchanged acetaminophen:  $P < .001$ ; acetaminophen glucuronide:  $P < 2.2 \times 10^{-16}$ ; 3-[N-acetyl-L-cystein-S-yl]-acetaminophen:

Table 2. Adjusted Associations Between Cord Plasma Acetaminophen Biomarkers and the Risk of Physician-Diagnosed Conditions<sup>a</sup>

Model	No. of Dyads		ADHD (n = 257)			ASD (n = 66)			ADHD and ASD (n = 42)			Other DDs (n = 304)		
	Total	ND Group	No (%)	aOR (95% CI)	P Value	No. (%)	aOR (95% CI)	P Value	No. (%)	aOR (95% CI)	P Value	No. (%)	aOR (95% CI)	P Value
<b>Cord Unchanged Acetaminophen<sup>b</sup></b>														
First tertile	332	132	62 (18.7)	1 [Reference]	NA	12 (3.6)	1 [Reference]	NA	8 (2.4)	1 [Reference]	NA	118 (35.5)	1 [Reference]	NA
Second tertile	332	83	75 (22.6)	1.48 (0.92-2.39)	.10	21 (6.3)	1.33 (0.57-3.18)	.51	17 (5.1)	2.01 (0.75-5.72)	.17	107 (32.2)	0.93 (0.64-1.37)	.73
Third tertile	332	NA	120 (36.1)	2.88 (1.80-4.66)	<.001	33 (9.9)	3.72 (1.70-8.55)	<.001	17 (5.1)	3.38 (1.25-9.85)	.02	79 (23.8)	0.86 (0.56-1.31)	.48
<b>Cord Acetaminophen Glucuronide<sup>b</sup></b>														
No detection	804	283	190 (23.6)	1 [Reference]	NA	50 (6.2)	1 [Reference]	NA	34 (4.2)	1 [Reference]	NA	247 (30.7)	1 [Reference]	NA
Any detection	192	44	67 (34.9)	2.25 (1.39-3.68)	<.001	16 (8.3)	2.29 (1.06-4.85)	.03	8 (4.2)	1.55 (0.53-4.15)	.40	57 (29.7)	1.27 (0.81-2.01)	.30
<b>Cord 3-(N-Acetyl-L-Cystein-S-yl)-Acetaminophen<sup>b</sup></b>														
No detection	661	234	151 (22.8)	1 [Reference]	NA	41 (6.2)	1 [Reference]	NA	30 (4.5)	1 [Reference]	NA	205 (31.0)	1 [Reference]	NA
Any detection	335	93	106 (31.6)	1.69 (1.13-2.53)	.01	25 (7.5)	1.38 (0.72-2.63)	.33	12 (3.6)	0.72 (0.29-1.66)	.45	99 (29.6)	1.02 (0.71-1.46)	.93
<b>Cord Acetaminophen Burden<sup>c</sup></b>														
First tertile	332	133	57 (17.2)	1 [Reference]	NA	11 (3.3)	1 [Reference]	NA	9 (2.7)	1 [Reference]	NA	122 (36.7)	1 [Reference]	NA
Second tertile	332	105	89 (26.8)	2.26 (1.40-3.69)	<.001	26 (7.8)	2.14 (0.93-5.13)	.08	17 (5.1)	2.1 (0.81-5.72)	.13	95 (28.6)	0.92 (0.62-1.35)	.66
Third tertile	332	89	111 (33.4)	2.86 (1.77-4.67)	<.001	29 (8.7)	3.62 (1.62-8.60)	.002	16 (4.8)	2.44 (0.92-6.82)	.08	87 (26.2)	0.83 (0.55-1.26)	.39

Abbreviations: ADHD, attention deficit/hyperactivity disorder; aOR, adjusted odds ratio; ASD, autism spectrum disorder; DDs, developmental disabilities; NA, not applicable; ND, neurotypical development.

<sup>a</sup> All adjusted models were compared with the ND group with adjustment for maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy,

alcohol use before or during pregnancy, maternal body mass index, parity, child's sex, delivery type, preterm birth, and low birthweight.

<sup>b</sup> Inverse normal transformed intensity.

<sup>c</sup> Sum of all the acetaminophen metabolites.

$P = 2.2 \times 10^{-16}$ ; acetaminophen burden:  $P = 3.3 \times 10^{-10}$ ). Among children with nondetectable maternal acetaminophen glucuronide and 3-(N-acetyl-L-cystein-S-yl)-acetaminophen, 315 children (48.6%) with nondetectable maternal acetaminophen glucuronide and 279 (52.1%) with nondetectable 3-(N-acetyl-L-cystein-S-yl)-acetaminophen had detectable corresponding cord acetaminophen metabolites. The results of subsequent analyses on maternal metabolites and child ADHD using the current data set (eTable 7 in the Supplement) are also compatible with a previously published study<sup>40</sup> (OR for second tertile acetaminophen burden, 1.75; 95% CI, 1.12-2.76; OR for third tertile acetaminophen burden, 2.45; 95% CI, 1.50-4.03).

## Discussion

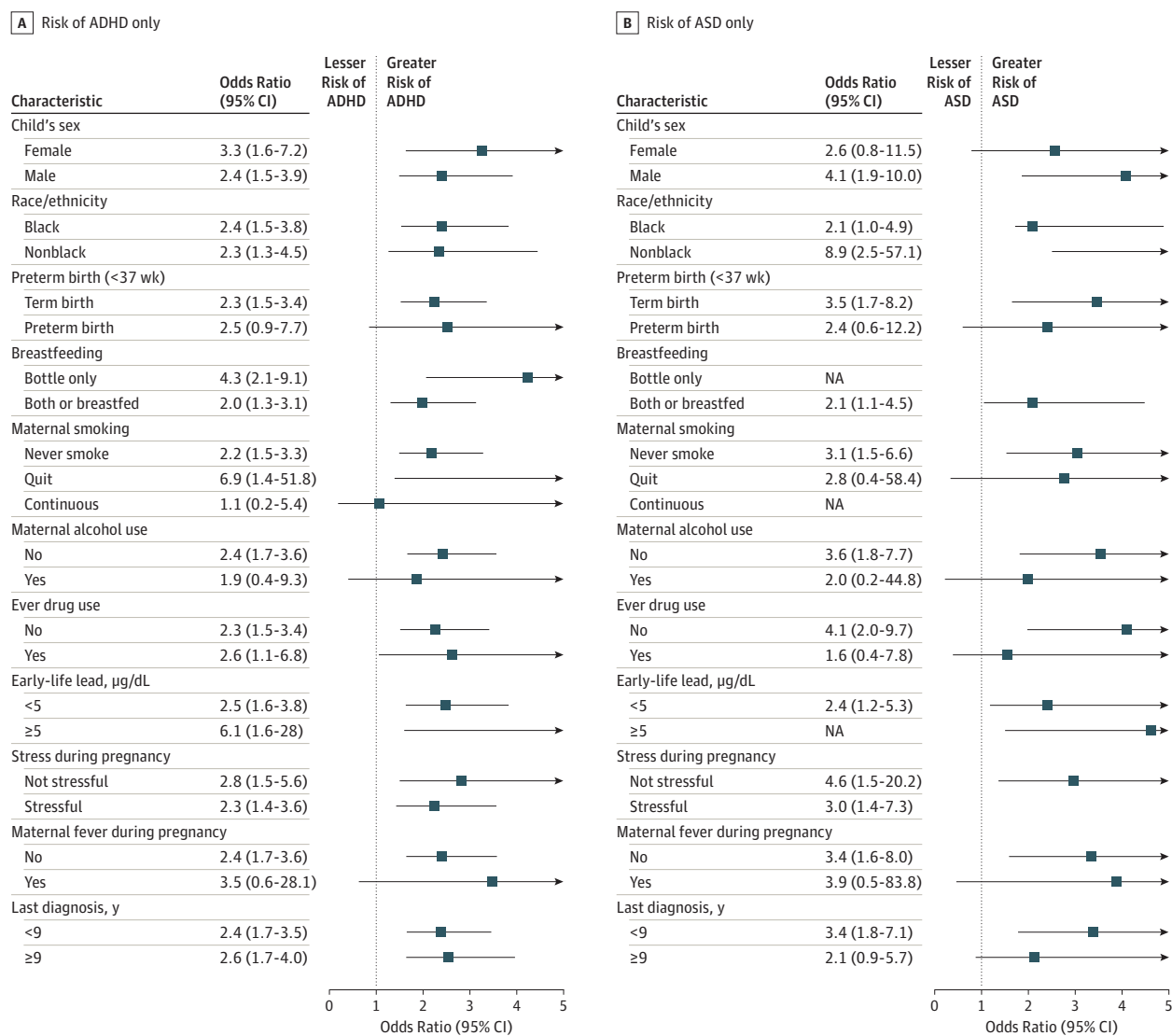
In this prospective birth cohort study, we identified a significant positive association between cord plasma acetaminophen metabolites and the risk of ADHD diagnosis and the risk of ASD in childhood. The positive associations between cord acetaminophen and ADHD and the cord acetaminophen and ASD were observed across strata of pertinent covariates, including maternal fever during pregnancy, which is an indicator for acetaminophen use. The associations also persisted after a series of further adjustment of potential confounders and differential inclusions. Furthermore, there were dose-

response patterns for cord uncharged acetaminophen and cord acetaminophen burden with the risk of ADHD and ASD. The findings from this study contribute knowledge to ongoing research regarding the potential adverse neurodevelopmental consequences of perinatal acetaminophen exposure.

To our knowledge, this was the first prospective birth cohort study to examine the associations between cord plasma metabolites of acetaminophen and several types of neurodevelopmental disabilities with adjustments for many potential covariates. A previous study<sup>40</sup> using maternal acetaminophen metabolites only partially overcame the methodologic limitations in previous studies<sup>13-17,30</sup> that used self-reported acetaminophen use as an exposure indicator and lacked quantification of acetaminophen intake. However, the previous study<sup>40</sup> only measured maternal acetaminophen metabolites at one time within 3 days after delivery, which limited the strength of the evidence. The current study using cord acetaminophen metabolites addressed the major limitations of the previous studies.<sup>13-17,30</sup> The cord plasma metabolites provide a direct measurement of fetal acetaminophen exposure before delivery. In addition, the dose-response associations found in the current study also addressed the methodologic issues identified by the SMFM, FDA, and AAP regarding the reliance on maternal self-reported acetaminophen exposures in previous cohort studies.<sup>33,34</sup>

In this study, all cord samples had detectable uncharged acetaminophen. Among children whose maternal acetaminophen

Figure 2. Forest Plots Summarizing the Subgroup Analyses



Subgroup analyses of the association between cord acetaminophen burden (second and third tertiles vs first tertile) and the risk of attention-deficit/hyperactivity disorder (ADHD) only (A) and the risk of autism spectrum disorder

(ASD) only (B) in childhood. Squares represent mean values, with whiskers indicating 95% CIs. NA indicates not applicable.

exposures were in the first tertile, more than 60% had second and third tertile cord unchanged acetaminophen exposure. This phenomenon may reflect the differences in metabolic capacity for acetaminophen between adults and neonates. This finding is also supported by a case study<sup>29</sup> that reported that acetaminophen and its metabolites were detectable until measurement of the infant's 47-hour urine sample after maternal intake of phenacetin-containing tablets 5.5 hours before delivery.

The liver is the primary location for metabolism of acetaminophen.<sup>50</sup> In adults with healthy liver function, 5% to 10% of acetaminophen is processed into the highly toxic metabolite *N*-acetyl-*p*-benzoquinone imine, which is responsible for the major hepatotoxicity of acetaminophen<sup>45</sup> and ultimately detoxified as 3-(*N*-acetyl-L-cystein-S-yl)-acetaminophen.<sup>50,51</sup> In neonates, because of limited metabolism capacity, the acetaminophen and

its toxic metabolites remain for longer after in utero exposure. Furthermore, acetaminophen could rapidly enter cerebrospinal fluid<sup>52-55</sup> and inhibit prostaglandin synthesis.<sup>25-27</sup> Although findings related to a low toxic burden on the liver, kidney, and intestines support the safety of acetaminophen use in the short term,<sup>56,57</sup> the long-term potential association of neurodisruption with acetaminophen exposure remains to be clarified.<sup>58</sup>

Whether there is a specific time window when the developing brain is most sensitive to acetaminophen exposure remains unclear. Animal experiments suggest that the perinatal period is the critical exposure window for acetaminophen to induce behavioral abnormalities in mice.<sup>59</sup> Our study consistently found that cord biomarkers of acetaminophen (reflecting perinatal exposure) were significantly associated with increased risk of ADHD and ASD in children.



## Limitations

The present study has some limitations. First, it only included a 1-time measurement of cord acetaminophen metabolites at birth. Given that the half-life of acetaminophen in adults is less than 3 hours,<sup>44</sup> the cord plasma measurement may at most reflect maternal use of acetaminophen during the peripartum period. Second, the metabolome panel did not capture acetaminophen sulfate, which is one of the major metabolites for acetaminophen.<sup>45</sup> This missing biomarker limits our ability to evaluate the overall cord acetaminophen burden for newborns. Third, we did not have a true nonexposed group as reference because of the 100% detection of unchanged acetaminophen, which may have biased our results toward the null. Fourth, because of our observational study design, we were unable to exclude the potential residual con-

founders because of unmeasured genetic and environmental factors. Fifth, caution is needed to apply our findings to other populations with different characteristics.

## Conclusions

In this study, cord biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ADHD and ASD in a dose-response fashion. Our findings support previous studies regarding the association between prenatal and perinatal acetaminophen exposure and childhood neurodevelopmental risk and warrant additional investigations.

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