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Behavioral Problems at Age 11 Years After Prenatal and Postnatal Exposure To Acetaminophen: Parent-reported and Self-reported Outcomes

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Running head: Acetaminophen exposure and SDQ at 11 years

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Abstract

Several studies have reported associations between prenatal acetaminophen exposure and behavioral outcomes in young children. We aimed to evaluate the associations of prenatal and postnatal exposures to acetaminophen with behavioral problems in children at age 11 years, using behavioral measures reported by parents and children. We studied 40,934 mother-child pairs from the Danish National Birth Cohort enrolled during 1996-2002. Parent-reported and child-reported Strengths and Difficulties Questionnaires (SDQ) were collected during the 11-year follow-up. We estimated risk ratios for behavioral problems including total difficulties, and internalizing or externalizing behaviors following prenatal (during pregnancy) or postnatal (within the first 18 months after birth) acetaminophen exposure. Parent-reported and child-reported SDQ scores were moderately correlated; higher for externalizing (r=0.59) than internalizing behaviors (r=0.49). Prenatal acetaminophen exposure was associated with 10-40% higher risks for total difficulties and internalizing and externalizing problems based on parent- or child-reported SDQ with the association being stronger for greater cumulative weeks of acetaminophen use. Postnatal exposure was associated with 16-19% higher risks for parent-reported internalizing behaviors, but the associations were weak or null for child-reported scores except for prosocial behavior. Our study corroborates published associations between prenatal exposures to acetaminophen and behavioral problems and extends the literature to early adolescence.

Keywords: Acetaminophen; paracetamol; behavioral problems; multiple informants' comparison; DNBC.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DNBC, Danish National Birth Cohort; SDQ, Strengths and Difficulties Questionnaires; RR, risk ratio; CI, confidence interval; IPSW, inverse probability of selection weight.

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Acetaminophen is one of the most common over-the-counter drugs to treat pain and fever (1,2). This medication has been considered safe to use in therapeutic doses even for pregnant women (3–5). In recent years, concerns have been raised by several large-scale birth cohort studies that its use during pregnancy may increase the risk of adverse reproductive and childhood neurodevelopmental outcomes (3,6–15). Potential underlying mechanisms include its endocrine-disrupting properties, such as its inhibition of androgen and prostaglandin synthesis (16,17), or its induction of oxidative stress leading to neuronal death in early development (18,19). The majority of epidemiological studies addressing neurobehavioral problems included children at ages 7 or younger and relied solely on parent-reported outcomes (3,6,10–12) with a few being able to collect neuropsychological measures in age 5 or younger administered by trained psychologists (8,9). Only a few cohorts had access to diagnoses or treatment data for attention-deficit/hyperactivity disorder (ADHD) ascertained from medical records through age around 10 to 15 years (7,13,20–22).

Debates over the validity of the findings from these cohort studies have mostly focused on uncontrolled confounding, particularly due to unmeasured or unknown factors affecting both maternal acetaminophen intake and child behavioral outcomes (23–25). Several studies tried to address this bias using a sibling-controlled design and negative-control analyses (3,10,11,13). These studies suggested that time-fixed confounding factors such as genetics, familial socioeconomic differences, or maternal chronic illnesses were not plausible reasons for the observed associations between prenatal acetaminophen exposure and ADHD-like behaviors in children. However, a recent meta-analysis with bias analysis suggested that the role of unmeasured confounder(s) needs to be further evaluated (25). Despite such elaborate discussion about

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unmeasured confounding on this topic, evaluation for another type of bias introduced when both exposures and outcomes are reported by the same informant is scarce. Some efforts were made by comparing results of maternal reports of exposure and child behavioral outcomes measures reported by mothers or teachers (8,9,26,27) but these were studies with less than 3,000 mother-child pairs. Behavioral difficulties self-reported by the children have rarely been available.

Addressing this issue is important given the potential for dependent and possibly differential misclassification (28) due to reporting by the same informant. For instance, mothers who more carefully report their pregnancy drug intake might also be more aware of or likely to later report their child's behavioral problems. A previous study has also shown that mothers' personality traits such as conscientiousness are associated with self-reported acetaminophen intake during pregnancy and these personality traits might be related to the perceptions and reports of child behaviors (29). In addition, the perception and reporting of behavioral and emotional problems differ across informants, with low to moderate agreement found between parent- and child-reports (30). Parent-child agreement tends to be higher on observable symptoms (i.e., externalizing problems) than unobservable symptoms (i.e., internalizing problems) and higher in younger children than adolescents (31). Studies investigating child-reported behavioral outcomes and their associations with prenatal acetaminophen use are lacking and they would provide invaluable information on the outcomes. Thus, it is imperative to examine behavioral problems reported by children themselves at older ages.

Furthermore, the possible impact of acetaminophen exposure in infancy on neurodevelopment is underexplored. While fetal development is likely the most sensitive period for environmental

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perturbation of neurodevelopment, the maturation of the central nervous system may be affected by exposures in infancy (16,17,32). In this context, we conducted a study in the Danish National Birth Cohort (DNBC) to examine the associations of prenatal and/or postnatal exposures to acetaminophen with behavioral problems at age 11 years assessed using both parent and child reports based on the Strengths and Difficulties Questionnaires (SDQ).

METHODS

Study participants

The DNBC was established in Denmark during 1996-2002 when 100,418 pregnant women enrolled in the cohort at their first general practitioner antenatal visit (during weeks 6 to 12) and the mothers and children have been followed since (33). For analyses of prenatal acetaminophen use, we restricted the cohort to live-born children whose mothers answered the study enrollment form and the three subsequent telephone interviews (scheduled around the 12th and 30th gestational weeks, and 6 months after birth), all of which collected information on prenatal acetaminophen use (n=64,322). Among them, 40,934 had SDQ outcome scores reported by both the mother and the child when the index child was 11 years old. For postnatal acetaminophen exposure analyses, we additionally restricted the cohort to mothers who had answered the interview conducted at 18 months after birth with information on the infant's acetaminophen treatment (n=27,742). Details in the study population selection are described in Web Figure 1. All participants provided written informed consent at the time of inclusion in the DNBC. The research protocol for this study was approved by the DNBC steering committee (project no: 2018-13), Danish data inspectorate (journal number 2016-051-000001, serial number 1297), and the Institutional Review Boards at UCLA (16-001849) and Yale University (2000024089).

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Exposures to Acetaminophen

Information about maternal acetaminophen use during pregnancy was ascertained from the study enrollment form and three computer-assisted telephone interviews. At the first contact, women answered questions regarding any supplement and medication use covering the period from 4 weeks before pregnancy to the gestational week of reporting. In the subsequent telephone interviews (scheduled around 12th and 30th week, and 6-month postpartum), women were specifically asked to report whether they had taken any pain killers during pregnancy provided with a list of 44 common medications, including acetaminophen as a single or combination drug. Women were asked to indicate the gestational week of intake for each medication and we used the weekly intake information to calculate trimester-specific and cumulative weeks of use. Information regarding acetaminophen exposure during infancy was ascertained through the computer-assisted telephone interviews at about 6 and 18 months postpartum. Mothers were asked to report whether their children had experienced any of 16 types of conditions or diseases and the specific pharmaceutical treatment for these conditions (Web Table 1).

Parental- and self-reports of children's behavioral problems at age 11 years

Children's behaviors were assessed based on the standardized SDQ, which is a 25 item screening tool that assesses behavioral problems and mental health status of children and adolescents between the ages of 4 and 18 years (34). When the DNBC children turned 11 years of age, both parents and children were invited to complete the SDQ. There are 5 SDQ subscales (emotional symptoms, conduct problems, hyperactivity/inattention, peer problems, and prosocial behavior), all consisting of 5 items. Based on the recommendations for scoring the SDQ (http://www.sdqinfo.com), we calculated a total difficulties score (range, 0-40) by summing the

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first 4 subscales ranging from 0 to 10 each, with higher scores indicating more negative behaviors and problems. We then dichotomized each subscale according to the recommended cut-off to indicate atypical behaviors for the parent-reported and child-reported SDQ (34). We also created an 'internalizing' subscale that combined the emotional symptoms and peer problems subscales, and an 'externalizing' subscale that combined the conduct and hyperactivity/inattention subscales (35,36). There are no recommended cut-off points for internalizing or externalizing composite scores; thus, the top 95th percentile of each distribution was defined *a priori* as the cut-off. A subset of parents also answered 6 questions (each with a possible response value of 0, 1, or 2) about their own behavioral problems during childhood when the index child turned 7 years of age (7), which allowed us to generate a parental behavioral problems score (range 0-12).

Statistical analysis

We calculated Pearson correlation coefficients (*r*), Cronbach's alpha, and kappa coefficients between parent-reported and child-reported SDQ. We employed modified Poisson regression models to estimate risk ratio [RR] and 95% confidence interval [CI] for acetaminophen exposure and binary classifications for overall behavioral problems, internalizing behaviors, externalizing behaviors, and each of the five subscales (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship, and prosocial behavior) reported either by parents or children. To compare relative risk estimates between parent-reported and child-reported SDQ, we computed p-values for heterogeneity using generalized linear mixed model including a product term for acetaminophen exposure and the rater of SDQ (i.e. parent or child). To account for potential differences in neurobehavioral development in boys and girls (37), we also conducted analyses stratified by child's sex to evaluate effect measure modification. We tested for

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heterogeneity using a product term for acetaminophen exposure and child's sex. For the prenatal period, we further analyzed trimester-specific exposure (used only in the first [1-12 weeks], the second [13-24 weeks] or the third trimester [25th-delivery], in any two trimesters, or in all trimesters) and cumulative weeks of exposure (1-5, 6-10, or >10 weeks). We also evaluated the linear exposure-response by fitting the number of weeks of acetaminophen use in pregnancy as a continuous variable.

Potential confounders were selected *a priori* considering factors that may affect child neuro-behavioral development and might also be associated with acetaminophen exposure. In all models, we included mother's age at childbirth (continuous), parity (1, 2, >2), socio-occupational status (low, medium, high), maternal pre-pregnancy body mass index (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), and birth year (continuous). In the model for acetaminophen exposure during pregnancy, we additionally adjusted for maternal smoking during pregnancy (never, ≤9, >9 cigarettes per day), maternal alcohol intake during pregnancy, mother's self-reported psychiatric illnesses before and during pregnancy, indications for maternal acetaminophen use including diseases of muscles or joints during pregnancy, episodes of fever during pregnancy, inflammation/infections during pregnancy, and prenatal use of nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen. In models estimating the effect of postnatal exposure to acetaminophen, we additionally adjusted for acetaminophen use during pregnancy, the major indications for acetaminophen use during infancy including fever, infection or inflammation of the eye, ear or throat, respiratory tract illnesses, born preterm defined as gestational age less than 37 weeks, and birth weight (<2500, 2500-4500, >4500 g). Ten simulated complete datasets were generated via imputation assuming

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multivariate normal distribution for about 8% of participants who had at least 1 missing covariate value (38).

We also conducted several sensitivity analyses. First, we reclassified the outcome defined as children who met both the SDQ cut-off in the parental and the child assessments (39). Second, we additionally controlled for parental childhood behavioral problem scores to account for familial and genetic risks (40). Third, given the potential confounding by mother's breastfeeding for postnatal exposure (41), we also adjusted for duration of breastfeeding (no, <3, 3-6, >6 months) in the analyses for infancy use of acetaminophen. Fourth, we employed negative binomial regression models to estimate adjusted relative ratio for increasing SDQ score as count data according to prenatal or postnatal acetaminophen exposure. Finally, we evaluated whether the results were sensitive to the SDQ cut-off point used to define behavioral difficulties by varying the cutoff from -2 to +2 of the scores employed in the main analyses.

In the main analyses, we used the inverse probability of selection weight (IPSW) technique to account for possible selection bias due to non-participation at the 11-year follow up (42). Stabilized IPSW and 95% CIs estimated with robust variance estimators were incorporated in all regression analyses. In sensitivity analyses, we compared results with and without IPSW. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

In our study sample, 53% of mothers reported using acetaminophen at least once during pregnancy, and 10% of the offspring received acetaminophen during the first 18 months after birth (Table 1).

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Parent- and child-reported behavioral problems

The medians of child-reported SDQ scores at age 11 tended to be higher than the parents-reported measures (Table 2). However, using the binary classification of atypical behavior with the recommended cut-offs for the instrument, a higher proportion of children were classified as having emotional problems (9.3% vs. 2.3%), peer problems (4.5% vs. 1.9%), and lack of prosocial behavior (5.5% vs. 3.3%) based on parent-report than child-report. The Pearson correlation coefficient between parent- and child-reported SDQ total difficulty scores at 11 years was moderate (r = 0.58) with a higher correlation for externalizing behaviors (r = 0.59) than internalizing behaviors (r = 0.49); among all SDQ sub-domain, measures for hyperactivity had the highest correlation (r = 0.57) and the prosocial subscale had the lowest correlation (r = 0.34). We found a consistent trend for alpha reliability and kappa coefficients.

Linking acetaminophen use during pregnancy to parent- and child-reported SDQ

For both parent and child-reported SDQ, maternal acetaminophen use during pregnancy was positively associated with the risks of SDQ total difficulties (parent-reported, RR=1.14, 95% CI=1.01-1.29; child-reported, RR=1.40, 95% CI=1.20-1.63), internalizing problems (parent-reported, RR=1.09, 95% CI =1.00-1.19; child-reported, RR=1.13, 95% CI=1.04-1.23), and externalizing problems (parent-reported, RR=1.07, 95% CI=0.99-1.15; child-reported, RR=1.13, 95% CI=1.05-1.22) (Table 3). We did not find evidence of heterogeneity in most of the rater-specific RRs comparisons except for the SDQ total difficulties (p=0.01). Some sex-specific differences were found; i.e. the exposure effect estimates of total difficulties for child-reported SDQ and externalizing behavior for both parent-reported and child-reported SDQ were stronger in boys and null for girls (Web Table 2).

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In analyses by trimester of use, associations between acetaminophen intake in the first or the third trimester only and SDQ total difficulties, internalizing or externalizing problems were slightly stronger compared with exposure in the second trimester (Table 4). The estimated RRs were higher for all parent-reported outcomes, and some child-reported outcomes when acetaminophen was used in more than one pregnancy trimesters. Greater cumulative weeks of acetaminophen use in pregnancy were also associated with SDQ total difficulties and internalizing behavioral problems and the findings were consistently seen with both parent- and child-reported SDQ (Table 5).

Linking acetaminophen use during infancy to parent- and child-reported SDQ

Postnatal acetaminophen use in the first 18 months of life was associated with parent-reported total difficulties (RR=1.18, 95% CI=0.95-1.48) and internalizing problems (RR=1.15, 95% CI=0.98-1.35) but the 95% CI of these effect estimates included the null (Table 3). There was no association between postnatal acetaminophen use and child-reported total difficulties, internalizing problems, and externalizing problems. There was no evidence of heterogeneity comparing the RRs by raters. Concerning SDQ subdomains, a positive association with peer problems (RR=1.19, 95% CI=1.00-1.42) was only found in parent-reported but not child-reported outcomes. In contrast, postnatal acetaminophen exposure was associated with the lack of prosocial behavior only in child-reported SDQ (RR=1.22, 95% CI=1.00-1.49) with no association for parental reports. Some inconsistencies were also found in analyses by child's sex such that the associations of postnatal acetaminophen exposure with total difficulties or internalizing behaviors were higher in boys based on parent-reports and higher in girls based on child-reports (Web Table 2).

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Sensitivity analyses

When using a combined outcome based on parent- and child-reported scores, we found that prenatal acetaminophen exposure consistently showed positive associations with total difficulties and internalizing and externalizing behaviors (Web Table 3). Results did not change when we additionally adjusted for parents' childhood behavioral scores or duration of breastfeeding (Web Table 4-5). Analyses using continuous SDQ scores as the outcome were also consistent for the associations between acetaminophen exposure during pregnancy and the parent- or the child-reported measures (Web Table 6). For postnatal exposure, positive associations were only found for parent- but not child-reported measures. Results did not change substantially in models without IPSW (Web Table 7). Our main findings were also robust to changing the SDQ cut-off by ±2 to define behavioral difficulties (Web Figure 2-3).

Discussion

In this large population-based cohort, maternal acetaminophen use during pregnancy was consistently associated with the increased risks for developing behavioral and emotional problems in the offspring at 11 years of age using outcome measures reported by the parent or the child. We also observed associations between infant treatment with acetaminophen during the first 18 months of life and internalizing behaviors, but these results were less consistent across parent- and child-reported outcomes.

Associations between maternal intake of acetaminophen during pregnancy and adverse neurobehavioral outcomes in young children have been reported in several birth cohorts, including three cohort studies that assessed behavioral problems in children using parent-reported SDQ

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(6,7,10). Prior studies neither simultaneously assessed prenatal and postnatal exposures nor used more than one informant for the outcome assessments. There was also little information on how much SDQ scores varied by the type of informant in the large population-based samples (43–45). In our study, we compared the SDQ reported by parents and their index children at 11 years of age in the DNBC. The parent-child correlation for the total difficulties score in this study (r=0.58) was higher than previous SDQ results in European children (r≈0.40) (46,47) and another meta-analytic mean of 119 studies worldwide on childhood behavioral and emotional problems (r=0.25) (48). Consistent with the literature (31), the parent-child agreement was higher for externalizing problems than for internalizing problems possibly because externalizing problems are more observable by the parents than internalizing problems (49,50). Despite the relatively high parent-child agreement, there are still non-shared variances between the two informants, suggesting that parents and children each provide unique information about the child's behavioral and emotional problems.

We found rather consistent associations between prenatal exposure to acetaminophen and behavioral problems in children using either parent- or child-reported SDQ. The acetaminophen exposure in pregnancy was based on maternal reports; therefore, a positive association found between the exposure and outcome assessed by different informants provided additional assurance that the finding is unlikely to be solely driven by shared-method variances in parental reports. The concerns for possible correlated errors are not completely resolved in these multiple informant comparisons because inherited personality traits or family factors might influence both parents and child outcome reports. However, if the observed association is strongly driven by correlated errors of exposure and outcome reports, we would expect to find stronger association

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for parent-rated than child-rated SDQ, which was only true for results concerning postnatal acetaminophen exposure but not for prenatal exposure. Moreover, the prevalence of infants exposed to acetaminophen was lower than that in previous reports (51,52) and there are some discrepancies in results based on different informants for postnatal exposure to acetaminophen. Further evaluations that address the possibility of a reporting bias for acetaminophen treatment of infants is needed.

Mechanisms underlying the neurodevelopmental toxicity of acetaminophen have not been established, but several have been proposed. It is known that acetaminophen crosses the placenta (53) and penetrates the blood-brain barrier (54). Animal and human studies found that acetaminophen has endocrine-disrupting properties, such as inhibiting androgen or prostaglandin synthesis (16,17). Given that endocrine homeostasis plays an important role in the development throughout both the prenatal and postnatal periods, its disruption may affect neurodevelopment of the fetus (55,56), and thus increase the risk of behavioral and emotional difficulties later on. For example, an experimental study in mice showed that paracetamol administration to neonates alters locomotor activity and spatial learning skills in adulthood possibly through affecting brain-derived neurotrophic factor levels in the neonatal brain (the neonatal period in mice corresponds to the third trimester of brain development in humans) (32). Another rodent study has shown that acetaminophen could interrupt brain development via direct neurotoxicity by inducing oxidative stress leading to neuronal cell deaths (18).

Consistent with previous studies (57), we estimated increased risks in childhood behavioral difficulties for greater cumulative weeks of acetaminophen use during pregnancy. However,

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studies used various classifications to investigate the duration or frequency of exposure in pregnancy according to the data each study collected. Also, it remains unclear whether there is a threshold for acetaminophen exposure effect on neurodevelopment. The DNBC collected gestational week-specific intake data and we found a smaller but still elevated risk for child-reported SDQ outcomes associated with less than 5 weeks of acetaminophen intake in pregnancy. The possibility for a lower dose exposure to affect a critical developmental period in pregnancy needs to be considered (58).

A major strength of our study is that study participants were enrolled in a well-established national longitudinal cohort and its large sample size provides adequate power to compare results based on parent- and child-reported SDQ. Another strength is the use of multiple informants in outcome assessments as well as a repeated assessment of prenatal and postnatal use of acetaminophen. Moreover, we utilized the IPSW to account for possible selection bias and we were able to control for a comprehensive set of potential confounders including diseases that leads to acetaminophen use by the mother and infant. However, our study also has several limitations. Exposure and outcome were based on subjective reports and measurement errors might be expected to occur. We had no information on the number of pills and dosage taken during pregnancy and infancy, which prevented us from conducting more detailed exposure-response analyses. The low prevalence of postnatal acetaminophen use in the DNBC might reflect the true use rate for the Danish population or represent under-reporting (51,52). Lastly, we cannot rule out the possibility of residual confounding, time-varying confounding by pregnancy-specific factors, and confounding by indications of drug use in our findings. Further investigations are needed to address these limitations due to measurement error and unmeasured confounding.

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In conclusion, we found that prenatal exposure to acetaminophen was associated with behavioral problems in children at 11 years of age, extending the previous literature focusing on early childhood to include results for late childhood and early adolescence. A positive association was also observed for the exposure of infants to acetaminophen. Since some findings were only seen with parent-reported outcomes, reporting bias is a concern here and further evaluation in future studies is warranted.

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Table 1. Maternal and child characteristics of the study population in the Danish National Birth Cohort (DNBC), 1996-2002.

Characteristics	Prenatal Exposure to Acetaminophen (n= 40934)		Postnatal Exposure to Acetaminophen [a] (n= 27742)	
	Yes, % (n= 21670)	No, % (n= 19264)	Yes, % (n= 2855)	No, % (n= 24887)
Mother's age (years)				
≤24	7.1	6.9	6.9	6.3
25-29	38.0	38.4	40.5	37.3
30-34	38.8	38.6	39.1	39.2
≥35	16.1	16.2	13.5	17.1
Child's sex				
Female	52.4	50.5	49.0	52.0
Male	47.6	49.5	51.0	48.1
Parental socio-occupational status				
Low	2.7	2.0	1.8	2.4
Medium	24.6	22.3	21.0	24.5
High	68.4	69.7	73.7	69.6
missing	4.3	6.0	3.5	3.5
Parity, %				
1	43.2	49.0	51.2	44.4
2	37.6	33.4	34.7	36.0
>2	16.5	14.5	11.2	16.9
missing	2.7	3.1	2.9	2.7
Mother's pre-pregnancy body mass index [b]				
<18.5	3.6	4.3	4.4	3.9
18.5-25	65.1	69.0	68.4	67.6
26-29	18.5	14.7	16.1	17.4
≥30	7.4	4.7	6.3	6.4
missing	5.5	7.3	4.8	4.7
Maternal smoking during pregnancy				
Never	75.5	79.4	79.0	78.8
≤9 cigarettes/d	12.7	10.6	12.2	11.2
>9 cigarettes/d	11.3	8.3	8.8	10.0
missing	0.5	1.7	0.0	0.01
Maternal ever alcohol intake during pregnancy	73.9	70.0	73.9	72.4
Missing	0.5	1.6	0.0	0.01
Mother ever had psychiatric illness	17.0	13.2	16.9	15.0
Fever during pregnancy	32.1	21.1	29.6	26.7
Muscle and joint disease during pregnancy	11.9	7.6	11.9	9.9
Infection and inflammation during pregnancy	17.0	12.1	17.9	15.0
Prenatal use of nonsteroidal anti-inflammatory drugs	13.6	11.7	14.6	12.4
Infection or inflammation of the index child	NA	NA	67.4	61.0
Fever episode of the index child	NA	NA	67.7	44.2
Preterm birth	NA	NA	4.3	4.0
Birth weight (g)				
<2500	NA	NA	2.7	2.8

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2500 to <4500	NA	NA	92.4	92.5
≥4500	NA	NA	5.0	4.7
Duration of breast feeding				
No	NA	NA	3.8	2.9
<3 moths	NA	NA	13.7	12.3
3-6 months	NA	NA	15.2	14.9
>6 months	NA	NA	60.3	64.6
missing	NA	NA	7.0	5.3
Parent's behavioral scores during their own childhood				
1-3	67.1	69.8	69.4	70.7
4-7	11.4	9.1	11.9	10.6
8-12	2.2	1.6	1.7	1.9
missing	19.3	19.5	17.0	16.8

NA, not applicable.

[a] During infancy in the first 18 months after birth

[b] Weight (kg)/height (m)^2

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Table 2. The correlations between parent- and child-reported Strengths and Difficulties Questionnaire (SDQ) scores at age 11 years in the Danish National Birth Cohort (DNBC), 1996-2002. (N=40934)

Informant	Parent-report				Child-report						
Scores	Median (25th-75th)	Cut-off to indicate behavioral difficulties	Children with behavioral difficulties (%) No.	%	Median (25th-75th)	Cut-off to indicate behavioral difficulties	Children with behavioral difficulties (%) No.	%	Pearson correlation coefficient	Cronbach's alpha (reliability)	κ coefficient
Composite score											
SDQ total difficulties [a]	4 (2-8)	17	1183	2.9	6 (3-10)	20	817	2.0	0.58	0.73	0.30
Internalizing [b]	2 (1-4)	8	2116	5.2	3 (1-5)	9	2232	5.5	0.49	0.66	0.29
Externalizing [c]	2 (1-4)	8	3029	7.4	3 (1-6)	9	3014	7.4	0.59	0.74	0.38
SDQ sub-domains [d]											
Emotional symptoms	1 (0-3)	5	3806	9.3	1 (0-3)	7	958	2.3	0.48	0.65	0.17
Conduct problems	0 (0-1)	4	1312	3.2	1 (0-2)	5	933	2.3	0.46	0.63	0.24
Hyperactivity	2 (0-3)	7	1792	4.4	2 (1-4)	7	2088	5.1	0.57	0.72	0.38
Peer problems	0 (0-1)	4	1852	4.5	1 (0-2)	6	782	1.9	0.40	0.57	0.20
Prosocial behavior	7 (6-8)	4	2250	5.5	8 (7-9)	4	1364	3.3	0.34	0.51	0.15

Abbreviations: SDQ, Strengths and Difficulties Questionnaire.

[a] The SDQ total difficulties range from 0 to 40, and is the sum of the emotional (0-10), conduct (0-10), hyperactivity (0-10), and peer problems (0-10) scales.

[b] The internalizing score ranges from 0 to 20 and is the sum of the emotional and peer problems scales. Cut-off was defined as 95th percentile.

[c] The externalizing score ranges from 0 to 20 and is the sum of the conduct and hyperactivity scales. Cut-off was defined as 95th percentile.

[d] Higher scores on the first four subscales reflect difficulties, whereas higher scores on the prosocial subscale (0-10) reflect strengths.

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Table 3. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at age 11 years according to prenatal and postnatal exposure to acetaminophen in the Danish National Birth Cohort (DNBC), 1996-2002.

Timing		During pregnancy				Postnatal (up to 18 months)			
		Number of users				Number of users			
Outcome	Score	Exposed (n= 21670)	Unexposed (n=19264)	Adjusted risk ratios [a]	95% CI	Exposed (n= 2855)	Unexposed (n= 24887)	Adjusted risk ratios [b]	95% CI
Parent-reported [c]									
Composite score									
SDQ total difficulties	≥17	710	473	1.14	1.01, 1.29	95	652	1.18	0.95, 1.48
Internalizing [d]	≥8	1223	893	1.09	1.00, 1.19	174	1256	1.15	0.98, 1.35
Externalizing [d]	≥8	1735	1294	1.07	0.99, 1.15	226	1783	1.06	0.92, 1.22
SDQ sub-domains									
Emotional symptoms	≥5	2220	1586	1.16	1.09, 1.24	295	2316	1.05	0.93, 1.18
Conduct problems	≥4	748	564	1.05	0.94, 1.17	92	770	1.01	0.81, 1.25
Hyperactivity	≥7	1043	749	1.12	1.02, 1.24	144	1020	1.12	0.94, 1.34
Peer problems	≥4	1010	842	0.99	0.90, 1.08	149	1087	1.19	1.00, 1.42
Prosocial behavior	≤6	1159	1091	0.92	0.85, 1.00	167	1325	1.07	0.91, 1.26
Child-reported [c]									
Composite score									
SDQ total difficulties	≥17	522	295	1.40	1.20, 1.63	53	488	0.97	0.73, 1.30
Internalizing [d]	≥9	1292	940	1.13	1.04, 1.23	159	1355	1.05	0.89, 1.24
Externalizing [d]	≥9	1754	1260	1.13	1.05, 1.22	205	1774	0.99	0.86, 1.15
SDQ sub-domains									
Emotional symptoms	≥7	563	395	1.17	1.02, 1.34	68	577	1.08	0.84, 1.39
Conduct problems	≥5	549	384	1.15	1.01, 1.32	56	557	0.89	0.67, 1.18
Hyperactivity	≥7	1236	852	1.18	1.08, 1.29	151	1257	1.02	0.86, 1.21
Peer problems	≥6	445	337	1.09	0.94, 1.26	48	455	0.96	0.71, 1.30
Prosocial behavior	≤4	743	621	1.05	0.94, 1.17	111	784	1.22	1.00, 1.49

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Abbreviations: SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted maternal age at birth, child's birth year, parity, socio-occupational status of mother, maternal pre-pregnancy body mass index, maternal smoking, alcohol drinking during pregnancy, mother's ever having had mental health problems, maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy, and NSAIDs intake during pregnancy.

[b] Adjusted maternal age at birth, child's birth year, parity, socio-occupational status of mother, and maternal pre-pregnancy body mass index, inflammation episode of the index child, fever episode of the index child, preterm birth, and birth weight, and maternal acetaminophen intake during the prenatal period.

[c] The p-values of heterogeneity were ≥0.10 for nearly all parent-rated and child-rated SDQ exposure-outcome comparisons, except for one stratum among SDQ total difficulties and prenatal acetaminophen exposure which the p-value of heterogeneity by raters was 0.01.

[d] Defined by 95th percentile of each composite score.

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Table 4. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at age 11 years according to prenatal exposure timing to acetaminophen in the Danish National Birth Cohort (DNBC), 1996-2002.

Outcome	Score	1st trimester only (n= 4366)		2nd trimester only (n= 2219)		3rd trimester only (n= 3992)		Any 2 trimesters (n= 5530)		All 3 trimesters (n= 3528)	
		Adjusted risk ratios [a]	95% CI	Adjusted risk ratios [a]	95% CI	Adjusted risk ratios [a]	95% CI	Adjusted risk ratios [a]	95% CI	Adjusted risk ratios [a]	95% CI
Parent-reported											
SDQ total difficulties	≥17	1.08	0.89, 1.31	0.91	0.69, 1.21	1.06	0.86, 1.31	1.22	1.03, 1.45	1.20	0.98, 1.46
Internalizing [b]	≥8	1.07	0.93, 1.24	1.00	0.82, 1.22	1.04	0.89, 1.21	1.12	0.99, 1.28	1.09	0.94, 1.27
Externalizing [b]	≥8	1.07	0.95, 1.21	0.91	0.77, 1.08	1.05	0.93, 1.18	1.09	0.98, 1.21	1.11	0.98, 1.26
Child-reported											
SDQ total difficulties	≥17	1.50	1.19, 1.88	1.09	0.78, 1.53	1.33	1.03, 1.71	1.17	0.94, 1.46	1.53	1.19, 1.96
Internalizing [b]	≥9	1.11	0.96, 1.27	1.17	1.02, 1.35	1.17	1.02, 1.35	1.05	0.93, 1.20	1.25	1.08, 1.44
Externalizing [b]	≥9	1.07	0.95, 1.21	1.02	0.86, 1.19	1.18	1.05, 1.33	1.15	1.03, 1.28	1.16	1.02, 1.32

Abbreviations: SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted maternal age at birth, child's birth year, parity, socio-occupational status of mother, maternal pre-pregnancy body mass index, maternal smoking, alcohol drinking during pregnancy, mother's ever having had mental health problems, maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy, and NSAIDs intake during pregnancy. Reference was never user (n=19264).

[b] Defined by 95th percentile of each composite score.

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Table 5. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at age 11 years according to cumulative weeks of acetaminophen use during pregnancy in the Danish National Birth Cohort (DNBC), 1996-2002.

Outcome	Score	1-5 week (n= 11093)		6-10 weeks (n= 1378)		>10 weeks (n= 2830)		*P*-trend
		Adjusted risk ratios [a]	95% CI	Adjusted risk ratios [a]	95% CI	Adjusted risk ratios [a]	95% CI	
Parent-reported								
SDQ total difficulties	≥17	1.07	0.92, 1.23	1.27	0.95, 1.70	1.32	1.06, 1.63	0.03
Internalizing [b]	≥8	1.04	0.94, 1.16	1.08	0.86, 1.36	1.17	0.99, 1.37	0.13
Externalizing [b]	≥8	1.02	0.93, 1.11	1.08	0.89, 1.30	1.11	0.97, 1.27	0.35
Child-reported								
SDQ total difficulties	≥17	1.25	1.04, 1.51	1.47	1.03, 2.12	1.58	1.22, 2.06	<0.01
Internalizing [b]	≥9	1.12	1.01, 1.24	1.12	0.89, 1.41	1.27	1.08, 1.48	<0.01
Externalizing [b]	≥9	1.12	1.02, 1.22	1.17	0.97, 1.42	1.16	1.02, 1.33	0.06

Abbreviations: SDQ, Strengths and Difficulties Questionnaire.
[a] Adjusted maternal age at birth, child's birth year, parity, socio-occupational status of mother, maternal pre-pregnancy body mass index, maternal smoking, alcohol drinking during pregnancy, mother's ever having had mental health problems, maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy, and NSAIDs intake during pregnancy. Reference was never user (n=19264).
[b] Defined by 95th percentile of each composite score.

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Web Material

Behavioral Problems at Age 11 Years After Prenatal and Postnatal Exposure to Acetaminophen: Parent-reported and Self-reported Outcomes

Kosuke Inoue; Beate Ritz; Andreas Ernst; Wan-Ling Tseng; Yuying Yuan; Qi Meng; Cecilia Høst Ramlau-Hansen; Katrine Strandberg-Larsen; Onyebuchi A. Arah; Carsten Obel; Jiong Li; Jørn Olsen; Zeyan Liew.

Web Table 1. Acetaminophen exposure in infancy and indications of use.
Web Table 2. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at 11 years of age according to prenatal and postnatal exposure to acetaminophen, stratified by children's sex.
Web Table 3. Risk ratios for behavioral difficulties at 11 years of age assessed with a combined measure including both parent- and child-reported SDQ scores according to prenatal and postnatal exposure to acetaminophen.
Web Table 4. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at 11 years of age according to prenatal and postnatal exposure to acetaminophen, additionally adjust for parent's behavioral scores in childhood.
Web Table 5. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at 11 years of age according to postnatal exposure to acetaminophen, additionally adjust for duration of breastfeeding.
Web Table 6. Relative ratios of parent- and child-reported SDQ score at 11 years of age according to prenatal and postnatal exposure to acetaminophen (negative binomial regression models).
Web Table 7. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at 11 years of age according to prenatal and postnatal exposure to acetaminophen, comparisons of model with or without implementing IPSW.

Web Figure 1. Flowchart of study population selection
Web Figure 2. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at 11 years of age according to prenatal exposure to acetaminophen ranging cut-off ±2 of the score employed in our main analysis.
Web Figure 3. Risk ratios for parent- and child-reported behavioral difficulties assessed by SDQ at 11 years of age according to postnatal exposure to acetaminophen ranging cut-off ±2 of the score employed in our main analysis.

Web Table 1. Acetaminophen exposure in infancy and indications of use.

Reported indication of use	Indications reported for postnatal use of acetaminophen in the first 18 months among 2,855 infants	
	N	**%** [a]
Fever >38.5 w/o other symptoms	1419	49.7%
Colds	657	23.0%
Ear infection	424	14.9%
Other and unspecified reasons	143	5.0%
Wheezy breathing	54	1.9%
Throat inflammation	34	1.2%
False croup	32	1.1%
Colic	29	1.0%
Pneumonia	28	1.0%
Eczema or skin eruptions	17	0.6%
Bronchitis	12	0.4%
Diarrhea	11	0.4%
Others [b]	12	0.4%

[a] The sum of the proportion is greater than 100% because some children took acetaminophen for several indications.
[b] Others include constipation, scarlet fever, inflammation of the eye, fungus in mouth, and pruritic skin eruption.