Published in final edited form as:

JAMA Pediatr. 2016 October 01; 170(10): 964–970. doi:10.1001/jamapediatrics.2016.1775.

Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding

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Abstract

Importance—Acetaminophen (paracetamol) is used by a large proportion of pregnant women. Research suggests that acetaminophen use in pregnancy is associated with abnormal fetal neurodevelopment. However, it is possible that this association might be confounded by unmeasured behavioral factors linked to acetaminophen use.

Objective—To examine associations between offspring behavioral problems and (1) maternal prenatal acetaminophen use, (2) maternal postnatal acetaminophen use, and (3) partner's acetaminophen use.

Design, Setting, and Participants—From February 2015 to March 2016, we collected and analyzed data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a

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Critical revision of the manuscript for important intellectual content: Thapar, Davey Smith.

Statistical analysis: Stergiakouli.

Administrative, technical, or material support: Stergiakouli, Davey Smith.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

prospective birth cohort. We studied 7796 mothers enrolled in ALSPAC between 1991 and 1992 along with their children and partners.

Exposures—Acetaminophen use was assessed by questionnaire completion at 18 and 32 weeks of pregnancy and when the child was 61 months old.

Main Outcomes and Measures—Maternal reports of behavioral problems using the Strengths and Difficulties Questionnaire (SDQ) when the children were 7 years old. We estimated risk ratios for behavioral problems in children after prenatal, postnatal, and partner's exposure to acetaminophen and mutually adjusted each association.

Results—Maternal prenatal acetaminophen use at 18 (n = 4415; 53%) and 32 weeks of pregnancy (n = 3381; 42%) was associated with higher odds of having conduct problems (risk ratio [RR], 1.42; 95% CI, 1.25-1.62) and hyperactivity symptoms (RR, 1.31; 95% CI, 1.16-1.49), while maternal acetaminophen use at 32 weeks was also associated with higher odds of having emotional symptoms (RR, 1.29; 95% CI, 1.09-1.53) and total difficulties (RR, 1.46; 95% CI, 1.21-1.77). This was not the case for maternal postnatal (n = 6916; 89%) or partner's (n = 3454; 84%) acetaminophen use. We found the associations between maternal prenatal acetaminophen use and all the SDQ domains unchanged even after adjusting for maternal postnatal or partner's acetaminophen use.

Conclusions and Relevance—Children exposed to acetaminophen prenatally are at increased risk of multiple behavioral difficulties, and the associations do not appear to be explained by unmeasured behavioral or social factors linked to acetaminophen use insofar as they are not observed for postnatal or partner's acetaminophen use. Although these results could have implications for public health advice, further studies are required to replicate the findings and to understand mechanisms.

Acetaminophen (paracetamol) is one of the most common pain-relieving medications and is considered generally safe for use during all stages of pregnancy, making it the first-choice pain and fever medication for pregnant women. Given the large number of pregnant women using the drug (>50% in the United States¹; 50%-60% in the European Union²), even a small increase in risk of adverse outcomes in the offspring can have important implications for public health.

Animal studies suggest that acetaminophen use in pregnancy can have important implications for neurodevelopment; acetaminophen administration during neonatal brain development in mice affected cognitive function and disrupted levels of BDNF (brain-derived neurotrophic factor) in the brain.³ The mechanism might involve disrupted endocrine function, which is important for neurodevelopment.⁴ For example, acetaminophen use in pregnancy has been found to disrupt endocrine testicular function in male embryos, and long-term acetaminophen use has been linked to an increase in risk of cryptorchidism.⁵

Acetaminophen use during pregnancy is associated with a higher risk of hyperkinetic disorders and attention-deficit hyperactivity disorder (ADHD)-like behaviors. This has been observed in a very large sample of children and their mothers from the Danish National Birth Cohort.⁶ Similar results were also reported in a cohort of children and their mothers from New Zealand.⁷ In addition, a sibling-controlled cohort study that partially controlled

for familial confounding found that long-term acetaminophen use during pregnancy was associated with adverse developmental outcomes at age 3 years.⁸

Although a large number of potential confounders were accounted for in the previous studies, there is still the possibility of unrecognized confounding. Maternal behaviors during pregnancy, including acetaminophen use, can be associated with multiple maternal factors, including socioeconomic ones, as well as disease and health outcomes such as behavioral difficulties in the offspring.⁹ One mechanism behind the association between maternally influenced prenatal factors and offspring outcome is genetic confounding, whereby a risk factor and a disease have shared genetic influences. For example, genetic confounding has been shown to be present in the association between smoking during pregnancy, another prenatal risk factor, and ADHD¹⁰ and behavioral problems.¹¹

To best inform public health advice, study designs must account for unmeasured and familial confounding when evaluating acetaminophen use during pregnancy.¹² Although these designs have been used to control for confounding in studies of prenatal acetaminophen exposure and asthma,¹³ they have not been used to investigate the association of prenatal acetaminophen use with offspring behavioral difficulties. The design of these studies includes comparisons between maternal prenatal exposures and maternal postnatal exposures as well as partner's exposures during pregnancy. If an intrauterine effect of acetaminophen exposure on offspring behavior is present, one would expect association with maternal prenatal exposure but not with maternal postnatal exposure or partner's exposure because only the maternal prenatal exposure has direct biological effect on the fetus.¹⁴ For example, effects of maternal smoking in pregnancy on birth weight¹⁴ but not offspring fat mass¹⁵ were stronger than that of partner's smoking in the Avon Longitudinal Study of Parents and Children (ALSPAC),^{16,17} in line with other evidence suggesting a causal intrauterine mechanism.

In this study, we assessed associations between behavioral problems in offspring at age 7 years in the ALSPAC population cohort and (1) maternal prenatal acetaminophen use, (2) maternal postnatal acetaminophen use, (3) partner's acetaminophen use.

Methods

Study Population

The ALSPAC is a prospective birth cohort study that recruited pregnant women from Bristol, England with expected delivery dates between April 1991 and December 1992. A total of 14 541 pregnant women were initially enrolled with 14 062 children born. Detailed information on health and development of children and their parents were collected from regular clinic visits and completion of questionnaires. A detailed description of the cohort has been published previously.^{16,17} The study website contains details of all the data available through a fully searchable data dictionary: <http://www.bristol.ac.uk/alspac/researchers/access/>. Written informed consent was obtained from all participants, and ethical approval was obtained from the ALSPAC law and ethics committee and the local ethics committees.

Acetaminophen Use by the Mother and Her Partner

Mothers were asked at 18 and 32 weeks of pregnancy if they had used acetaminophen in the previous 3 months. The same question was asked again of the mother and her partner when the child was 61 months old. They were also asked if they had muscle and joint problems, infections (including cold or flu, urinary, or other infections), migraine, or headaches at the same periods. However, they were not asked detailed questions on dose or duration or indications of use.

Outcomes

We assessed children's behavioral problems using the Strengths and Difficulties Questionnaire (SDQ),¹⁸ a child behavior screening questionnaire (age range, 4-16 years) that includes questions in 5 domains: emotional symptoms, conduct problems, hyperactivity symptoms, peer relationship problems, and prosocial behaviors scored from 0 to 10 each.¹⁸ A total difficulties score (range, 0-40) can be obtained by summing the scores from the following 4 subscales: emotional symptoms, conduct problems, hyperactivity symptoms, and peer relationship problems (not including prosocial behavior, for which a higher score indicates less behavioral problems) (<http://www.sdqinfo.com>). Mothers' reports on their children's behavioral problems were obtained when the children were 7 years old. Cutoffs were used to dichotomize each of the 5 SDQ subscales as well as the total difficulties score as in previous studies.¹⁸

Confounding Factors

We repeated all our analyses including the following potential confounding factors: maternal age at birth, parity, socioeconomic status, smoking and alcohol consumption during pregnancy, prepregnancy body mass index (BMI), maternal self-reported psychiatric illness, and possible indications for acetaminophen use. Mothers were asked to report whether they smoked or consumed alcohol during pregnancy by completing a questionnaire at 32 weeks of pregnancy. At the same time, they were also asked if they had muscle and joint problems, infections (including cold or flu, urinary, or other infections), migraine, or headaches in the previous 3 months. We decided to include these factors in the model because they are the most common indications for acetaminophen use.

Genetic Confounders

Composite scores of molecular genetic risk factors for ADHD (polygenic risk scores) were calculated for 8340 ALSPAC mothers using available genotype data (details on the quality control procedure have been published previously¹⁹) according to the method described by the International Schizophrenia Consortium.²⁰ Polygenic risk scores were computed using "risk alleles" based on the results of an independent case-control United Kingdom/Ireland ADHD genome-wide association study (GWAS) (discovery sample). Quality control procedures, ascertainment of these samples, and GWAS results have been described in detail previously.²¹ In line with previous studies,^{22,23} a threshold of $P < .50$ was used to select alleles more common in cases than controls from the discovery sample (single-nucleotide polymorphisms [SNPs] in relative linkage equilibrium in the discovery sample GWAS were selected first). These identified SNPs were used to calculate a polygenic score for each

individual in ALSPAC, corresponding to the mean number of score alleles (weighted by the logarithm of the odds ratio) across the set of SNPs. Analysis was performed using PLINK. 24 Logistic regression was used to test if maternal ADHD polygenic risk scores were associated with maternal prenatal and postnatal acetaminophen use. Paternal genotype data were unavailable.

Statistical Analyses

We used generalized linear models with a log-link function and a Poisson distribution to estimate risk ratios (RRs) and 95% CIs for prenatal and postnatal acetaminophen use and the dichotomized SDQ domains. As a sensitivity analysis, SDQ domains were also analyzed as continuous outcomes after logarithmic transformation.

To address potential confounding by unmeasured genetic and nongenetic confounders, we compared maternal prenatal acetaminophen use with maternal postnatal acetaminophen use as exposures for each outcome. Then we mutually adjusted each association and compared the effect of the adjustment. The same analysis with mutual adjustment was carried out to compare maternal prenatal acetaminophen use with partner's postnatal acetaminophen use as exposures.

All analyses were repeated with the inclusion of potential confounding factors. All information on confounding factors was obtained by questionnaire completion from the mother and her partner.

Results

Acetaminophen use was reported by 4415 mothers (53%) at 18 weeks of pregnancy and by 3381 mothers (42%) at 32 weeks. A total of 6916 mothers (89%) and 3 454 partners (84%) used acetaminophen postnatally, and 5% of children had behavioral problems, as indicated by the total difficulties score of the SDQ. (See eTable 1 in the Supplement for details on the number of children with behavioral problems.) The mean (SD) age of children at completion of the SDQ questionnaire by the parents was 79.0 (1.3) months. Other characteristics of mothers reporting acetaminophen use in ALSPAC and their children are listed in Table 1. All of these characteristics were included in the adjusted analyses reported in eTables 2 through 5 in the Supplement.

Maternal prenatal acetaminophen use at 18 weeks of pregnancy was associated with higher odds of offspring conduct problems (RR, 1.20; 95% CI, 1.06-1.37) and hyperactivity symptoms (RR, 1.23; 95% CI, 1.08-1.39), while maternal acetaminophen use at 32 weeks of pregnancy was associated with higher odds of offspring having emotional symptoms (RR, 1.29; 95% CI, 1.09-1.53), conduct problems (RR, 1.42; 95% CI, 1.25-1.62), hyperactivity symptoms (RR, 1.31; 95% CI, 1.16-1.49), and total difficulties (RR, 1.46; 95% CI, 1.21-1.77), as assessed by the SDQ (Table 2). This was not the case for maternal postnatal acetaminophen use or partner's acetaminophen use, which were not associated with any of the SDQ domains (Table 3). Inclusion of covariates did not change the RRs, although CIs were wider owing to the reduced sample size when covariates were included (eTables 2 and 3 in the Supplement).

After mutual adjustment of maternal prenatal and maternal postnatal acetaminophen use, the associations between maternal prenatal acetaminophen use and all the SDQ domains remained unchanged, while the associations for maternal postnatal acetaminophen use were attenuated (Table 4).

When adjusting maternal prenatal acetaminophen use for partner's acetaminophen use, we found that the effect was unchanged despite the smaller sample size in this analysis (Table 5).

All analyses were repeated with potential confounders including genetic ones, and results are summarized in eTables 2 through 5 in the Supplement. In linear regression models, results were similar (eTables 6 through 9 in the Supplement).

There was little evidence of association between maternal ADHD polygenic risk scores and maternal prenatal acetaminophen use at 18 weeks of pregnancy (odds ratio [OR] per SD of polygenic risk score, 0.99; 95% CI, 0.95-1.05; $P = .90$), 32 weeks of pregnancy (OR per SD of polygenic risk score, 0.98; 95% CI, 0.94-1.03; $P = .48$), or with postnatal acetaminophen use (OR per SD of polygenic risk score, 0.92; 95% CI, 0.85-1.00; $P = .06$).

Discussion

In this study, we have demonstrated that children exposed prenatally to acetaminophen in the second and third trimesters are at increased risk of multiple behavioral difficulties, including hyperactivity and conduct problems. Prenatal acetaminophen exposure at 32 weeks' gestation was also associated with emotional problems. The associations did not change when maternal postnatal or partner's acetaminophen use were included in the model. Similar to the Danish National Registry observations,⁶ the associations were also not confounded by maternal migraine, infections, and other measured factors. In addition, an index of ADHD genetic risk in the mothers was not associated with acetaminophen use during pregnancy. These findings, when coupled with those from the previous discordant sibling design study,⁸ suggest that the association between prenatal acetaminophen exposure and childhood behavioral problems is not explained by unmeasured familial factors linked to both acetaminophen use and childhood behavioral problems and that the findings are consistent with an intrauterine effect. Our results could have important implications for public health advice, which currently considers acetaminophen safe to use during pregnancy.

Our results also suggest that the timing of acetaminophen use might be important. More specifically, we found stronger association between maternal acetaminophen use and multiple behavioral and emotional problem domains during the third trimester than during the second trimester, in agreement with previous studies that have included multiple measurement times during pregnancy.⁸ Given that there is active brain development and growth during the third trimester, this finding could indicate that there are developmental periods when the brain is more sensitive to acetaminophen exposure.

The mechanism through which adverse effects of acetaminophen on fetal neurodevelopment might be mediated are not well understood.¹² One mechanism might involve the endocrine-disrupting properties of acetaminophen. The disruption of the maternal hormonal

environment could affect fetal brain development. It is well known that thyroid hormones, for example, are important for fetal brain development.⁴ It is also known that acetaminophen crosses the placenta,²⁵ and animal studies have shown that the fetus is capable of producing the toxic metabolites of acetaminophen.²⁶ This highlights the need for further experimental research to identify potential causal mechanisms. Another possibility is that acetaminophen disrupts brain development through oxidative stress. Studies in humans suggest that long-term use of acetaminophen reduces serum antioxidants and disrupts oxidant-antioxidant balance.²⁷ Increased amounts of oxidants in the fetus can then lead to neuronal death at critical points during development.²⁸

One strength of this study is the availability of prospective information on acetaminophen use during the second and third trimesters of pregnancy and postnatally by the mother and by her partner. This enabled us to use a nested quasi-experimental design in which we assessed the effect of acetaminophen use during pregnancy on offspring behavioral difficulties and compare it with maternal postnatal acetaminophen use and partner's acetaminophen use. Postnatal and partner use are likely associated with stable social and familial factors, as is prenatal maternal use, but cannot have a biological effect on fetal brain development. This approach has been used previously in ALSPAC to suggest that the association between prenatal acetaminophen use and asthma in the offspring is not confounded by unmeasured behavioral factors.¹³ Our study also had the advantage of assessing the effect of acetaminophen at 2 different times in fetal development.

We were also able to adjust the associations for a large number of potential confounders as well as ADHD genetic risk scores in the mothers. The same genetic factors might influence offspring behavioral problems as well as risky maternal behaviors during pregnancy that would result in genetic confounding. This has been shown to contribute to the association between maternal smoking during pregnancy and offspring ADHD.¹⁰ However, ADHD polygenic risk scores were not associated with maternal acetaminophen use during pregnancy in ALSPAC. Another advantage of our study was the use of the SDQ, which is a validated and reliable screening instrument for behavioral problems in children.²⁹ Finally, recall bias for acetaminophen use should not be present in this study because the questionnaire on acetaminophen use was administered several years before the SDQ.

A limitation of this study is that there was no maternally reported information on the indications for acetaminophen use. However, we were able to adjust for the most common reasons for use, which include headaches, musculoskeletal problems, and infections during pregnancy. While there is little evidence of a possible correlation between these health conditions during pregnancy and behavioral problems in the offspring, we cannot rule out the possibility of residual confounding or fetal effects on maternal health during pregnancy. We also did not have information on dosage or duration of acetaminophen use to test whether long-term use or large doses of acetaminophen are more detrimental than casual use. However, only 0.1% of women reported acetaminophen use every day during the previous 3 months.

Another concern could be that information on postnatal acetaminophen use was only collected when the child was 5 years old. However, regardless of the timing, postnatal

acetaminophen use for mother and partner cannot have a causal biological intrauterine effect, and it is a valid indicator of stable confounding factors shared within families. Nonetheless, this will not be the case for confounding factors that have changed since the birth of the child. In addition, although the majority of partners (97%) considered themselves the biological father of their child, and they were all living with the mothers at the time the questionnaire was completed, there were no genetic data on partners to confirm paternity. An additional limitation is that polygenic risk scores for complex disorders explain only a small proportion of phenotype variance.³⁰ However, there is no reason to believe that the genetic contribution to ADHD not picked up by these scores would have a different association with acetaminophen use. Finally, measures of exposures and outcomes involved maternal reports; thus, shared rater effects cannot be completely ruled out. However, mothers also reported on postnatal use of acetaminophen.

Conclusions

Children exposed to acetaminophen use prenatally are at increased risk of multiple behavioral difficulties. The associations were not observed for postnatal or partner's acetaminophen use, which indicates that these behavioral difficulties might not be explained by unmeasured behavioral or social factors linked to acetaminophen use. Our findings suggest that the association between acetaminophen use during pregnancy and offspring behavioral problems in childhood may be due to an intrauterine mechanism. Further studies are required to elucidate mechanisms behind this association as well as to test alternatives to a causal explanation. Given the wide-spread use of acetaminophen among pregnant women, this can have important implications on public health advice. However, the risk of not treating fever or pain during pregnancy should be carefully weighed against any potential harm of acetaminophen to the offspring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: Drs Stergiakouli and Davey Smith work in the Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol, which is supported by the MRC and the University of Bristol (grant code, MC_UU_12013/1). Dr Thapar works in the MRC Centre for Neuropsychiatric Genetics and Genomics, which is supported by the MRC, the Wellcome Trust, and Cardiff University (grant code, 079711/Z/06/Z). The MRC and the Wellcome Trust (grant ref, 092731) and the University of Bristol provide core support for ALSPAC.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, analysis or interpretation of data; drafting, review or approval of the manuscript; and decision to submit the manuscript for publication.

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Key Points

Question

Is the association between maternal acetaminophen use during pregnancy and behavioral problems in children consistent with an intrauterine mechanism?

Findings

In this longitudinal birth cohort study of parents and children, maternal prenatal acetaminophen use was associated with increased odds of behavioral problems in children, whereas maternal postnatal and partner's acetaminophen use were not.

Meaning

Children exposed to acetaminophen use prenatally are at increased risk of multiple behavioral difficulties, and the associations do not appear to be explained by unmeasured behavioral or social factors, since they are not linked to postnatal or partner's acetaminophen use.

Table 1
Characteristics of Mothers Reporting Acetaminophen Use in ALSPAC and Their Children

Characteristic	Maternal Acetaminophen Use ^a			
	At 32 wk of Pregnancy		Postnatal Use	
	Never	Ever	Never	Ever
Maternal age at birth, mean (SD), y	29.2 (4.5)	29.1 (4.5)	29.7 (4.8)	29.1 (4.5)
Participants evaluated	4681 (58)	3381 (42)	845 (11)	6916 (89)
Gestational age, mean (SD), wk	39.5 (1.8)	39.6 (1.7)	39.5 (1.8)	39.5 (1.7)
Participants evaluated	4326 (58)	3071 (42)	794 (11)	6603 (89)
Birth weight, mean (SD), g	3419.1 (531.4)	3446.9 (526.1)	3404.8 (549.8)	3433.7 (526.8)
Participants evaluated	4272 (58)	3038 (42)	785 (11)	6525 (89)
Maternal prepregnancy BMI, mean (SD)	22.6 (3.5)	23.3 (3.9)	22.9 (3.8)	22.9 (3.7)
Participants evaluated	4039 (59)	2832 (41)	732 (11)	6139 (89)
Socioeconomic status				
Low	609 (15.8)	429 (16.3)	142 (20.6)	2431 (42)
Intermediate	1631 (42.4)	1121 (42.6)	287 (41.7)	2465 (42.6)
High	1608 (41.8)	1082 (41.1)	259 (37.7)	896 (15.5)
Maternal psychiatric illness				
No	3922 (93.3)	2641 (89.8)	688 (91.4)	5875 (91.9)
Yes	283 (6.7)	300 (10.2)	65 (8.6)	518 (8.1)
Maternal smoking during pregnancy				
Never	3582 (83.3)	2398 (78.7)	626 (79.7)	5354 (81.4)
Ever	720 (16.7)	650 (21.3)	159 (20.3)	1370 (18.6)
Maternal alcohol consumption during pregnancy				
Never	1992 (46.5)	1217 (40.1)	358 (45.8)	2851 (43.6)
Ever	2295 (53.5)	1820 (59.9)	424 (54.2)	3691 (56.4)

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children^{16,17}; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^aUnless otherwise indicated, data are reported as number (percentage) of participants.

Table 2
Risk Ratios for SDQ Behavioral Problems and Maternal Acetaminophen Use at 18 Weeks and 32 Weeks of Pregnancy

SDQ Domain	Risk Ratio (95% CI)	
	18 wk (n = 8317)	32 wk (n = 8062)
SDQ total difficulties (score 17)	1.16 (0.97-1.40)	1.46 (1.21-1.77)
Emotional symptoms (score 5)	1.11 (0.94-1.31)	1.29 (1.09-1.53)
Conduct problems (score 4)	1.20 (1.06-1.37)	1.42 (1.25-1.62)
Hyperactivity symptoms (score 7)	1.23 (1.08-1.39)	1.31 (1.16-1.49)
Peer problems (score 4)	1.07 (0.91-1.25)	1.09 (0.92-1.28)
Prosocial behavior (score 6)	1.00 (0.91-1.09)	1.04 (0.95-1.14)

Abbreviation: SDQ, Strengths and Difficulties Questionnaire.¹⁸

Table 3
Risk Ratios for SDQ Behavioral Problems and Maternal Postnatal and Partner's
Postnatal Acetaminophen Use^a

SDQ Domain	Risk Ratio (95% CI)	
	Maternal (n = 7761)	Partner's (n = 4095)
SDQ total difficulties (score 17)	1.29 (0.92-1.83)	1.09 (0.74-1.61)
Emotional symptoms (score 5)	1.26 (0.94-1.71)	1.23 (0.87-1.74)
Conduct problems (score 4)	1.10 (0.89-1.37)	1.38 (1.02-1.88)
Hyperactivity symptoms (score 7)	1.10 (0.89-1.36)	1.27 (0.96-1.69)
Peer problems (score 4)	1.05 (0.8-1.38)	0.91 (0.66-1.26)
Prosocial behavior (score 6)	1.02 (0.88-1.19)	0.97 (0.82-1.16)

Abbreviation: SDQ, Strengths and Difficulties Questionnaire.¹⁸

^aPostnatal acetaminophen use was measured at 61 months postnatally.

Table 4
Comparison of Maternal Prenatal and 61-Month Postnatal Acetaminophen Use After Mutual Adjustment

SDQ Domain	Maternal Acetaminophen Use, Risk Ratio (95% CI)			
	At 18 wk of Pregnancy ^a (n = 7535)	At 32 wk of Pregnancy ^a (n = 7317)	Postnatal Use ^b (n = 7535)	Postnatal Use ^c (n = 7317)
SDQ total difficulties (score 17)	1.12 (0.92-1.37)	1.47 (1.20-1.80)	1.23 (0.87-1.75)	1.14 (0.80-1.63)
Emotional symptoms (score 5)	1.06 (0.89-1.26)	1.24 (1.04-1.48)	1.22 (0.90-1.67)	1.14 (0.83-1.55)
Conduct problems (score 4)	1.18 (1.03-1.36)	1.40 (1.22-1.60)	1.05 (0.84-1.31)	0.98 (0.78-1.23)
Hyperactivity symptoms (score 7)	1.21 (1.06-1.38)	1.34 (1.17-1.53)	1.05 (0.84-1.31)	1.05 (0.84-1.32)
Peer problems (score 4)	1.05 (0.89-1.24)	1.08 (0.91-1.28)	1.00 (0.76-1.32)	0.98 (0.74-1.30)
Prosocial behavior (score 6)	0.99 (0.90-1.09)	1.03 (0.93-1.13)	1.03 (0.88-1.20)	1.04 (0.89-1.22)

Abbreviation: SDQ, Strengths and Difficulties Questionnaire.

^a Adjusted for postnatal use.

^b Adjusted for prenatal use at 18 weeks.

^c Adjusted for prenatal use at 32 weeks.

Table 5
Comparison of Maternal Prenatal and Partner's 61-Month Postnatal Acetaminophen Use After Mutual Adjustment

SDQ Domain	Maternal and Partner's Acetaminophen Use, Risk Ratio (95% CI)			
	Maternal Use at 18 wk of Pregnancy ^a (n = 4044)	Maternal Use at 32 wk of Pregnancy ^a (n = 3951)	Partner's Postnatal Use ^b (n = 4044)	Partner's Postnatal Use ^c (n = 3951)
SDQ total difficulties (score 17)	1.41 (1.06-1.88)	1.85 (1.39-2.47)	1.05 (0.71-1.55)	1.15 (0.75-1.75)
Emotional symptoms (score 5)	1.04 (0.83-1.32)	1.20 (0.94-1.52)	1.25 (0.88-1.77)	1.34 (0.92-1.95)
Conduct problems (score 4)	1.39 (1.14-1.70)	1.53 (1.25-1.87)	1.36 (1.00-1.86)	1.38 (1.00-1.89)
Hyperactivity symptoms (score 7)	1.27 (1.05-1.53)	1.43 (1.18-1.73)	1.26 (0.95-1.68)	1.28 (0.95-1.71)
Peer problems (score 4)	1.22 (0.96-1.57)	1.21 (0.95-1.56)	0.89 (0.65-1.24)	0.97 (0.69-1.36)
Prosocial behavior (score 6)	1.00 (0.88-1.14)	1.03 (0.91-1.17)	0.96 (0.81-1.14)	0.97 (0.81-1.15)

Abbreviation: SDQ, Strengths and Difficulties Questionnaire.

^a Adjusted for partner's use.

^b Adjusted for maternal prenatal use at 18 weeks.

^c Adjusted for maternal prenatal use at 32 weeks.