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Systematic Reviews and Meta- and Pooled Analyses

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

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Acetaminophen is the analgesic and antipyretic most commonly used during pregnancy. Evidence of neurodisruptive properties is accumulating. Therefore, we sought to evaluate the risk for attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) in the offspring of women exposed to acetaminophen during pregnancy. We searched MEDLINE, Embase, and Cochrane databases for relevant studies up to January 2017. Data were independently extracted and assessed by 2 researchers. Seven eligible retrospective cohorts included 132,738 mother-child pairs, with follow-up periods ranging from 3 to 11 years. The pooled risk ratio for ADHD was 1.34 (95% confidence interval (CI): 1.21, 1.47; $I^2 = 72\%$); for ASD, the risk ratio was 1.19 (95% CI: 1.14, 1.25; $I^2 = 14\%$), and for hyperactivity symptoms, it was 1.24 (95% CI: 1.04, 1.43; $I^2 = 93\%$). In meta-regression analysis, the association between exposure and ADHD increased with the child's age upon follow-up ($\beta = 0.03$, 95% CI: 0.00, 0.07) and with the mean duration of exposure ($\beta = 0.00$, 95% CI: 0.00, 0.01). The available data is of observational nature only. Studies differed widely in exposure and outcome assessment. Acetaminophen use during pregnancy is associated with an increased risk for ADHD, ASD, and hyperactivity symptoms. These findings are concerning; however, results should be interpreted with caution given that the available evidence consists of observational studies and is susceptible to several potential sources of bias.

acetaminophen; attention deficit hyperactivity disorder; autistic spectrum disorder; meta-analysis; offspring; pregnancy; risk

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorder; CI, confidence interval; NOS, Newcastle-Ottawa Scale; RR, risk ratio.

Acetaminophen (also called paracetamol) is the analgesic and antipyretic medication most commonly used during pregnancy (1–4). It is classified as category B for safety in pregnancy (no risks have been found in humans) by the US Food and Drug Administration and is widely considered the drug of choice for fever and pain in pregnant and lactating women (5–7). In recent years, exposure to acetaminophen during pregnancy and early infancy has been associated with potential harmful effects, even with exposure to therapeutic doses. Reported harmful effects have included predisposition to asthma (8, 9), in vitro testicular toxicity and an increased risk for cryptorchidism (10–12), and neurodisrupting properties and an increased risk for neurodevelopmental disorders (13–18).

Several studies have evaluated acetaminophen's potentially neurodisruptive properties. Recent studies reported that acetaminophen has (in rats) direct neurotoxic toxic effects in cortical neurons and (in mice) inhibits fetal testosterone production, areas that are critical for brain development (10, 19). Moreover, acetaminophen crosses the human placental barrier (20), and an association between exposure to acetaminophen during pregnancy and neurodevelopmental impairment in humans has been reported (13, 21, 22).

Neurodevelopmental effects that have been reported include attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD), and impairment of neurological development (16, 23, 24). These studies have reported that even small

doses of acetaminophen may affect neurodevelopment and that this effect is sometimes apparent years after exposure. Such information is cause for significant concern, given the common use of acetaminophen during pregnancy and the sharp increases in incidence of ADHD and ASD (1, 3, 4, 25–27). However, reports on this observed association are inconsistent and include studies that did not detect a significant link between acetaminophen and neurodevelopmental outcomes (14–17, 28, 29).

These reports have significant potential public health implications. Therefore, there is a pressing need to evaluate the available evidence. We performed a systematic review, meta-analysis, and meta-regression analysis to assess the association between exposure to acetaminophen during pregnancy and the risk for neurodevelopmental disorders.

METHODS

Data sources and search strategy

Our systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 framework guidelines and the Meta-Analysis for Observational Studies in Epidemiology (MOOSE) checklist (Web Appendices 1 and 2, available at https://academic.oup.com/aje) (30, 31). The systematic review was conducted using the MEDLINE, Embase, and Cochrane databases up to January 2017 to identify all published randomized controlled trials, cohort studies, and case-control studies that studied the association between acetaminophen exposure during pregnancy and the development of ADHD or ASD in the offspring. We identified relevant studies using the following terms, in different combinations and using appropriate Medical Subject Headings terms: "acetaminophen," "paracetamol," "analgesic," "ADHD," "attention deficit hyperactivity disorder," "hyperactivity," "hyperkinetic," "autism," "ASD," "autistic spectrum disorder," "neurodevelopment," "pregnancy," and "risk." To ensure identification of all studies, we subsequently searched and evaluated published systematic reviews, online resources, conference abstracts, and expert opinion. No language or date restrictions were applied. The review protocol was registered at the PROSPERO registry of systematic reviews in January 2017 (CRD42017055827) (32). Authors of included studies were contacted for further data extraction. No approval from an institutional review board was required.

Selection criteria for studies

We applied the following screening criteria to determine eligibility for inclusion: prospective and historical cohort studies and case-control studies reporting hazard ratios, risk ratios, incidence rate ratio, odds ratio, mean difference, *r* regression coefficient, or β regression coefficient for ADHD or ASD in the offspring of women exposed to acetaminophen during pregnancy. Outcomes reported by the same author in different publications were included only once in each analysis, and subcohorts were not included in the analysis. Relevant studies were required to reach at least a 5-star level in the Newcastle-Ottawa Scale (NOS) (33, 34). We excluded cross-sectional studies, case reports, guidelines, expert opinion, editorials, letters to the author, and comments.

Data extraction

The studies were identified through search by 2 investigators (R.M. and E.G.). Titles and abstracts were independently screened by 2 investigators (R.M. and E.G.). Disagreements were resolved by consensus and/or by referral to a third investigator (I.M.). The full text of the resulting references was then retrieved by 2 investigators (R.M. and E.G.). The primary endpoints of this analysis were ADHD, ASD and emotional problems, and hyperactivity symptoms. Secondary outcome was conduct disorder. Meta-regression was performed to examine whether the strength of association between acetaminophen exposure during pregnancy and the risk for ADHD in later life was modified by potentially relevant covariates.

Risk of bias and quality assessment

Risk of bias and study quality were assessed using the NOS for assessing the quality of nonrandomized studies (33, 34). Summary assessments of risk of bias were derived and an overall star rating of bias was determined. A total star rating of 5 and below was designated "high risk" of bias, a star rating between 6 and 7 "intermediate risk" of bias, and a maximal star rating of 8 and above was considered "low risk" of bias.

Statistical analysis

Meta-analysis. We conducted random effects (inverse variance) meta-analysis to pool the results of primary and secondary outcomes using R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and the "metafor" package, version 1.9-9 (35). Random effects models were used under the assumption that the effect size varies across the studies because of real differences in the exposure effect and sampling variability (36, 37). Forest plots were created using R, version 3.3.2, and the "metafor" package version 1.9-9 (35). The primary outcomes were ADHD diagnosis, ASD diagnosis and emotional problems, and hyperactivity symptoms. Secondary outcome was conduct disorder. Pooled risk ratios and 95% confidence intervals for outcomes were calculated from the number of cases in the exposed and in the nonexposed groups in the included studies, by calculating log risk ratios and standard errors. For studies not reporting the number of cases, we contacted the authors to request the data. When incidence data was still unavailable despite these efforts, we calculated the log risk ratios and standard errors from the reported measures using the "compute.es" package, version 0.2-4, and the "epiR" package, version 0.9-79, in R, version 3.3.2 (38–42). Heterogeneity was assessed using the I^2 statistic. I^2 values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively (43). Statistical significance was defined using a 2-sided α of 0.05, and interpretations of clinical significance emphasized confidence intervals.

Meta-regression. Meta-regression uses trial-level covariates to detect possible sources of heterogeneity and to relate the size of the reported effect (e.g., ADHD diagnosis) to one or more characteristic of the studies in the analysis (44). Meta-regression is weighted in order to assess within-trial exposure effects and between-trial variances. In order to identify covariates that may moderate the association between prenatal acetaminophen exposure and the risk for ADHD, meta-regression

analysis was performed using "metafor" package, version 1.9-9, in R, version 3.3.2 (35). We evaluated whether differences in the populations included in the studies modified the link between acetaminophen and the outcomes evaluated and explained the heterogeneity in the estimated effect size. Covariates included in this analysis included mean age of child at follow-up, maternal fever, maternal age at birth, maternal smoking, maternal socioeconomic status, latitude of country, NOS score, and duration of exposure to acetaminophen. In order to conduct meta-regression, the mean duration of exposure was calculated based on data from the studies as follows: 7 days in the study by Streissguth et al. (29), 4 days in the study by Brandlistuen et al. (28), and 7 days in the study by Liew et al. (14). Each of these factors was included separately in a meta-regression model. The residual between-trial variance was estimated using the restricted maximum likelihood method, and statistical significance was defined using a 2-sided α of 0.05.

Sensitivity analysis. Sensitivity analysis was performed for ADHD or ASD by excluding a study performed 3 decades ago (29), when the public awareness and scales for diagnosis and assessment were different from today's. Also, sensitivity analysis was performed for ADHD or ASD diagnosis, excluding the study by Brandlistuen et al. (28), because exposure to acetaminophen was considerably long (≥28 days) and was with a sibling-control study design.

RESULTS

Trial flow

Our search yielded 121 relevant titles. Initial screening led to the exclusion of 56 records. The remaining 65 titles were reviewed by abstract. Twenty-three records were excluded based on inclusion criteria, and 25 were identified as duplicate records, leaving 17 publications for full review. Upon full review, 10 additional duplicates were excluded, leaving 7 cohort studies eligible for analysis. The selection process is illustrated in Figure 1.

Study characteristics

The studies included in the analysis are listed in Table 1, with additional detail in Web Table 1. Out of 132,738 mother-child

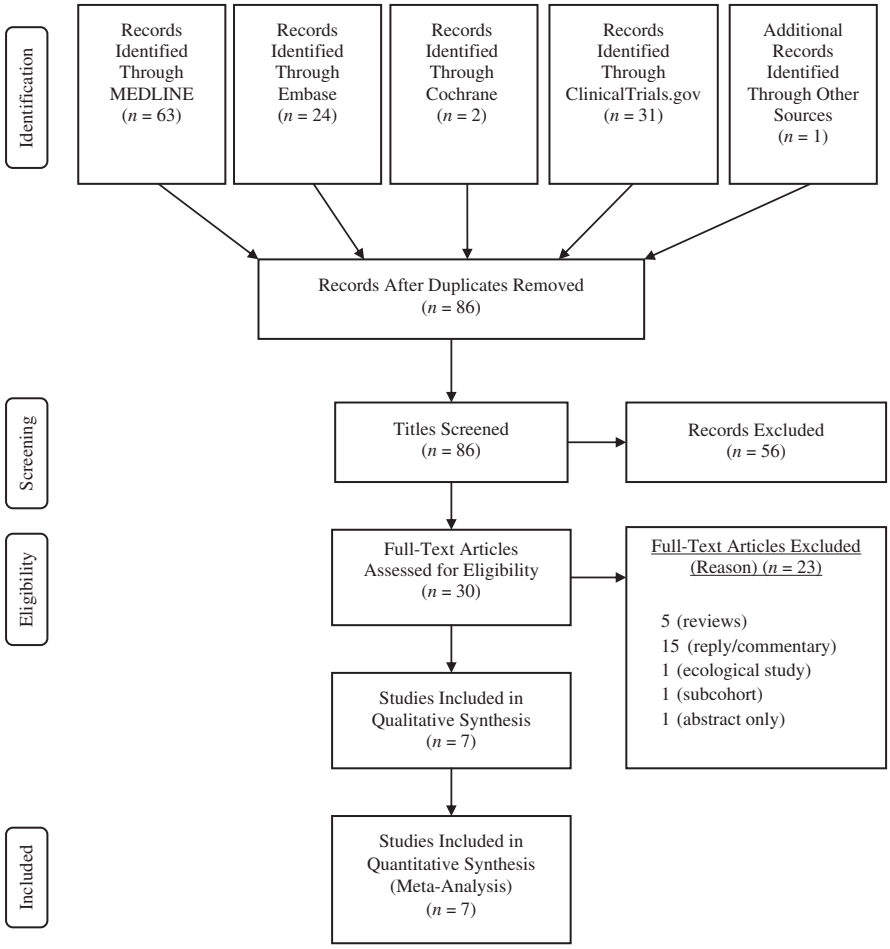

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of studies through the review process for a meta-analysis of studies of prenatal exposure to acetaminophen and risk of attention deficit hyperactivity disorder and autistic spectrum disorder, United States and Europe, 2018.

Table 1. Covariates Adjusted for in Published Studies, Meta-Analysis of Studies of Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder, United States and Europe, 2018

First Author, Year (Reference No.)	Adjustment
Streissguth, 1987 (29)	Maternal education, alcohol, nicotine, caffeine consumption, maternal height, prepregnancy weight, antibiotic use, maternal nutritional status, maternal and paternal education, race, birth order, sex of child, and socioeconomic status.
Brandlistuen, 2013 (28)	Infections, fever, back pain, headache or migraine, concomitant use of other medications, maternal psychological distress, maternal age at delivery, years between pregnancies, parity, smoking, alcohol use, maternal education, and maternal chronic diseases.
Liew, 2014 (14)	Child's birth year, birth weight, and sex; maternal age at child's birth, parity, gestational age at delivery, socioeconomic status, smoking and alcohol drinking during pregnancy, prepregnancy body mass index, mother's self-reported psychiatric illness, parental behavioral scores in childhood, maternal disease (joint/muscle), and maternal fever or infection/inflammation during pregnancy.
Thompson, 2014 (16)	Small size for gestational age, sex, age mother left school, maternal smoking during pregnancy, paternal smoking during pregnancy, marital status at birth, parity, socioeconomic status, maternal prepregnancy body mass index, maternal stress in the last month of pregnancy, alcohol consumption in the first trimester, living with the child's biological father at age 3.5 years and child activity levels at age 3.5 years, high fever during pregnancy, visiting general practitioner for psychological conditions including depression and anxiety, and taking medication during pregnancy for psychological conditions.
Liew, 2016 (18)	Child's sex, birth year, and weight; maternal age at birth, parity, socioeconomic status, maternal smoking and alcohol drinking during pregnancy, maternal prepregnancy body mass index, folic acid intake during pregnancy, mother's psychiatric illnesses, maternal diseases in muscles/joints, fever/infection/inflammation during pregnancy, maternal use of nonsteroidal antiinflammatory drugs during pregnancy, folic acid consumption, and use of antibiotics, sleep medications, and antidepressants.
Avella-Garcia, 2016 (15)	Region, child's sex, age at testing, gestational age at birth, quality of test as rated by the performing psychologist (only for Bayley Scales of Infant Development and McCarthy Scales of Children's Abilities), maternal social class, intelligence quotient, education, whether the mother reported having any chronic illness or fever or urinary tract infection (not necessarily related to acetaminophen use) during pregnancy, and prematurity.
Stergiakouli, 2016 (17)	Maternal age at birth, parity, socioeconomic, status, smoking and alcohol consumption during pregnancy, prepregnancy body mass index, maternal self-reported psychiatric illness, possible indications for acetaminophen use, smoking, alcohol consumption, muscle and joint problems, infections, migraine, or headaches in the previous 3 months.

pairs, 61,601 were exposed to acetaminophen during pregnancy. Six studies reported ADHD diagnosis (14–17, 28, 29), and 5 studies reported ASD diagnosis and emotional problems (15, 17, 18, 28, 29). Mean follow-up time was 6.7 (range, 3–12) years across all studies. Three studies reached a NOS of 7 (14, 17, 18), 3 reached a score of 6 (15, 16, 29), and 1 reached a score of 5 (28). The studies assessed exposure to acetaminophen during pregnancy using one of the following methods: telephone interviews (18, 23), prenatal and postnatal questionnaires (28), self-report of medication and dose at 5 months of gestation (29), prospective interviews (15), questionnaires at 18 and 32 weeks of gestation (17), and interview with the mother soon after birth (16). Range of duration of exposure to acetaminophen varied from 4–28 days to ≥28 days. Gestational week at exposure varied between studies, with some studies reporting results of exposure during the first 32 weeks of pregnancy (15, 17, 29) while others reported results for exposure anytime during pregnancy. The mean duration of exposure to acetaminophen was calculated from 3 studies and ranged from 4 to 7 days (14, 28, 29). Study characteristics, including adjustments made for potential confounding variables, are detailed in Web Table 1 and Table 1.

Meta-analysis

Attention deficit hyperactivity disorder. Six studies evaluated the association between exposure to acetaminophen during pregnancy and ADHD diagnosis. As shown in Figure 2, acetaminophen use during pregnancy was significantly associated with an increased risk for the development of ADHD (risk ratio (RR) = 1.34, 95% confidence interval (CI): 1.21, 1.47; $I^2 = 72\%$).

Sensitivity analysis: ADHD. In a sensitivity analysis performed without Streissguth et al. (29) and Brandlistuen et al. (28), the association remained unchanged (without Streissguth, RR = 1.39, 95% CI: 1.25, 1.53; $I^2 = 49\%$; without Brandlistuen, RR = 1.34, 95% CI: 1.20, 1.49; $I^2 = 41\%$).

ASD and emotional problems. Five studies evaluated the association between exposure to acetaminophen during pregnancy and ASD and emotional problems. As shown in Figure 3, acetaminophen use during pregnancy was significantly associated with an increased risk for ASD and emotional problems (RR = 1.19, 95% CI: 1.14, 1.25; $I^2 = 14\%$).

Sensitivity analysis: ASD and emotional problems. In sensitivity analysis performed without Streissguth et al. (29) and Brandlistuen et al. (28), this association remained unchanged (without Streissguth, RR = 1.19, 95% CI: 1.13, 1.25; $I^2 = 14\%$; without Brandlistuen, RR = 1.19, 95% CI: 1.13, 1.25; $I^2 = 13\%$).

Hyperactivity symptoms

Five studies evaluated the association between exposure to acetaminophen during pregnancy and hyperactivity symptoms. As shown in Figure 4, acetaminophen use during pregnancy was significantly associated with an increased risk for the development of hyperactivity symptoms (RR = 1.24, 95% CI: 1.04, 1.43; $I^2 = 93\%$).

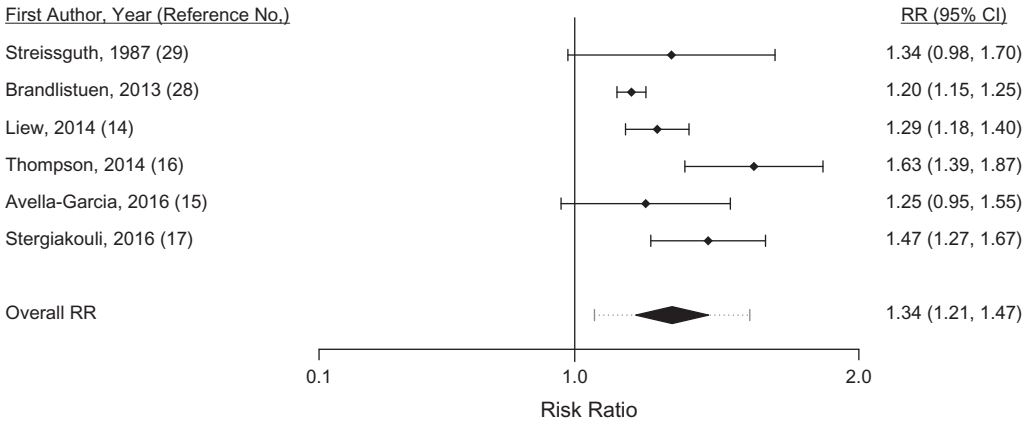

Figure 2. Risk ratios (RRs) and confidence intervals (CIs) from a random effects meta-analysis of 6 cohort studies on the risk for attention deficit hyperactivity disorder after exposure to acetaminophen during pregnancy, United States and Europe, 2018. Test for heterogeneity: $I^2 = 72\%$; $P = 0.03$. For log RRs, standard errors, and number exposed, refer to Web Table 2.

Conduct disorder

Four studies evaluated the association between exposure to acetaminophen during pregnancy and conduct disorder. As shown in Figure 5, acetaminophen use during pregnancy was significantly associated with an increased risk for the development of conduct disorder (RR = 1.23, 95% CI: 1.04, 1.42; $I^2 = 93\%$).

Meta-regression

Moderator analysis was conducted to explore sources of heterogeneity in the association between exposure to acetaminophen during pregnancy and ADHD diagnosis. In these analyses, several covariates were evaluated as potentially modifying factors for the association between acetaminophen and the development of ADHD via a series of exploratory meta-regression models. The results of these models are detailed in Table 2. Notably, these models found that children's age at follow-up significantly modified the association between exposure to acetaminophen and the development of ADHD, such that the association was greater in studies with older age at follow-up (β = 0.03, 95% CI: 0.00, 0.07), as shown in Figure 6. Likewise, duration of exposure to acetaminophen also significantly modified the association between exposure to acetaminophen and the development of ADHD, such that the association was greater in studies with longer duration of exposure (β = 0.00, 95% CI: 0.00, 0.01). In contrast, maternal age significantly moderated the association such that the association was decreased in studies with a younger maternal age (β = −0.17, 95% CI: −0.28, −0.60). Maternal fever, maternal smoking, high socioeconomic status, NOS score, and country latitude were not found to be significant moderators (Table 2).

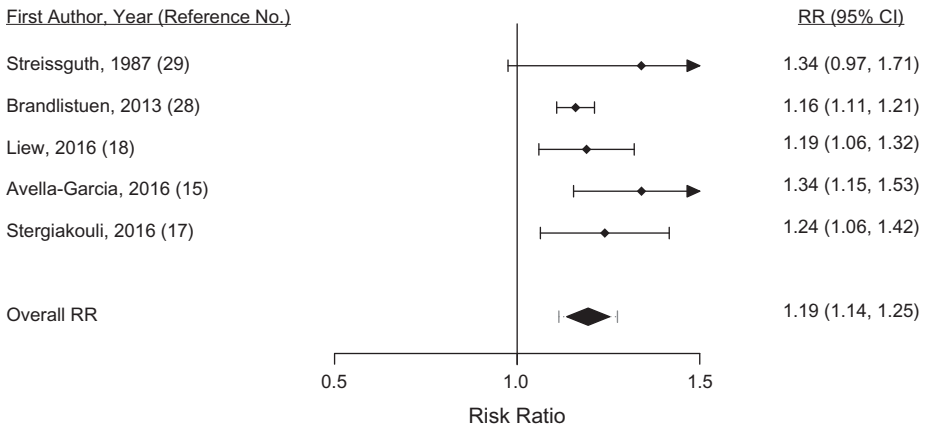

Figure 3. Risk ratios (RRs) and confidence intervals (CIs) from a random effects meta-analysis of 5 cohort studies on the risk for autistic spectrum disorder after exposure to acetaminophen during pregnancy, United States and Europe, 2018. Test for heterogeneity: $I^2 = 14\%$; $P = 0.31$. For log RRs, standard errors, and number exposed, refer to Web Table 2.

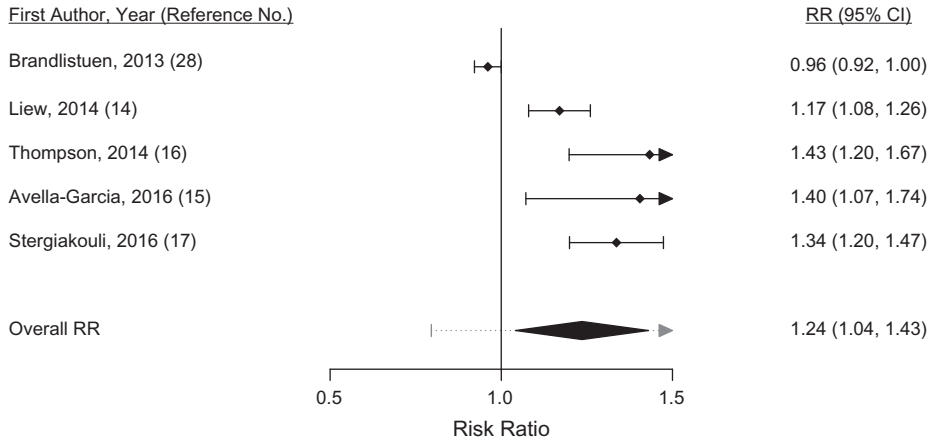

Figure 4. Risk ratios (RRs) and confidence intervals (CIs) from a random effects meta-analysis of 5 cohort studies on the risk for hyperactivity symptoms after exposure to acetaminophen during pregnancy, United States and Europe, 2018. Test for heterogeneity: $I^2 = 93\%$; $P < 0.0001$. For log RRs, standard errors, and number exposed, refer to Web Table 2.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis examining the association between acetaminophen exposure in pregnancy and offspring's neurodevelopmental outcomes. Although widely considered the analgesic and antipyretic of choice in pregnancy (2, 3, 45), our analysis of the available evidence indicates that acetaminophen exposure during pregnancy is associated with a 20%–30% increased risk for neurodevelopmental disorders. However, results should be interpreted with caution, because there was evidence of heterogeneity between study estimates of the outcomes. In addition, given that all of the included studies were of observational design, the results are susceptible to potential confounding factors, most notably confounding by indication, as well as potential misclassification of exposure or of outcomes.

It has been suggested that the observed neurodevelopmental disorders following exposure to acetaminophen in utero may be the result of acetaminophen's neurodisruptive mechanisms. Acetaminophen may interfere with endogenous hormones and signaling pathways in the developing fetus (11, 46). It also has been suggested that acetaminophen increases the risk for ASD by causing neuronal oxidative stress (13, 22). Investigators in previous studies have reported a significant association between exposure to acetaminophen during pregnancy and an increased risk for neurodevelopmental disorders and symptoms (15–18, 23, 28). Our analysis found a 30% increased risk of ADHD and 20% increased risk of ASD. It is important to keep in mind that in our analysis, 3 of 7 studies (18, 23, 28) were heavily weighted due to their large sample sizes. Streissguth et al. (29) did not find any association between exposure to acetaminophen and neurodevelopmental disorders. This

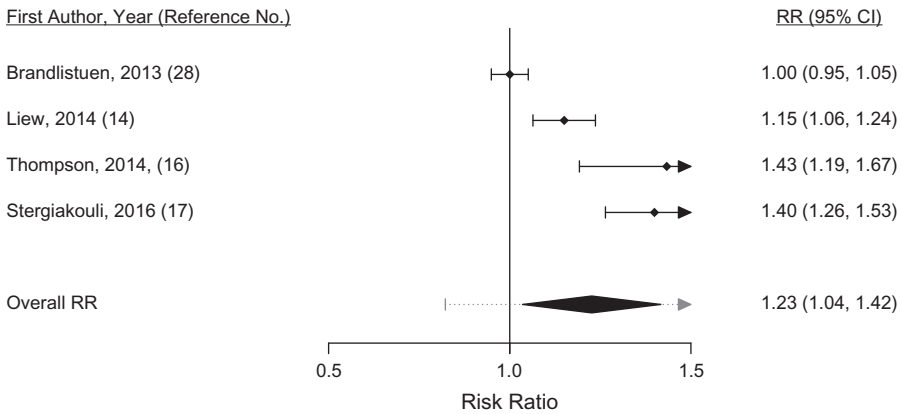

Figure 5. Risk ratios (RRs) and confidence intervals (CIs) from a random effects meta-analysis of 4 cohort studies on the risk for conduct disorder after exposure to acetaminophen during pregnancy, United States and Europe, 2018. Test for heterogeneity: $I^2 = 93\%$; $P < 0.0001$. For log RRs, standard errors, and number exposed, refer to Web Table 2.

Table 2. Meta-Regression Models for Attention Deficit Hyperactivity Disorder Outcome, Meta-Analysis of Studies of Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder, United States and Europe, 2018

Moderator	Moderator Range Value in Cohort	No. of Studies	Interaction Coefficient, β[a]	95% CI[a]	% Heterogeneity Explained (R^2)
Age of follow-up (mean)	3–13.5	6	0.03	0.00, 0.07	49
Maternal fever, %	4.5–28	3	0.00	−0.03, 0.03	0.01
Maternal age, years	29–31	4	−0.17	−0.28, −0.60	99
Maternal smoking, %	7.5–31	5	0.00	−0.01, 0.01	0.01
High/low SES	2.5–13	3	0.01	−0.05, 0.06	0.001
Country latitude, degrees North	40–60	6	0.00	−0.02, 0.01	0.001
Mean duration of exposure to acetaminophen, days	4–28	3	0.00	0.00, 0.01	99
Quality (NOS score)	5–7	6	0.09	−0.09, 0.28	0.001

Abbreviations: CI, confidence interval; NOS, Newcastle-Ottawa Scale; SES, socioeconomic status.
[a] Very small values rounded to 0.00.

may be due to the small size of the cohort and due to limitations inherent in the diagnostic tools available at the time.

The link identified in the present analysis may have also resulted from methodological limitations inherent in the design of the included studies. Assessment of exposure to acetaminophen was carried out by personal interviews (23, 28, 29). Therefore, the results may suffer from recall and interview bias (47, 48). Exposure to acetaminophen as a single ingredient has not been reported to increase risk for birth defects in any trimester. Acetaminophen's safety during pregnancy has also been assessed in combination with other medications. In some studies that assessed the prenatal safety of common cold medications, which included acetaminophen as one of the ingredients, investigators reported an increased risk for gastroschisis and small intestinal atresia (49). Li et al. (50) reported an association between analgesic and antipyretic exposure during pregnancy and an increased risk for neural tube defect (odds ratio = 4.89, 95% CI: 0.92, 25.07). The observed risks for ADHD and ASD may be due to additional environmental or medication exposure during pregnancy and after labor or to their combination rather than acetaminophen exposure alone. Importantly, confounding by indication may distort the observed association when assessing associations between prenatal exposures and future illnesses in the offspring. Women with comorbidities and fever likely use acetaminophen more frequently than healthy pregnant women. Also, individuals using one medication are more likely to use other medications, for indications other than fever and pain. These concomitant exposures may themselves increase the risk for neurodevelopmental adverse effects and contribute to confounding by indication (51, 52). It has been reported that maternal infection and fever of different sources are associated with pregnancy adverse outcomes. In a meta-analysis by Moretti et al. (53), maternal hyperthermia was associated with an increased risk neural tube defects. Also, studies suggest a link between maternal hyperthermia and negative behavioral outcomes, including ASD, in the offspring (53, 54). Negative associations have also been found between maternal infections and pregnancy outcomes (55). Therefore, any observed association could, in fact, be the result of maternal characteristics and due to confounding by indication (54). It should be noted that the included studies attempted to address this potential limitation by controlling for a wide range of potentially confounding factors. Moreover, Brandlistuen et al. (28) reported an increased risk for neurodevelopmental disorders despite using a sibling-matched analysis design, which would be expected to minimize the effect of maternal characteristics on the observed association.

While the studies included in our analysis all tended toward an increased risk for neurodevelopmental outcomes, there was evidence of significant heterogeneity. This heterogeneity can likely be explained by differences in design, setting, and populations in the studies included. Studies assessed and extracted ADHD and ASD diagnosis information using different tools

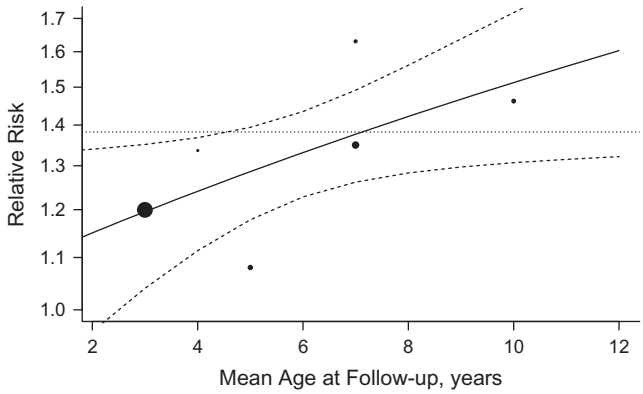

Figure 6. Relative risk for attention deficit hyperactivity disorder according to mean age at follow-up (years), from a meta-analysis of studies of prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder, United States and Europe, 2018. Area of each circle is proportional to the weight of each study according to sample size. Dotted horizontal line represents pooled risk ratio of the meta-analysis. Dotted curved lines represent 95% confidence intervals.

and scales (Web Table 1). Methods used included hospital admission registries (18, 23), assessment by trained psychologists, parent questionnaire and teacher assessment questionnaire (15), parent questionnaire only (17, 28), parent and child questionnaires (16), and assessment by trained psychometrists (29). There is fierce debate regarding the validity of questionnaires, without a certified specialist examination, to record the diagnoses of ADHD or ASD. The variability in outcome assessment and data-extraction method in the studies included in our meta-analysis likely contributed to the high heterogeneity of the observed associations measured in our analysis. The use of independent, uniform, and systematic outcome assessment by certified specialists may reduce outcome measurement error. In addition, we also conducted meta-regression analysis, both to identify potential sources of the observed heterogeneity and to try to obtain insight into the effect of acetaminophen exposure by evaluating covariates that could be observed as modifying the effect of acetaminophen on ADHD diagnosis. The prenatal and perinatal environments play an important role in the development of neurodevelopmental disorders. The timing of exposure to these environmental risks is crucial. Established prenatal risk factors for ADHD include smoking, alcohol consumption, medications, stress, and poor maternal diet (56–60).

Our meta-regression showed that the association between acetaminophen exposure and ADHD was moderated by age of follow-up, duration of exposure, and maternal age. As diagnosis frequency and precision increase with the child's age, it is logical to observe a weaker association in studies evaluating younger children. The increased rate of misclassification and the reduced frequency of the outcome in younger children would be expected to weaken the strength of any association and reduce the power to detect one. Of note, the modifying effect of duration of exposure on the association between acetaminophen and neurodevelopmental outcomes can be viewed as suggesting a dose-response effect. However, it is important to note that this effect is based on study-level data from 3 studies only and is therefore susceptible to ecological fallacy (i.e., it is possible no link between duration of exposure and outcome exists on the individual level). There was a wide range of durations of exposure to acetaminophen in the included studies. The total durations of exposure ranged from 4–28 days to ≥28 days. Furthermore, gestational week at exposure ranged from the first 20 weeks of pregnancy to any point during pregnancy. This variability may contribute to the high heterogeneity of the observed effect. In the most recent study by Ystrom et al. (61), the use of acetaminophen during pregnancy for less than 8 days was not associated with an increased risk for ADHD, and exposure for 22–28 days was associated with a significant increased risk for ADHD (hazard ratio = 6.15, 95% CI: 1.71, 22.05), which is consistent with our results. In addition, studies with a longer duration of exposure to acetaminophen may imply greater maternal comorbidities in the acetaminophen group, given that women using acetaminophen for longer periods during pregnancy likely suffer from more serious comorbid conditions, which may themselves affect the risk for neurodevelopmental disorders in the offspring (62, 63). As the age of the mother decreased, the observed effect size decreased; this observation may be attributed to the fact that advanced maternal age is associated with an increased risk for neurodevelopmental disorders (64), and it is therefore possible that due to this higher baseline risk, pregnancies in older mothers are also more susceptible to detrimental effects of exposure to disruptive factors such as acetaminophen.

Maternal and paternal neurobehavioral disorders play a pivotal role in the pathophysiology and future risk for ADHD or ASD in the offspring (65). Five of the cohort studies included in the analysis (Table 1) adjusted the analysis for maternal psychological/psychiatric illnesses (14, 16–18, 28), maternal intelligence quotient (15), and parental behavioral scores during childhood (14). Although, we cannot know the exact contribution of parental genetics to the observed effects, and despite the possibility of recall bias, we still observed significant increased associations with ADHD and ASD.

Strengths and limitations

Our study has several notable strengths as well as important limitations. To our knowledge, this study is the first systematic review of all published studies evaluating the association between acetaminophen in pregnancy and neurodevelopmental outcomes of the offspring. We conducted a thorough and extensive search of all available evidence and used structured methods for the collection, evaluation, and reporting of our findings. We used random effects methods to pool results (36, 37), because studies were heterogeneous in nature. Sensitivity analysis was performed to examine the strength of association, which remained unchanged, by excluding studies with a long duration of exposure and exceptional study design. We also investigated the contribution of relevant covariates to the observed heterogeneity by conducting a meta-regression.

While we believe the results of this study are cause for concern, it is important to view them with caution, given that there are several limitations to consider. Only a limited number of studies were available for analysis, and all of the studies included were of observational design. Most of the studies had some risk of bias, and the results indicated significant heterogeneity. We must bear in mind that although ADHD is one of the most common disorders in childhood, the diagnostic tools available are based mainly on subjective clinical assessment (66). Parent-based questionnaires for determining outcomes may have introduced bias and can add difficulty in interpreting the clinical significance of the results. In addition, ASD diagnosis is known to be strongly related to advancing paternal age (67); however, none of the studies included paternal age as a covariate. Studies assessing outcomes during school years (16–18, 23) may have reached a more accurate diagnosis and been more likely to reject the null hypothesis (68). Due to the limited number of studies, we were also unable to evaluate the risk of publication bias. Great caution is advised when considering whether the link we found between acetaminophen exposure and neurodevelopmental outcomes is causal, because the available studies were susceptible to confounding and bias (i.e., confounding by indication, recall bias, and exposure or outcome misclassification).

We were unable to pool results for the risk for ADHD or ASD according to exposure to acetaminophen as a single ingredient or a combined ingredient of a medical product, or to conduct a subgroup analysis for outcomes according to short- and long-term exposure to acetaminophen. Exposure assessment and validation

is limited because acetaminophen is a nonprescription drug sold over the counter and is also found in many combined medical products. Last, care should also be exercised in the interpretation of the modifying effects of factors we evaluated in our meta-regression, because the factors were evaluated based on study-level data, such that any observed effect (or lack thereof) may not be true on the individual level due to the ecological fallacy (44, 69).

Abstaining from pain and fever treatment during pregnancy may have harmful effects on the developing fetus (70), and acetaminophen is still regarded as the drug of choice during pregnancy (2, 71). However, evidence is accumulating regarding neurodisruptive properties of acetaminophen. Our study provides pivotal information regarding the association between exposure to acetaminophen during pregnancy and the risk for neurodevelopmental disorders in childhood.

Implications for policy and practice

Our findings, together with additional recent alarming evidence on the teratogenicity of acetaminophen, warrant further investigation. Research resources should be directed toward developing validated and robust drug-exposure assessment tools and neurodevelopmental disorders outcomes assessment. As clinicians, we are obliged to provide pregnant women with the most up-to-date information regarding medication safety during pregnancy, especially for a widely and commonly used medication such as acetaminophen. Our results indicate a small increase in the risks for ADHD and ASD in the offspring of women exposed to acetaminophen during pregnancy. However, due to the high heterogeneity in the observed association, the potential for exposure and outcome misclassification, and the possibility of residual confounding (including environmental factors, maternal characteristics, and genetic factors), further investigation evaluating this observed link is warranted.

Considering the significant limitations inherent in the available research, we believe care should be taken to avoid overstating the significance of the results of our analysis, because this could promote unnecessary anxiety among pregnant women. Although a causal link between exposure to acetaminophen and neurodevelopmental disorders cannot be established, careful inspection of current health policies and patient leaflets is also needed, due to the unsupervised and wide use of acetaminophen as a safe nonprescription medication.

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