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## Original Contribution

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

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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 Questionnaire (SDQ) responses were collected during the 11-year follow-up. We estimated risk ratios for behavioral problems including total difficulties as well as 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 ($r = 0.49$) behaviors. 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.

acetaminophen; behavioral problems; DNBC; multiple informants' comparison; paracetamol

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

Acetaminophen is one of the most common over-the-counter drugs used 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 might 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 epidemiologic 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 approximate ages 10–15 years (7, 13, 20–22).

Debates over the validity of the findings from these cohort studies have focused mostly 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 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 with 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 perturbation of neurodevelopment, the maturation of the central nervous system might 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 Questionnaire (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 6–12), 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 3 subsequent telephone interviews (scheduled at approximately the 12th and 30th gestational weeks and at 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 (available at https://doi.org/10.1093/aje/kwaa257). 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 no.: 2016–051-000001, serial no.: 1297), and the institutional review boards at the University of California, Los Angeles (16–001849), and Yale University (2000024089).

### Exposures to acetaminophen

Information about maternal acetaminophen use during pregnancy was ascertained from the study enrollment form and 3 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, women were specifically asked to report whether they had taken any painkillers during pregnancy and 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 first 4 subscales, ranging from 0–10 each, with higher scores indicating more negative behaviors and problems. We then dichotomized each subscale according to the recommended cutoff to indicate atypical behaviors for the parent-reported and child-reported SDQ (34). We also created an "internalizing" subscale, which 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 cutoff points for internalizing or externalizing composite scores; thus, the top 95th percentile of each distribution was defined a priori as the cutoff. 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 α, and κ coefficients between parent-reported and child-reported SDQ. We employed modified Poisson regression models to estimate risk ratio and 95% confidence interval for acetaminophen exposure and binary classifications for overall behavioral problems, internalizing behaviors, externalizing behaviors, and each of the 5 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 a 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 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), second (13–24 weeks), or third trimester (25th week to delivery), in any 2 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 might affect child neurobehavioral 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 prepregnancy body mass index (calculated as weight (kg)/height $(m)^2$; <18.5, 18.5–24.9, 25.0–29.9, ≥30.0), and birth year (continuous). In the model for acetaminophen exposure during pregnancy, we additionally adjusted for maternal smoking during pregnancy (never and ≤9 or >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, and inflammation/infections during pregnancy), and prenatal use of nonsteroidal antiinflammatory 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, and respiratory tract illnesses), being born preterm (defined as gestational age less than 37 weeks), and birth weight in grams (<2,500, 2,500–4,500, >4,500). Ten simulated complete data sets were generated via imputation assuming 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 the SDQ cutoff in both 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 (none or, in months, <3, 3–6, >6) 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 cutoff 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 nonparticipation at the 11-year follow-up (42). Stabilized IPSW and 95% confidence intervals 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).

### Parent- and child-reported behavioral problems

The medians of child-reported SDQ scores at age 11 years tended to be higher than the parent-reported measures (Table 2). However, using the binary classification of atypical behavior with the recommended cutoffs 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

**Table 1.** Maternal and Child Characteristics of the Study Population in the Danish National Birth Cohort, 1996–2002

| Characteristic | Prenatal Exposure to Acetaminophen (*n* = 40,934) | | Postnatal Exposure to Acetaminophen[a] (*n* = 27,742) | |
|---|---|---|---|---|
| | % Yes (*n* = 21,670) | % No (*n* = 19,264) | % Yes (*n* = 2,855) | % No (*n* = 24,887) |
| 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 prepregnancy body mass index[b] | | | | |
| <18.5 | 3.6 | 4.3 | 4.4 | 3.9 |
| 18.5–24.9 | 65.1 | 69.0 | 68.4 | 67.6 |
| 25.0–29.9 | 18.5 | 14.7 | 16.1 | 17.4 |
| ≥30.0 | 7.4 | 4.7 | 6.3 | 6.4 |
| Missing | 5.5 | 7.3 | 4.8 | 4.7 |
| Maternal smoking during pregnancy, cigarettes/day | | | | |
| Never | 75.5 | 79.4 | 79.0 | 78.8 |
| ≤9 | 12.7 | 10.6 | 12.2 | 11.2 |
| >9 | 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 antiinflammatory drugs | 13.6 | 11.7 | 14.6 | 12.4 |

**Table continues**

**Table 1.** Continued

| Characteristic | Prenatal Exposure to Acetaminophen ($n$ = 40,934) | | Postnatal Exposure to Acetaminophen[a] ($n$ = 27,742) | |
|---|---|---|---|---|
| | % Yes ($n$ = 21,670) | % No ($n$ = 19,264) | % Yes ($n$ = 2,855) | % No ($n$ = 24,887) |
| Infection or inflammation of the index child | N/A | N/A | 67.4 | 61.0 |
| Fever episode of the index child | N/A | N/A | 67.7 | 44.2 |
| Preterm birth | N/A | N/A | 4.3 | 4.0 |
| Birth weight, g | | | | |
| <2,500 | N/A | N/A | 2.7 | 2.8 |
| 2,500–4,999 | N/A | N/A | 92.4 | 92.5 |
| ≥4,500 | N/A | N/A | 5.0 | 4.7 |
| Duration of breast feeding | | | | |
| No | N/A | N/A | 3.8 | 2.9 |
| <3 moths | N/A | N/A | 13.7 | 12.3 |
| 3–6 months | N/A | N/A | 15.2 | 14.9 |
| >6 months | N/A | N/A | 60.3 | 64.6 |
| Missing | N/A | N/A | 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 |

Abbreviation: N/A, not applicable.
[a] During infancy in the first 18 months after birth.
[b] Weight (kg)/height $(m)^2$.

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 subdomains, 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 α reliability and κ 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, risk ratio (RR) = 1.14, 95% confidence interval (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 risk ratios 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)).

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 risk ratios were higher for all parent-reported outcomes and some child-reported outcomes when acetaminophen was used in more than 1 pregnancy trimester. 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

**Table 2.** Correlations Between Parent- and Child-Reported Strengths and Difficulties Questionnaire Scores at Age 11 Years in the Danish National Birth Cohort ($n$ = 40,934), 1996–2002

| Score | Parent Report | | | | Child Report | | | | Pearson Correlation Coefficient | Cronbach's α (Reliability) | κ Coefficient |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median (IQR) | Cutoff to Indicate Behavioral Difficulties | Children With Behavioral Difficulties | | Median (IQR) | Cutoff to Indicate Behavioral Difficulties | Children With Behavioral Difficulties | | | | |
| | | | No. | % | | | No. | % | | | |
| Composite score | | | | | | | | | | | |
| SDQ total difficulties[a] | 4 (2–8) | 17 | 1,183 | 2.9 | 6 (3–10) | 20 | 817 | 2.0 | 0.58 | 0.73 | 0.30 |
| Internalizing[b] | 2 (1–4) | 8 | 2,116 | 5.2 | 3 (1–5) | 9 | 2,232 | 5.5 | 0.49 | 0.66 | 0.29 |
| Externalizing[c] | 2 (1–4) | 8 | 3,029 | 7.4 | 3 (1–6) | 9 | 3,014 | 7.4 | 0.59 | 0.74 | 0.38 |
| SDQ subdomains[d] | | | | | | | | | | | |
| Emotional symptoms | 1 (0–3) | 5 | 3,806 | 9.3 | 1 (0–3) | 7 | 958 | 2.3 | 0.48 | 0.65 | 0.17 |
| Conduct problems | 0 (0–1) | 4 | 1,312 | 3.2 | 1 (0–2) | 5 | 933 | 2.3 | 0.46 | 0.63 | 0.24 |
| Hyperactivity | 2 (0–3) | 7 | 1,792 | 4.4 | 2 (1–4) | 7 | 2,088 | 5.1 | 0.57 | 0.72 | 0.38 |
| Peer problems | 0 (0–1) | 4 | 1,852 | 4.5 | 1 (0–2) | 6 | 782 | 1.9 | 0.40 | 0.57 | 0.20 |
| Prosocial behavior | 7 (6–8) | 4 | 2,250 | 5.5 | 8 (7–9) | 4 | 1,364 | 3.3 | 0.34 | 0.51 | 0.15 |

Abbreviations: IQR, interquartile range; SDQ, Strengths and Difficulties Questionnaire.

[a] The SDQ total difficulties score ranges 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. Cutoff was defined as 95th percentile.

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

[d] Higher scores on the first 4 subscales reflect difficulties, whereas higher scores on the prosocial subscale (0–10) reflect strengths.

**Table 3.** Risk Ratios for Parent- and Child-Reported Behavioral Difficulties Assessed by Strengths and Difficulties Questionnaire at Age 11 Years According to Prenatal and Postnatal Exposure to Acetaminophen in the Danish National Birth Cohort, 1996–2002

| Outcome | Score | During Pregnancy | | | | Postnatal (Up to 18 Months) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. of Users | | Adjusted Risk Ratios[a] | 95% CI | No. of Users | | Adjusted Risk Ratios[b] | 95% CI |
| | | Exposed (*n* = 21,670) | Unexposed (*n* = 19,264) | | | Exposed (*n* = 2,855) | Unexposed (*n* = 24,887) | | |
| 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 | 1,223 | 893 | 1.09 | 1.00, 1.19 | 174 | 1,256 | 1.15 | 0.98, 1.35 |
| Externalizing[d] | ≥8 | 1,735 | 1,294 | 1.07 | 0.99, 1.15 | 226 | 1783 | 1.06 | 0.92, 1.22 |
| SDQ subdomains | | | | | | | | | |
| Emotional symptoms | ≥5 | 2,220 | 1,586 | 1.16 | 1.09, 1.24 | 295 | 2,316 | 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 | 1,043 | 749 | 1.12 | 1.02, 1.24 | 144 | 1,020 | 1.12 | 0.94, 1.34 |
| Peer problems | ≥4 | 1,010 | 842 | 0.99 | 0.90, 1.08 | 149 | 1,087 | 1.19 | 1.00, 1.42 |
| Prosocial behavior | ≤4 | 1,159 | 1,091 | 0.92 | 0.85, 1.00 | 167 | 1,325 | 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 | 1,292 | 940 | 1.13 | 1.04, 1.23 | 159 | 1,355 | 1.05 | 0.89, 1.24 |
| Externalizing[d] | ≥9 | 1754 | 1,260 | 1.13 | 1.05, 1.22 | 205 | 1,774 | 0.99 | 0.86, 1.15 |
| SDQ subdomains | | | | | | | | | |
| 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 | 1,236 | 852 | 1.18 | 1.08, 1.29 | 151 | 1,257 | 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 |

Abbreviations: CI, confidence interval; SDQ, Strengths and Difficulties Questionnaire.

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

[c] The *P* values for heterogeneity were ≥0.10 for nearly all parent-rated and child-rated SDQ exposure-outcome comparisons, except for 1 stratum among SDQ total difficulties and prenatal acetaminophen exposure, for which the *P* value of heterogeneity by raters was 0.01.

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

**Table 4.** Risk Ratios for Parent- and Child-Reported Behavioral Difficulties Assessed by Strengths and Difficulties Questionnaire at Age 11 Years According to Prenatal Exposure Timing to Acetaminophen in the Danish National Birth Cohort, 1996–2002

| Outcome | Score | First Trimester Only (*n* = 4,366) | | Second Trimester Only (*n* = 2,219) | | Third Trimester Only (*n* = 3,992) | | Any 2 Trimesters (*n* = 5,530) | | All 3 Trimesters (*n* = 3,528) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 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: CI, confidence interval; SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted for maternal age at birth, child's birth year, parity, socio-occupational status of mother, maternal prepregnancy 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* = 19,264).

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

**Table 5.** Risk Ratios for Parent- and Child-Reported Behavioral Difficulties Assessed by Strengths and Difficulties Questionnaire at Age 11 Years According to Cumulative Weeks of Acetaminophen Use During Pregnancy in the Danish National Birth Cohort, 1996–2002

| Outcome | Score | 1–5 Weeks (*n* = 11,093) | | 6–10 Weeks (*n* = 1,378) | | >10 Weeks (*n* = 2,830) | | *P* for 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: CI, confidence interval; SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted maternal age at birth, child's birth year, parity, socio-occupational status of mother, maternal prepregnancy 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* = 19,264).

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

(RR = 1.15, 95% CI: 0.98, 1.35), but the 95% confidence intervals of these effect estimates included the null (Table 3). There was no association between postnatal acetaminophen use and child-reported total difficulties, internalizing problems, or externalizing problems. There was no evidence of heterogeneity comparing the risk ratios by raters. Concerning SDQ subdomains, a positive association with peer problems (RR = 1.19, 95% CI: 1.00, 1.42) was found only 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 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).

### 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 found only for parent- and 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 cutoff 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 increased risks for offspring developing behavioral and emotional problems 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 3 cohort studies that assessed behavioral problems in children using parent-reported SDQ (6, 7, 10). Prior studies neither simultaneously assessed prenatal and postnatal exposures nor used more than 1 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 ($r \approx$ 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 nonshared variances between the 2 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 driven solely 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 parent 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 for parent-rated than child-rated SDQ, which was true only 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 evaluation that addresses 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 development throughout both the prenatal and postnatal periods, its disruption might 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, 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 an 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 that a lower dose exposure can 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 used IPSW to account for possible selection bias, and we were able to control for a comprehensive set of potential confounders including indications for acetaminophen use by the mother and infant. However, our study also has several limitations. Exposure and outcome were based on reports from the participants, 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 underreporting (51, 52). Last, 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.

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. Because some findings for postnatal exposure were seen only with parent-reported outcomes, reporting bias is a concern here, and further evaluation in future studies is warranted.

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## REFERENCES

1. Werler MM, Mitchell AA, Hernandez-Diaz S, et al. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol*. 2005;193(3):771–777.
2. Servey J, Chang J. Over-the-counter medications in pregnancy. *Am Fam Physician*. 2014;90(8):548–555.
3. Brandlistuen RE, Ystrom E, Nulman I, et al. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol*. 2013;42(6):1702–1713.
4. Jensen MS, Rebordosa C, Thulstrup AM, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology*. 2010;21(6):779–785.
5. Brune K, Renner B, Tiegs G. Acetaminophen/paracetamol: a history of errors, failures and false decisions. *Eur J Pain*. 2015;19(7):953–965.
6. Thompson JMD, Waldie KE, Wall CR, et al. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PLoS One*. 2014;9(9):e108210.
7. Liew Z, Ritz B, Rebordosa C, et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr*. 2014;168(4):313–320.
8. Liew Z, Bach CC, Asarnow RF, et al. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. *Int J Epidemiol*. 2016;45(6):2009–2017.
9. Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. *Int J Epidemiol*. 2016;45(6):1987–1996.
10. Stergiakouli E, Thapar A, Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. *JAMA Pediatr*. 2016;170(10):964–970.
11. Liew Z, Kioumourtzoglou M-A, Roberts AL, et al. Use of negative control exposure analysis to evaluate confounding: an example of acetaminophen exposure and attention-deficit/hyperactivity disorder in Nurses' Health Study II. *Am J Epidemiol*. 2019;188(4):768–775.
12. Bornehag C-G, Reichenberg A, Hallerback MU, et al. Prenatal exposure to acetaminophen and children's language development at 30 months. *Eur Psychiatry*. 2018;51:98–103.
13. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics*. 2017;140(5):e20163840.
14. Kristensen DM, Mazaud-Guittot S, Gaudriault P, et al. Analgesic use—prevalence, biomonitoring and endocrine and reproductive effects. *Nat Rev Endocrinol*. 2016;12(7):381–393.
15. Lind DV, Main KM, Kyhl HB, et al. Maternal use of mild analgesics during pregnancy associated with reduced anogenital distance in sons: a cohort study of 1027 mother-child pairs. *Hum Reprod*. 2017;32(1):223–231.
16. Albert O, Desdoits-Lethimonier C, Lesné L, et al. Paracetamol, aspirin and indomethacin display endocrine disrupting properties in the adult human testis in vitro. *Hum Reprod*. 2013;28(7):1890–1898.
17. Kristensen DM, Lesné L, Le Fol V, et al. Paracetamol (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis. *Int J Androl*. 2012;35(3):377–384.
18. Posadas I, Santos P, Blanco A, et al. Acetaminophen induces apoptosis in rat cortical neurons. *PLoS One*. 2010;5(12):e15360.
19. Nuttall SL, Khan JN, Thorpe GH, et al. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharm Ther*. 2003;28(4):289–294.
20. Liew Z, Ritz B, Virk J, et al. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: a Danish national birth cohort study. *Autism Res*. 2016;9(9):951–958.
21. Chen M-H, Pan T-L, Wang P-W, et al. Prenatal exposure to acetaminophen and the risk of attention-deficit/hyperactivity disorder: a nationwide study in Taiwan. *J Clin Psychiatry*. 2019;80(5):18m12612.
22. Ji Y, Azuine RE, Zhang Y, et al. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry*. 2020;77(2):180–189.
23. Cooper M, Langley K, Thapar A. Antenatal acetaminophen use and attention-deficit/hyperactivity disorder: an interesting

observed association but too early to infer causality. *JAMA Pediatr*. 2014;168(4):306–307.
24. Olsen J, Liew Z. Fetal programming of mental health by acetaminophen? Response to the SMFM statement: prenatal acetaminophen use and ADHD. *Expert Opin Drug Saf*. 2017; 16(12):1395–1398.
25. Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: a causal association or bias? *Paediatr Perinat Epidemiol*. 2020;34(3):309–317.
26. Parker SE, Collett BR, Werler MM. Maternal acetaminophen use during pregnancy and childhood behavioural problems: discrepancies between mother- and teacher-reported outcomes. *Paediatr Perinat Epidemiol*. 2020;34(3):299–308.
27. Rifas-Shiman SL, Cardenas A, Hivert M-F, et al. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. *Paediatr Perinat Epidemiol*. 2020;34(3):287–298.
28. Hernán MA, Cole SR. Invited commentary: causal diagrams and measurement bias. *Am J Epidemiol*. 2009;170(8): 959–962.
29. Ystrom E, Vollrath ME, Nordeng H. Effects of personality on use of medications, alcohol, and cigarettes during pregnancy. *Eur J Clin Pharmacol*. 2012;68(5):845–851.
30. De Los Reyes A, Augenstein TM, Wang M, et al. The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychol Bull*. 2015;141(4): 858–900.
31. De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. *Psychol Bull*. 2005;131(4):483–509.
32. Viberg H, Eriksson P, Gordh T, et al. Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicol Sci*. 2014; 138(1):139–147.
33. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health*. 2001;29(4):300–307.
34. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38(5): 581–586.
35. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry*. 2001;40(11):1337–1345.
36. Niclasen J, Skovgaard AM, Andersen A-MN, et al. A confirmatory approach to examining the factor structure of the Strengths and Difficulties Questionnaire (SDQ): a large scale cohort study. *J Abnorm Child Psychol*. 2013;41(3):355–365.
37. Kesmodel US, Falgreen Eriksen H-L, Underbjerg M, et al. The effect of alcohol binge drinking in early pregnancy on general intelligence in children. *BJOG*. 2012;119(10): 1222–1231.
38. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10(4):585–598.
39. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet*. 2019;51(1):63–75.
40. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet*. 2016;387(10024):1240–1250.
41. Strøm M, Mortensen EL, Kesmodel US, et al. Is breast feeding associated with offspring IQ at age 5? Findings from prospective cohort: Lifestyle During Pregnancy Study. *BMJ Open*. 2019;9(5):e023134.
42. Liew Z, Nohr EA, Morgen CS, et al. Prenatal exposure to acetaminophen and overweight in childhood. *Obesity (Silver Spring)*. 2019;27(8):1314–1322.
43. Kuhn C, Aebi M, Jakobsen H, et al. Effective mental health screening in adolescents: should we collect data from youth, parents or both? *Child Psychiatry Hum Dev*. 2017;48(3): 385–392.
44. Aebi M, Kuhn C, Banaschewski T, et al. The contribution of parent and youth information to identify mental health disorders or problems in adolescents. *Child Adolesc Psychiatry Ment Health*. 2017;11:23.
45. Salbach-Andrae H, Klinkowski N, Lenz K, et al. Agreement between youth-reported and parent-reported psychopathology in a referred sample. *Eur Child Adolesc Psychiatry*. 2009; 18(3):136–143.
46. Koskelainen M, Sourander A, Kaljonen A. The Strengths and Difficulties Questionnaire among Finnish school-aged children and adolescents. *Eur Child Adolesc Psychiatry*. 2000;9(4):277–284.
47. Van Roy B, Groholt B, Heyerdahl S, et al. Understanding discrepancies in parent-child reporting of emotional and behavioural problems: effects of relational and socio-demographic factors. *BMC Psychiatry*. 2010;10:56.
48. Achenbach TM, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull*. 1987;101(2):213–232.
49. Seiffge-Krenke I, Kollmar F. Discrepancies between mothers' and fathers' perceptions of sons' and daughters' problem behaviour: a longitudinal analysis of parent-adolescent agreement on internalising and externalising problem behaviour. *J Child Psychol Psychiatry*. 1998;39(5): 687–697.
50. Sourander A, Helstelä L, Helenius H. Parent-adolescent agreement on emotional and behavioral problems. *Soc Psychiatry Psychiatr Epidemiol*. 1999;34(12):657–663.
51. Magnus MC, Karlstad Ø, Håberg SE, et al. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. *Int J Epidemiol*. 2016;45(2):512–522.
52. Piler P, Švancara J, Kukla L, et al. Role of combined prenatal and postnatal paracetamol exposure on asthma development: the Czech ELSPAC study. *J Epidemiol Community Health*. 2018;72(4):349–355.
53. Horowitz RS, Dart RC, Jarvie DR, et al. Placental transfer of *N*-acetylcysteine following human maternal acetaminophen toxicity. *J Toxicol Clin Toxicol*. 1997;35(5):447–451.
54. Kumpulainen E, Kokki H, Halonen T, et al. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics*. 2007;119(4):766–771.
55. Frye CA, Bo E, Calamandrei G, et al. Endocrine disrupters: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. *J Neuroendocrinol*. 2012;24(1):144–159.
56. Colborn T. Neurodevelopment and endocrine disruption. *Environ Health Perspect*. 2004;112(9):944–949.
57. Masarwa R, Levine H, Gorelik E, et al. Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: a systematic review, meta-analysis, and meta-regression analysis of cohort studies. *Am J Epidemiol*. 2018;187(8):1817–1827.
58. Vandenberg LN, Colborn T, Hayes TB, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev*. 2012;33(3): 378–455.