Original Investigation

Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders

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IMPORTANCE Acetaminophen (paracetamol) is the most commonly used medication for pain and fever during pregnancy in many countries. Research data suggest that acetaminophen is a hormone disruptor, and abnormal hormonal exposures in pregnancy may influence fetal brain development.

OBJECTIVE To evaluate whether prenatal exposure to acetaminophen increases the risk for developing attention-deficit/hyperactivity disorder (ADHD)–like behavioral problems or hyperkinetic disorders (HKDs) in children.

DESIGN, SETTING, AND PARTICIPANTS We studied 64 322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002.

EXPOSURES Acetaminophen use during pregnancy was assessed prospectively via 3 computer-assisted telephone interviews during pregnancy and 6 months after child birth.

MAIN OUTCOMES AND MEASURES To ascertain outcome information we used (1) parental reports of behavioral problems in children 7 years of age using the Strengths and Difficulties Questionnaire; (2) retrieved HKD diagnoses from the Danish National Hospital Registry or the Danish Psychiatric Central Registry prior to 2011; and (3) identified ADHD prescriptions (mainly Ritalin) for children from the Danish Prescription Registry. We estimated hazard ratios for receiving an HKD diagnosis or using ADHD medications and risk ratios for behavioral problems in children after prenatal exposure to acetaminophen.

RESULTS More than half of all mothers reported acetaminophen use while pregnant. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95% CI, 1.01-1.27). Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes (ie, HKD diagnosis, ADHD medication use, and ADHD-like behaviors; *P* trend < .001). Results did not appear to be confounded by maternal inflammation, infection during pregnancy, the mother's mental health problems, or other potential confounders we evaluated.

CONCLUSIONS AND RELEVANCE Maternal acetaminophen use during pregnancy is associated with a higher risk for HKDs and ADHD-like behaviors in children. Because the exposure and outcome are frequent, these results are of public health relevance but further investigations are needed.

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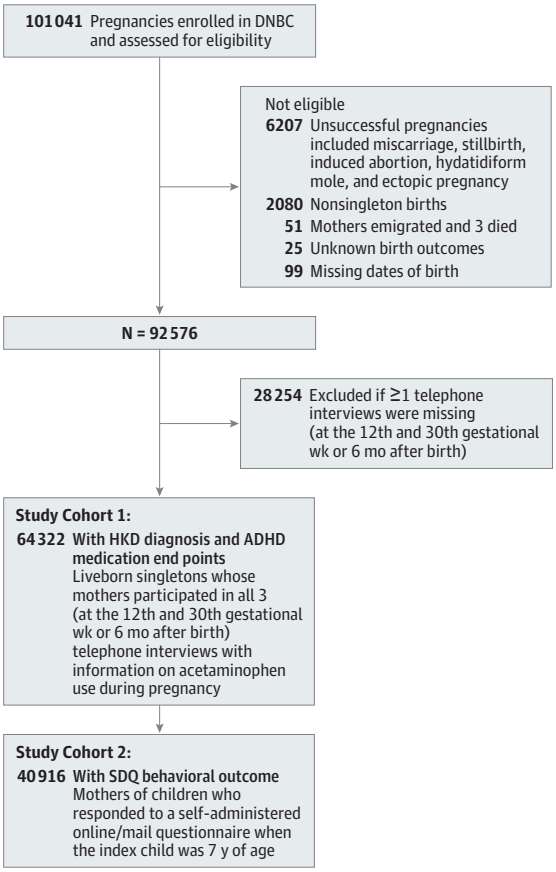
While some medications used in pregnancy may adversely affect the fetus, most over-the-counter (OTC) drugs are generally considered safe. Acetaminophen (paracetamol) is the most commonly used OTC pain and fever medication,[1,2] with more than 50% of pregnant women reporting use in the United States[1] and Denmark.[3,4]

Recent animal and human studies suggested that acetaminophen has endocrine-disrupting properties.[5,6] Prenatal exposure to endocrine disruptors may affect neurodevelopment and cause behavioral dysfunction[7,8] (eg, by interfering with sex hormone or thyroid hormone function essential for normal brain development[7,9,10]).

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders worldwide,[11] characterized by inattention, hyperactivity, increased impulsivity, and motivational/emotional dysregulation. Hyperkinetic disorder (HKD; *International Statistical Classification of Diseases, 10th Revision*) is a particularly severe form of ADHD (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]).[12,13] The etiology of HKD/ADHD is not well understood but both environmental and genetic factors are believed to contribute.[14,15]

Figure. Flowchart of Study Population Selection



ADHD indicates attention-deficit/hyperactivity disorder; DNBC, Danish National Birth Cohort; HKD, hyperkinetic disorder; SDQ, Strengths and Difficulties Questionnaire.

The rapid increase in childhood neurodevelopmental disorders, including ADHD, observed over the past decades[16] was suggested to be not solely attributable to changes in diagnoses[17] or parental awareness[12] necessitating the search for avoidable environmental causes to prevent or slow down the epidemic. Part of the neuropathology of ADHD may already be present at birth making exposures during pregnancy and/or infancy of particular interest.[18] Marketed since the 1950s, acetaminophen has been increasingly used as a safe OTC drug during pregnancy for decades.[19]

Here, we used the Danish National Birth Cohort (DNBC) to evaluate the risk for developing ADHD-like behaviors at age 7 years, receiving a diagnosis of HKD, or using ADHD medications after fetal exposure to acetaminophen.

Methods

The Danish National Birth Cohort is a nationwide cohort study of pregnancies and children with the aim to study causes of pregnancy complications and diseases in offspring operating in early life, with a special focus on adverse effects from medications and infections (for details, see Olsen et al[20]). Briefly, women were recruited between 6 and 12 weeks of gestation from 1996 to 2002 by approximately 50% of all general practitioners in Denmark; 60% of women invited agreed to participate. Women were ineligible if they spoke insufficient Danish or intended to not carry their pregnancy to term (for English version of questionnaires, see http://www.bsmb.dk). Written informed consent was obtained from all participants, and the study was approved by the Danish data inspectorate and the University of California, Los Angeles, institutional review board.

Study Population

Altogether, the DNBC enrolled 101 041 pregnancies, but we restricted the cohort to live-born children whose mothers answered all 3 telephone interviews (at the 12th and 30th gestational weeks and 6 months after birth) that collected information on pregnancy acetaminophen use. We excluded unsuccessful pregnancies (n = 6207), nonsingleton births (n = 2080), if the mother emigrated (n = 51) or died (n = 3), and those with unknown birth outcomes (n = 25), missing birth dates (n = 99), or having missed an interview (n = 28 254). For HKD diagnoses and ADHD medication analyses, the cohort included 64 322 children. However, to assess ADHD-like behaviors, we further excluded children whose caregiver did not respond to a self-administered online/mail questionnaire when the child turned 7 years. The selection of study participants from the DNBC is shown in the **Figure**.

Acetaminophen Use During Pregnancy

In the telephone interviews, women were asked to report whether they had taken any pain killer during pregnancy, and respondents who answered yes were provided with a list of 44 common pain killers, including acetaminophen, as a singular and combination drug whether available as an OTC or via prescription. Interviewees were also allowed to report additional pain killers not listed. Women also reported gesta-

tional weeks of use on a week-by-week basis, and this information was used to calculate trimester-specific and duration of use.

Outcome Measures

Parental Reports of Children's ADHD-Like Behaviors at Age 7 Years

We assessed children's ADHD-like behaviors based on the standardized Strengths and Difficulties Questionnaire (SDQ), a screening tool that assesses 5 domains including emotional symptoms, conduct problems, hyperactivity, peer relationship, and prosocial behavior in children and adolescents ages 4 to 16 years.[21] Mothers or main caregivers were asked 25 questions about their 7-year-old child's behavior during the previous 6 months. As recommended for scoring of the SDQ (http://www.sdqinfo.com), we created a total difficulties score (range, 0-40) by summing 4 subscales (emotional symptoms, conduct problems, hyperactivity, and peer problems), ranging from 0 to 10 each, with higher scores indicating an increasing number of behavioral problems, and omitting the prosocial behavior subscale (range, 0-10), for which higher scores indicate positive social behaviors. Parents also answered 6 questions (possible value of 0, 1, or 2 for each) about their own behavioral problems during childhood, allowing us to generate a parental behavioral problems score (range, 0-12) of ADHD-like symptoms.

Hospital Diagnoses for HKDs

An HKD diagnosis was identified for children at or after their fifth birthday, relying on unique civil registration numbers from the Danish National Hospital Registry[22] with nationwide data for all somatic admissions and the Danish Psychiatric Central Registry[23] for all admissions to mental hospitals throughout the follow-up period. Since 1995, outpatient and emergency department visits have been added to both registries. Hyperkinetic disorder primary or secondary diagnoses are based on the *International Statistical Classification of Diseases, 10th Revision* (F90.0-F90.9); 97.5% of HKD cases received a primary diagnosis and mainly as outpatient admissions (96%). If children received diagnoses solely prior to age 5 years (n = 50) but not afterwards, they were not considered an HKD case owing to higher diagnostic uncertainty at younger ages.

Use of ADHD Medications

Relying on the civil registration number, we also searched for children who filled 2 or more ADHD medication prescriptions (methylphenidate [Ritalin] [N06BA04], atomoxetine [N06BA09], or modafinil [N06BA07]) listed in the Danish Prescription Registry,[24] which receives data on dispensed prescriptions including drug Anatomical Therapeutic Chemical Classification System code and dispensing date from all pharmacies in Denmark since January 1995.

Statistical Analysis

Women were classified as ever users of acetaminophen during the entire pregnancy or during the first (1-12 weeks), second (13-24 weeks), or third (25th-delivery) trimester; women not taking acetaminophen during pregnancy were the unexposed reference. Pregnancy trimester–specific use was also assigned according to the gestational time of interview when women were unable to recall the exact week of their acetaminophen use. Weeks of use (1, 2-5, 6-10, 11-20, >20 weeks) were used to examine exposure response, and trend test was fitted based on linear models including the number of weeks of exposure as a continuous variable.

Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc). We used generalized linear models with a log-link function and a Poisson distribution to estimate risk ratios and 95% CIs for prenatal acetaminophen use and ADHD-like behaviors.[25] Following Goodman,[21] SDQ scores were dichotomized using a cut-off point, resulting in high specificity for ADHD-like behaviors (total difficulties scores ≥ 17).

Using Cox proportional hazards regression, we estimated hazard ratios and 95% CIs for pregnancy acetaminophen use of mothers and HKD diagnosis and ADHD medication use in children. Person-time follow-up started at the child's fifth birthday and ended at the time of hospital diagnosis of HKD or the ADHD medication prescription date (ie, at the time of receiving the first medication if ≥2 prescriptions in total), death, emigration, or end of follow-up, whichever came first. Follow-up ended on the last date of each respective record linkage (ie, for HKD diagnoses on August 1, 2011, and for ADHD medications on December 31, 2011).

Potential confounders to be included in our analyses were child's birth year, birth weight, and sex, as well as maternal age at child's birth, parity, gestational age at delivery, socioeconomic status, smoking and alcohol drinking during pregnancy, prepregnancy body mass index (calculated as weight in kilograms divided by height in meters squared), and mother's self-reported psychiatric illnesses. Women were asked to self-report whether they had psychiatric illnesses and had seen a doctor or psychologist because of depression, anxiety, childhood psychiatric disorder, family problems/life crisis, or other mental health problems. We also considered parent's self-reported childhood behavior problem for the analysis of ADHD-like behaviors (SDQ scale) in children. Additionally, other potential confounders, such as father's age at the child's birth, Apgar scores, and season of conception, were evaluated but not included in final models because changes in effect estimate size were minimal (<1%).

To address potential confounding by indication, we further adjusted for diseases or conditions that may trigger use of acetaminophen during pregnancy: muscle and joint diseases, fever, and inflammation or infections. Maternal inflammation or infections in pregnancy are of particular interest because they have previously been reported to increase ADHD risk in offspring.[26,27] Thus, we present stratified analyses according to self-reported episodes of fever, inflammation, or infection during pregnancy.

For about 5% of participants with at least 1 missing value for covariates, we used multiple imputations (PROC MI and PROC MIANALYZE in SAS version 9.2), generating 5 simulated complete data sets, and then we used standard analytical procedures for complete data and combining the results as proposed.[28]

We performed several sensitivity analyses. In addition to dichotomizing the SDQ score, we used linear regression on continuous SDQ scores with or without logarithmic transforma-

Table 1. Sociodemographic Characteristics of Study Population in the Danish National Birth Cohort

Characteristic	%[a]			
	Cohort 1 for HKD Diagnosis and ADHD Medication End Points		Cohort 2 for SDQ Behavioral Outcome	
	All Participants (N = 64 322)	Participants' Reported Use of Acetaminophen (n = 36 187)	All Participants (n = 40 916)	Participants' Reported Use of Acetaminophen (n = 22 687)
Mother's age, y				
≤24	8.7	9.0	7.6	7.7
25-29	38.8	38.4	38.4	38.0
30-34	37.4	37.4	38.3	38.6
≥35	15.1	15.2	15.7	15.7
Socioeconomic status[b]				
Low	3.7	4.1	3.2	3.6
Medium	29.2	30.4	27.5	28.6
High	66.8	65.1	69.1	67.6
Gestational age, d				
<259	3.8	3.7	3.7	3.6
259-293	86.9	87.3	87.1	87.4
≥294	9.1	8.9	9.0	8.8
Maternal smoking during pregnancy				
Never	74.0	71.5	76.3	74.0
≤9 cigarettes/d	12.5	13.2	12.1	12.9
>9 cigarettes/d	13.5	15.3	11.6	13.1
Mother's prepregnancy BMI				
<18.5	4.2	3.8	4.2	3.8
18.5-25	66.5	63.8	68.5	66.1
26-29	19.3	21.0	18.5	20.1
≥30	8.4	9.7	7.3	8.5
Mother ever had psychiatric illness	14.9	16.7	18.1	20.2
Fever during pregnancy	28.7	33.4	28.2	33.0
Muscle and joint disease during pregnancy	11.2	13.3	10.5	12.5
Infection and inflammation during pregnancy	11.4	13.2	11.4	13.3
Parent's behavioral scores during their own childhood				
1-3	NA	NA	83.6	81.8
4-7	NA	NA	13.5	14.7
8-12	NA	NA	2.5	3.0

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HKD, hyperkinetic disorder; NA, not applicable; SDQ, Strengths and Difficulties Questionnaire.

[a] Because several variables have missing values, percentages do not sum up to 100% for several factors.

[b] Mother's socioeconomic status is a composed variable derived from the mother's and father's education level and occupation.

tions. We also restricted analyses to study participants whose SDQ score had been reported by the mother (n = 40 542; 99.1%) and not the father or other caregivers (n = 374; 0.9%). Most HKD diagnoses (n = 696; 83.5%) came from the Psychiatric Central Registry, while 78 (9.4%) were diagnosed only in the National Hospital Registry and 60 (7%) in both. Thus, we stratified by hospital type to assess diagnostic differences. Finally, we stratified by child's sex and adjusted for the most commonly used nonsteroidal anti-inflammatory drugs among pregnant women in this cohort (ie, the OTC drugs ibuprofen and acetylsalicylic acid [aspirin]).[4]

Results

More than half of all mothers reported ever having used acetaminophen during pregnancy both in the cohort for which we identified HKD diagnoses and ADHD medications as end points (56%; n = 36 187) and in the smaller cohort used to identify ADHD-like behaviors using the SDQ (55%; n = 22 687) (**Table 1**). The mean age of children at the end of follow-up for HKD diagnoses was 10.7 years (range, 8.2-13.4 years) and for ADHD medications was 11.2 years (range, 8.6-13.9 years).

We observed an increased risk for ADHD-like behaviors in children at age 7 years with maternal acetaminophen use during pregnancy (total difficulties scores ≥17, risk ratio, 1.13; 95% CI, 1.01-1.27) (**Table 2**), as well as use in more than 1 pregnancy trimester, especially in later pregnancy, and a stepwise increase in risks with increasing frequency of use throughout pregnancy (**Table 3**; *P* trend < .001). In linear regression models, each additional week of prenatal acetaminophen use during pregnancy was associated with higher SDQ behavioral score (eTable 1 in Supplement).

Table 2. Risk Ratios for ADHD-Like Behavioral Problems in Children at Age 7 Years and Maternal Acetaminophen Use During Pregnancy

Outcome	Users, No. (%)		Risk Ratios	
	Ever (n = 22 623)	Never (n = 18 188)	Crude	Adjusted (95% CI)[a]
SDQ total difficulties (scores ≥17)[b]	774 (3.4)	458 (2.5)	1.36	1.13 (1.01-1.27)
Emotional symptoms (scores ≥5)	1763 (7.8)	1251 (6.9)	1.13	1.05 (0.98-1.13)
Conduct problems (scores ≥4)	1370 (6.1)	836 (4.6)	1.32	1.14 (1.05-1.25)
Hyperactivity (scores ≥7)	1286 (5.7)	787 (4.3)	1.31	1.17 (1.07-1.28)
Peer problems (scores ≥4)	1026 (4.5)	727 (4.0)	1.13	1.01 (0.91-1.11)
Prosocial behavior (scores ≤6)	509 (2.3)	396 (2.2)	1.03	1.00 (0.88-1.15)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal prepregnancy body mass index, parent's behavioral scores in childhood, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy.

[b] Defined as summing over the scores from emotional symptoms, conduct problems, hyperactivity, and peer problems.

Table 3. Risk Ratios for ADHD-Like Behavioral Problems (Higher SDQ Scores) in Children at Age 7 Years and Maternal Acetaminophen Use (Timing and Weeks) During Pregnancy

Prenatal Exposure and Timing	No.		Risk Ratios	
	Total Difficulties (Scores ≥17)	Noncases	Crude	Adjusted (95% CI)[a]
Acetaminophen use during pregnancy				
Never user	458	17 730	1.00	1 [Reference]
1st trimester only	111	3915	1.09	0.97 (0.78-1.19)
2nd trimester only	59	2031	1.12	1.06 (0.81-1.40)
3rd trimester only	150	4350	1.32	1.04 (0.86-1.25)
Both 1st and 2nd trimesters	48	1601	1.16	1.03 (0.76-1.38)
Both 2nd and 3rd trimesters	68	1477	1.75	1.44 (1.12-1.87)
Both 1st and 3rd trimesters	104	2682	1.48	1.23 (0.99-1.53)
All 3 trimesters	162	3938	1.57	1.24 (1.03-1.48)
Duration of acetaminophen use throughout pregnancy, wk				
0	458	17 730	1.00	1 [Reference]
1	160	5689	1.09	0.95 (0.79-1.14)
2-5	199	5550	1.37	1.18 (1.00-1.40)
6-10	65	1453	1.70	1.30 (1.00-1.70)
11-20	50	1374	1.39	1.09 (0.81-1.47)
>20	87	1714	1.92	1.46 (1.16-1.85)
P value for trend[b]				<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal prepregnancy body mass index, parent's behavioral scores in childhood, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy.

[b] Week of acetaminophen use is modeled as a continuous variable in trend test.

Prenatal exposure to acetaminophen also increased the risk for receiving an HKD diagnosis or ADHD medications (**Table 4**). Point estimates for use in either the first, second, or third trimesters were similar and confidence intervals overlapped largely. However, we estimated consistently higher risks for use in 2 or 3 trimesters and a significant trend with increasing number of weeks of use (*P* trend <.001). When women reported having used acetaminophen for 20 or more weeks during pregnancy, the risk for HKD diagnosis in children almost doubled (hazard ratio, 1.84; 95% CI, 1.39-2.45) and the risk for receiving ADHD medication increased by 50% (hazard ratio, 1.53; 95% CI, 1.21-1.94). Results were similar when restricting to mothers who did not report psychiatric illnesses or episodes of fever, inflammation, and infections during pregnancy (eTable 2 in Supplement).

Results were also similar for children with both an HKD diagnosis and ADHD medication use (eTable 3 in Supplement), or when we stratified analyses for number of weeks of acetaminophen use by pregnancy trimester (eTable 4 in Supplement). Effect estimates were slighter higher in girls than boys, but confidence intervals were wide and HKD was much less prevalent in girls (eTable 5 in Supplement). Finally, exclusion of children for whom fathers or other caregivers provided SDQ information, relying on either the Danish National Hospital Registry or Danish Psychiatric Central Registry hospital systems for HKD diagnoses only, adjusting for each type of maternal psychiatric illness or for maternal use of ibuprofen and aspirin during pregnancy, did not change results (eTable 6 in Supplement).

Table 4. Hazard Ratios for HKD Hospital Diagnosis or ADHD Medication Redemption According to Maternal Acetaminophen Use During Pregnancy

Prenatal Exposure and Timing	Hospital-Diagnosed HKD			ADHD Medication		
	No. of Cases (Person-years)	Hazard Ratios		No. of Cases (Person-years)	Hazard Ratios	
		Crude	Adjusted (95% CI)[a]		Crude	Adjusted (95% CI)[a]
Acetaminophen use during pregnancy						
Never used	283 (159 209)	1.00	1 [Reference]	478 (170 264)	1.00	1 [Reference]
Ever used	551 (204 042)	1.52	1.37 (1.19-1.59)	877 (217 945)	1.43	1.29 (1.15-1.44)
1st trimester only	88 (34 887)	1.42	1.35 (1.07-1.72)	120 (37 288)	1.15	1.09 (0.89-1.33)
2nd trimester only	43 (18 714)	1.29	1.26 (0.91-1.73)	70 (20 011)	1.25	1.20 (0.91-1.55)
3rd trimester only	103 (41 418)	1.40	1.22 (0.97-1.53)	182 (44 262)	1.47	1.28 (1.08-1.52)
Both 1st and 2nd trimesters	37 (14 771)	1.41	1.31 (0.93-1.85)	52 (15 789)	1.17	1.09 (0.81-1.45)
Both 2nd and 3rd trimesters	37 (14 009)	1.49	1.30 (0.92-1.84)	77 (14 936)	1.84	1.63 (1.28-2.07)
Both 1st and 3rd trimesters	70 (25 291)	1.56	1.41 (1.08-1.84)	116 (26 938)	1.53	1.39 (1.13-1.71)
All 3 trimesters	120 (36 463)	1.84	1.61 (1.30-2.01)	181 (38 980)	1.65	1.44 (1.21-1.72)
Duration of acetaminophen use throughout pregnancy, wk						
0	283 (159 209)	1.00	1 [Reference]	478 (170 264)	1.00	1 [Reference]
1	128 (51 493)	1.40	1.30 (1.05-1.61)	197 (55 123)	1.27	1.18 (1.00-1.40)
2-5	115 (49 338)	1.32	1.19 (0.95-1.48)	211 (52 807)	1.43	1.29 (1.10-1.52)
6-10	44 (13 026)	1.90	1.65 (1.19-2.28)	68 (13 984)	1.74	1.49 (1.15-1.93)
11-20	43 (12 348)	1.97	1.66 (1.20-2.30)	55 (13 264)	1.49	1.24 (0.94-1.65)
>20	61 (16 341)	2.07	1.84 (1.39-2.45)	88 (17 431)	1.78	1.53 (1.21-1.94)
P value for trend[b]			<.001			<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HKD, hyperkinetic disorder.

[a] Adjusted maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal prepregnancy body mass index, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy.

[b] Week of acetaminophen use is modeled as a continuous variable in trend test.

Discussion

In this large pregnancy cohort with prospective data, children born to mothers who used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD, ADHD medications, or having ADHD-like behaviors during follow-up. The associations were stronger for acetaminophen use in more than 1 trimester, and we found exposure response trends with increasing frequency of use during gestation. Results did not appear to be confounded by maternal inflammation and infection during pregnancy, mother's mental health problems, or any of the other factors we evaluated. If these results reflect causal associations, acetaminophen should no longer be considered a safe drug for use in pregnancy.

Acetaminophen can cross the placenta barrier and recent studies suggested that maternal use of acetaminophen increases the risk for cryptorchidism (undescended testis) in boys due to its endocrine-disrupting properties.[4,29] Maternal hormones, such as sex hormones and thyroid hormones, play critical roles in regulating fetal brain development,[10,30] and it is possible that acetaminophen may interrupt brain development by interfering with maternal hormones or via neurotoxicity such as the induction of oxidative stress that can cause neuronal death.[31,32]

The SDQ is a reliable screening instrument for emotional and behavioral problems in school-aged children and has been used to evaluate determinants of children's ADHD-like behaviors.[33,34] The use of a cutoff point for the total difficulties scores of 17 or greater resulted in few children being classified as exhibiting these behaviors (ie, 3%-4% of our population at age 7 years, which is comparable with a 3.6% prevalence of mental problems previously reported for Danish children ages 5-7 years based on the same SDQ scale and cutoff).[35] We adjusted for self-reported childhood behavioral problems in parents, previously identified as a strong predictor for high parents' rating of their children on the SDQ scale[36]; this adjustment resulted in an approximate 10% attenuation of our effect estimates for acetaminophen use.

A major strength of our study was the availability of multiple end points to assess the outcome addressing different levels of ADHD. In addition to the SDQ, we retrieved information on HKD hospital diagnoses and ADHD medications prescribed to children from nationwide comprehensive medical and pharmaceutical registries. Seventeen percent of children with behavioral problems measured by SDQ also received an HKD diagnosis, and 79% of all children diagnosed as having HKD had redeemed medications at least twice. The treatment and hospital outcomes during follow-up do not require patient's response, and more than 11 years on average resulted in only 813 children (1.3%) lost to follow-up because of death or emigration, thus minimizing selection bias. Children with HKD are treated as outpatients in hospitals or are treated by private practicing child psychiatrists but the ADHD medication prescription data will identify all treated HKD cases

whether hospitalized or not.[37] Depending on diagnostic skills of the treating physician, disease misclassification is an issue when using ADHD medication records, but we would expect it to be nondifferential with respect to maternal acetaminophen use during pregnancy. Furthermore, methylphenidate (Ritalin) is a highly specific indicator for an ADHD diagnosis and it has only 1 additional rare indication—narcolepsy.[38]

Prospective data collection via multiple interviews is another important strength of this study because acetaminophen is mainly sold over the counter and prescription databases do not capture use.[39] Recall bias is not be expected to be differential because mothers were interviewed before the children developed HKD. Similarly, excluding mothers with missing interviews at baseline is also expected to be independent of disease status in the children (ie, the incidence of HKD in this population at the end of follow-up is approximately 1.3% and stable before [1225 in 92 576 children] or after [834 in 64 322 children] the exclusion of the mothers who missed an interview). Flawed recall of drug names, frequency, and timing of use would likely be nondifferential with respect to children's disease status, leading to underestimation of effects. We were unable to assess the influence of dosage or number of pills taken because mothers were unable to recall this information accurately, and about 28% of mothers who reported acetaminophen use were unable to specify the gestational week of use; thus, we assigned trimester of exposures according to the time of interview. Excluding these women when assessing duration of exposures impacted the precision of effect estimation, but results and conclusions did not change.

Maternal infections or immunological factors have previously been linked to childhood ADHD.[26,27] Acetaminophen is often used by mothers to relieve symptoms due to infections, which may induce confounding by indication in our study. We adjusted for several indications that might have triggered maternal acetaminophen use in analyses, and results also did not differ for women who did and did not report infections/inflammations during pregnancy or when controlling for use of common nonsteroidal anti-inflammatory drugs. Nevertheless, the possibility of unmeasured residual confounding by indication for drug use, ADHD-related genetic factors, or coexposures to other medications cannot be dismissed. Nonparticipation in the DNBC has been shown to have small, if any, effects on internal validity, but it may limit the generalizability of our results.[40]

Conclusions

Using prospective data from a well-designed large cohort of pregnant women with a long duration of follow-up and registry-based outcome assessment, we found that prenatal exposures to acetaminophen may increase the risk in children of receiving a hospital diagnosis of HKD or ADHD medication and of exhibiting ADHD-like behaviors, with higher use frequency increasing risk in an exposure-response manner. Because the exposure is frequent, these associations might explain some of the increasing incidence in HKD/ADHD but further studies are needed.

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Study concept and design: Liew, Olsen.
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