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1. **Title Page**

Acetaminophen use during pregnancy and behavioral problems in childhood: evidence against confounding

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2. Abstract

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

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

Design Avon Longitudinal Study of Parents and Children (ALSPAC). Participants enrolled between 1991 and 1992 in Bristol, UK.

Setting Prospective birth cohort of parents and children.

Participants We studied 7796 mothers with their children and partners from ALSPAC

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 of age. 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 and 32 weeks was associated with higher odds of having conduct problems (risk ratio: 1.42 (95% CI: 1.25 - 1.62)) and hyperactivity symptoms (risk ratio: 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 (risk ratio: 1.29 (95% CI: 1.09 - 1.53)) and total difficulties (risk ratio: 1.46 (95% CI: 1.21 - 1.77)). This was

not the case for maternal postnatal or partner's acetaminophen use. The associations between maternal prenatal acetaminophen use and all the SDQ domains remained unchanged even when 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/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.

3. Main Text

Introduction

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 US,[1] 50 - 60% in the EU[2]), 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 could be through 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 with long-term acetaminophen use linked to an increase in risk of cryptorchidism.[5]

Acetaminophen use during pregnancy is associated with higher risk of hyperkinetic disorders and 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 accounted for familial confounding found that long-term acetaminophen use during pregnancy was associated with adverse developmental outcomes at 3 years of age.[8]

Although a large number of potential confounders were accounted for in the previous studies, there is still the possibility of unmeasured confounding being present. Maternal behaviors during pregnancy, including acetaminophen use, can be associated with multiple maternal

factors including socio-economic 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 ADHD[10] and behavioral problems.[11]

Study designs that take into account unmeasured and familial confounding are required to inform public health advice on acetaminophen use in pregnancy.[12] Although they have already been applied to suggest that the association between prenatal acetaminophen exposure and asthma is unlikely to be due to unmeasured behavioral factors,[13] they have not been employed to investigate the effect of prenatal acetaminophen on 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 the latter two exposures cannot have a direct biological effect on the fetus.[14] For example, effects of maternal smoking in pregnancy on birth weight[14] were stronger than that of partner's smoking in the Avon Longitudinal Study of Parents and Children (ALSPAC) in line with other evidence suggesting a causal intrauterine mechanism. However, partner's smoking had a similar effect to maternal smoking on offspring body fat mass.[15]

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

Methods

Study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective birth cohort which recruited pregnant women with expected delivery dates between April 1991 and December 1992 from Bristol UK. 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 that is available through a fully searchable data dictionary: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. 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 three 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 suffered from muscle and joint problems, infections (including cold/flu, urinary or other infections), migraine or headaches at the same periods. However, they were not asked detailed questions on dose, duration and indications of use.

Outcomes

We assessed children's behavioral problems using the Strengths and Difficulties Questionnaire (SDQ), a behavioral screening questionnaire (age range 4–16 years) which includes questions on five domains: emotional symptoms, conduct problems, hyperactivity symptoms, peer relationship problems and prosocial behaviors ranging from 0 to 10 each.[18] A total difficulties score can be obtained by summing the following subscales: emotional

symptoms, conduct problems, hyperactivity symptoms and peer relationship problems (not including prosocial behavior for which a higher score indicates less behavioral problems). SDQ total difficulties score ranges from 0 to 40 (www.sdqinfo.com). Mother reports on their children's behavioral problems were obtained at 7 years of age. Cut-offs were used to dichotomize each of the five SDQ subscales as well as total difficulties score according to previous studies.[18]

Confounding factors

We repeated all our analyses including potential confounding factors: maternal age at birth, parity, socioeconomic status, smoking and alcohol consumption during pregnancy, pre-pregnancy 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 point they were also asked if they suffered from muscle and joint problems, infections (including cold/flu, urinary or other infections), migraine or headaches in the previous 3 months. We decided to include the previous factors in the model as 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 8 340 ALSPAC mothers using available genotype data (details on the quality control procedure have been published previously[19]) according to the method described by the International Schizophrenia Consortium (ISC).[20] Polygenic risk scores were computed using "risk alleles" based on the results of an independent case-control UK/Irish 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 $p<0.5$ was used to select alleles more common in cases than controls from the discovery sample (SNPs in relative linkage equilibrium in the discovery sample GWAS were first selected). 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 employed 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 and 95% confidence intervals (CIs) for prenatal and postnatal acetaminophen use and the dichotomized SDQ domains. As a sensitivity analysis, SDQ domains were also analysed as continuous outcomes after logarithmic transformation.

To address potential confounding by unmeasured genetic and non-genetic confounders, we compared maternal prenatal acetaminophen use to 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 to partner's postnatal acetaminophen use as exposures.

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

Results

Acetaminophen use was reported by 4 415 mothers (53%) at 18 weeks of pregnancy and by 3 381 mothers (42%) at 32 weeks. 6 916 mothers (89%) and 3 454 partners (84%) used acetaminophen postnatally. 5% of children had behavioral problems as indicated by the total difficulties score of the SDQ (eTable 1 in Supplement for details on the number of children with behavioral problems). The mean age of children at completion of the SDQ questionnaire by the parents were 6 years and 7 months (SD 1.3 months). Other characteristics of mothers reporting acetaminophen use in ALSPAC and their children are described in Table 1. All of them were included in the adjusted analysis reported in eTables 2-5 in Supplement.

Maternal prenatal acetaminophen use at 18 weeks was associated with higher odds of offspring conduct problems (risk ratio: 1.20 (95% CI: 1.06 - 1.37)) and hyperactivity symptoms (risk ratio: 1.23 (95% CI: 1.08 - 1.39)), while maternal acetaminophen use at 32 weeks was associated with higher odds of offspring having emotional symptoms (risk ratio: 1.29 (95% CI: 1.09 - 1.53)), conduct problems (risk ratio: 1.42 (95% CI: 1.25 - 1.62)), hyperactivity symptoms (risk ratio: 1.31 (95% CI: 1.16 - 1.49)) and total difficulties (risk ratio: 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 risk ratios, although confidence intervals were wider due to the reduced sample size when including covariates (eTables 2 and 3 in 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, 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 are presented in eTables 2-5 in Supplement. In linear regression models, results were similar (eTables 6-9 in Supplement).

We could not find evidence of robust association between maternal ADHD polygenic risk scores and maternal prenatal acetaminophen at 18 weeks (beta coefficient per SD of polygenic risk score: -0.002 (95% CI: (-0.01 to 0.009), p=0.8), 32 weeks (beta coefficient per SD of polygenic risk score: -0.004 (95% CI: (-0.02 to 0.007), p=0.5) or with postnatal acetaminophen use (beta coefficient per SD of polygenic risk score: -0.008 (95% CI: (-0.01 to 0.0009), p=0.06).

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 exposure at 32 weeks 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, there was no evidence of association between an index of ADHD genetic risk in the mothers and acetaminophen use in pregnancy. These findings when coupled with those from the previous discordant sibling design study[8] suggest that the association between prenatal acetaminophen exposure on childhood behavioral problems does not appear to be 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 suggest that the timing of acetaminophen use might be important. More specifically, we report stronger association between maternal acetaminophen use and multiple behavioral/emotional problem domains during the third trimester compared to the second in accordance with previous studies that have included multiple time points in pregnancy.[8] Given that there is active brain development and growth during the third trimester, this finding could indicate that there are developmental time points when the brain is more sensitive to acetaminophen exposure.

The mechanism through which adverse outcomes of acetaminophen on fetal neurodevelopment could be mediated are not well understood.[12] One mechanism could be

through the endocrine-disrupting properties of acetaminophen. The disruption of the maternal hormonal milieu can impact on 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 trimester of pregnancy and postnatally by the mother as well as by her partner. This enables us to use a nested quasi-experimental design whereby we assess the effect of acetaminophen use during pregnancy on offspring behavioral difficulties and compare it with maternal postnatal acetaminophen use and partner's acetaminophen use which are likely associated with stable social and familial factors as 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 does not appear to be confounded by unmeasured behavioral factors.[13] Our study also had the advantage of assessing the effect of acetaminophen at two different time points 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 could be influencing behavioral problems as well as risky 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 which include headaches, musculoskeletal problems and infections during pregnancy. While there is no 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 or large doses of acetaminophen are more detrimental than casual use. However, only 0.1% 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, irrespective of the timing, postnatal acetaminophen use for mother and partner cannot have a causal biological intra-uterine effect 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 genetic 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 outcome 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 these might not be explained by unmeasured behavioral/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 test alternatives to a causal explanation. Given the widespread use of acetaminophen amongst 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 to the offspring.

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Study concept and design: Davey Smith, Stergiakouli.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Stergiakouli.

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

Statistical analysis: Stergiakouli.

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Study supervision: Davey Smith.

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6. Tables

Table 1. Characteristics of mothers reporting acetaminophen use in ALSPAC and their children

Characteristic	Maternal prenatal use 32 weeks (n, %)		Maternal postnatal use (n, %)	
Maternal age at birth (years)				
	Never (n = 4 681, 58%)	Ever (n = 3 381, 42%)	Never (n = 845, 11%)	Ever (n = 6 916, 89%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	29.2 (4.5)	29.1 (4.5)	29.7 (4.8)	29.1 (4.5)
Gestational age (weeks)				
	Never (n = 4 326, 58%)	Ever (n = 3 071, 42%)	Never (n = 794, 11%)	Ever (n = 6 603, 89%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	39. 5 (1.8)	39.6 (1.7)	39.5 (1.8)	39.5 (1.7)
Birthweight (g)				
	Never (n = 4 272, 58%)	Ever (n = 3 038, 42%)	Never (n = 785, 11%)	Ever (n = 6 525, 89%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	3 419.1 (531.4)	3 446.9 (526.1)	3 404.8 (549.8)	3 433.7 (526.8)
Maternal pre-pregnancy BMI				
	Never (n = 4 039, 59%)	Ever (n = 2 832, 41%)	Never (n = 732, 11%)	Ever (n = 6 139, 89%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	22.6 (3.5)	23.3 (3.9)	22.9 (3.8)	22.9 (3.7)
Socioeconomic status	Never (n, %)	Ever (n, %)	Never (n, %)	Ever (n, %)
Low	609 (15.8)	429 (16.3)	142 (20.6)	2 431 (42)
Intermediate	1 631 (42.4)	1 121 (42.6)	287 (41.7)	2 465 (42.6)
High	1 608 (41.8)	1 082 (41.1)	259 (37.7)	896 (15.5)
Maternal psychiatric illness	Never (n, %)	Ever (n, %)	Never (n, %)	Ever (n, %)
No psychiatric illness	3 922 (93.3)	2 641 (89.8)	688 (91.4)	5 875 (91.9)
Presence of psychiatric illness	283 (6.7)	300 (10.2)	65 (8.6)	518 (8.1)
Maternal smoking during pregnancy	Never (n, %)	Ever (n, %)	Never (n, %)	Ever (n, %)
Never smoker	3 582 (83.3)	2 398 (78.7)	626 (79.7)	5 354 (81.4)
Ever smoker	720 (16.7)	650 (21.3)	159 (20.3)	1 370 (18.6)
Maternal alcohol consumption during pregnancy	Never (n, %)	Ever (n, %)	Never (n, %)	Ever (n, %)
No alcohol	1 992 (46.5)	1 217 (40.1)	358 (45.8)	2 851 (43.6)
Ever alcohol	2 295 (53.5)	1 820 (59.9)	424 (54.2)	3 691 (56.4)

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; SD, Standard Deviation

Table 2. Risk ratios (RR) for SDQ behavioral problems domains and maternal acetaminophen use at 18 weeks and 32 weeks of pregnancy

	Maternal prenatal use at 18 weeks	**Maternal prenatal use at 32 weeks**
	N = 8 317	N = 8 062
Outcome	RR (95% CIs)	RR (95% CIs)
SDQ total difficulties (scores >=17)	1.16 (0.97 - 1.40)	1.46 (1.21 - 1.77)
Emotional symptoms (scores >=5)	1.11 (0.94 - 1.31)	1.29 (1.09 - 1.53)
Conduct problems (scores >=4)	1.20 (1.06 - 1.37)	1.42 (1.25 - 1.62)
Hyperactivity symptoms (scores >=7)	1.23 (1.08 - 1.39)	1.31 (1.16 - 1.49)
Peer problems (scores >=4)	1.07 (0.91 - 1.25)	1.09 (0.92 - 1.28)
Prosocial behavior (scores <=6)	1.00 (0.91 - 1.09)	1.04 (0.95 - 1.14)

Abbreviations: SDQ, Strengths and Difficulties Questionnaire; RR, Risk Ratio; CIs, Confidence Intervals

Table 3. Risk ratios (RR) for SDQ behavioral problems domains and maternal postnatal (61 months) and partner's postnatal acetaminophen use (61 months)

	Maternal postnatal use	**Partner's postnatal use**
	N = 7 761	N = 4 095
Outcome	RR (95% CIs)	RR (95% CIs)
SDQ total difficulties (scores >=17)	1.29 (0.92 - 1.83)	1.09 (0.74 - 1.61)
Emotional symptoms (scores >=5)	1.26 (0.94 - 1.71)	1.23 (0.87 - 1.74)
Conduct problems (scores >=4)	1.10 (0.89 - 1.37)	1.38 (1.02 - 1.88)
Hyperactivity symptoms (scores >=7)	1.10 (0.89 - 1.36)	1.27 (0.96 - 1.69)
Peer problems (scores >=4)	1.05 (0.8 - 1.38)	0.91 (0.66 - 1.26)
Prosocial behavior (scores <=6)	1.02 (0.88 - 1.19)	0.97 (0.82 - 1.16)

Abbreviations: SDQ, Strengths and Difficulties Questionnaire; RR, Risk Ratio; CIs, Confidence Intervals

Table 4. Comparison of effects of maternal prenatal (18 and 32 weeks) and postnatal (61 months) acetaminophen use on SDQ behavioral problems domains after mutual adjustment

	Maternal prenatal use at 18 weeks adjusted for postnatal use	**Maternal prenatal use at 32 weeks adjusted for postnatal use**	**Maternal postnatal use adjusted for prenatal use at 18 weeks**	**Maternal postnatal use adjusted for prenatal use at 32 weeks**
	N = 7 535	N = 7 317	N = 7 535	N = 7 317
Outcome	RR (95% CIs)	RR (95% CIs)	RR (95% CIs)	RR (95% CIs)
SDQ total difficulties (scores >=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 (scores >=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 (scores >=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 (scores >=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 (scores >=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 (scores <=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)

Abbreviations: SDQ, Strengths and Difficulties Questionnaire; RR, Risk Ratio; CIs, Confidence Intervals

Table 5. Comparison of effects of maternal prenatal (18 and 32 weeks) and partner's postnatal (61 months) acetaminophen use on SDQ behavioral problems domains after mutual adjustment

	Maternal prenatal use at 18 weeks adjusted for partner's use	**Maternal prenatal use at 32 weeks adjusted for partner's use**	**Partner's use adjusted for maternal prenatal use at 18 weeks**	**Partner's use adjusted for maternal prenatal use at 32 weeks**
	N = 4 044	N = 3 951	N = 4 044	N = 3 951
Outcome	RR (95% CIs)	RR (95% CIs)	RR (95% CIs)	RR (95% CIs)
SDQ total difficulties (scores >=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 (scores >=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 (scores >=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 (scores >=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 (scores >=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 (scores <=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)

Abbreviations: SDQ, Strengths and Difficulties Questionnaire; RR, Risk Ratio; CIs, Confidence Intervals