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Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behavoiur

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Abstract

Background: Over-the-counter analgesics during pregnancy or infancy may be related to neurobehavoiural problems in children, but little is known about effects of different analgesic types, dosage, and timing.

Objectives: Examine associations of acetaminophen and ibuprofen use during pregnancy and infancy with executive function and behaviour problems in children.

Methods: We included 1225 mother-child pairs from Project Viva, a pre-birth cohort study. We assessed prenatal acetaminophen and ibuprofen use in early and mid-pregnancy and infant use in the first-year of life using questionnaires. Parents and classroom teachers assessed child behaviours in mid-childhood (median 8 years), using the Behavoiur Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ), with higher scores indicating worse functioning for both. We examined associations of acetaminophen and ibuprofen use during pregnancy and infancy with mid-childhood neurobehavoiural outcomes using linear regression models adjusted for potential confounders.

Results: During pregnancy, 46.1% of mothers used acetaminophen ≥10 times and 18.4% used any ibuprofen. In the first year, 65.3% and 39.6% of infants received acetaminophen and ibuprofen ≥6 times, respectively. Higher (≥10 versus <10 times) prenatal acetaminophen (β 1.64 points; 95% confidence interval [CI] 0.59, 2.68) and any ibuprofen (β 1.56, 95% CI 0.19, 2.92) were associated with higher parent-rated BRIEF global scores. Patterns of association were linear across categories and were similar for other parent and teacher-rated outcomes. Infancy exposure (≥6 versus <6 times) to acetaminophen (β 1.69, 95% CI 0.51, 2.87) and ibuprofen (β 1.40, 95% CI 0.25, 2.55)

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were associated with higher parent-rated BRIEF GEC scores but associations with teacher-rated scores were weaker.

Conclusions: Prenatal and early-life exposure to acetaminophen and ibuprofen were associated with poorer executive function and behavoiur in childhood. These findings highlight the need for further research on the mechanisms through which analgesics may act on fetal and child brain development.

Keywords

pregnancy; infancy; acetaminophen; ibuprofen; child behavoiur; child executive function

Social media quote

We found that prenatal and infant exposures to acetaminophen and ibuprofen were associated with mid-childhood executive function and behavoiural problems, and the associations were not explained by measured confounders.

Background

A large proportion of women use over-the-counter analgesics during pregnancy to relieve pain or fever.[1] The US Food and Drug Administration considers acetaminophen the safest analgesic to take throughout pregnancy and recommends avoiding ibuprofen in the third trimester due to an increased risk of birth defects.[2] However, acetaminophen readily crosses the placenta,[3] and multiple human and animal studies suggest that prenatal acetaminophen use is associated with abnormal offspring neurodevelopment.[4–10] The mechanism may involve disrupted endocrine function, which has been shown in animal studies to affect fetal brain development.[11,12] Another possibility is that acetaminophen disrupts brain development through dysregulation of oxidative stress.[13]

In a 2018 meta-analysis of 7 studies including 132,738 participants, prenatal exposure to acetaminophen was associated with a 20 to 30% increase in the risk of neurodevelopmental disorders, including attention deficit hyperactivity disorder, autism spectrum disorders, and hyperactivity symptoms.[14] However, there was evidence of heterogeneity between study estimates of the outcomes. An important additional limitation of the included studies was the potential for confounding by indication.[14] In addition, few prior studies examined prenatal exposure to ibuprofen,[32] or acetaminophen and ibuprofen use by the child in infancy.[16] Also, behavoiural outcomes in most prior studies were reported by mothers only[7,8,10] (versus both mothers and teachers).[6] Subtle, subclinical behavoiur problems may be more apparent in a school setting rather than at home;[17] and any bias in reporting of outcomes by teachers is less likely related to prenatal and infant analgesic use, minimizing misclassification.

The purpose of this study was to investigate associations of acetaminophen and ibuprofen use during pregnancy and infancy with children’s executive function and behavoiur problems as reported by parents and classroom teachers in the pre-birth cohort study Project Viva.

Methods

Between 1999 and 2002, we recruited women into Project Viva in early pregnancy from 8 obstetric offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts. Details of recruitment and retention are published.[15] Of the 2128 women who delivered a live singleton infant, we excluded from this analysis 903 with no outcome data in mid-childhood. Compared with the 1225 participants in this analysis, the 903 nonparticipants were somewhat less likely to have college-educated mothers (58.7% versus 68.9%) and to have annual household income exceeding $70,000 (54.7% versus 60.1%), and mean maternal age was slightly lower (31.3 versus 32.2 years). Gestational age at delivery (mean of 39.3 versus 39.5 weeks) and acetaminophen (69.7% versus 69.8% any intake) and ibuprofen (17.4% versus 18.4% any intake) use during pregnancy, however, were similar.

After obtaining written informed consent, we performed in-person study visits with participating mothers at the end of the first and second trimesters of pregnancy and with mothers and children during the first few days after delivery and in infancy, early childhood, and mid-childhood (median age of 8 years). Mothers also completed mailed questionnaires at 1 year postpartum. The institutional review board of Harvard Pilgrim Health Care approved this study protocol.

Exposures: Intake of acetaminophen and ibuprofen

During interviews conducted during early and mid-pregnancy, we asked mothers to categorize their acetaminophen and ibuprofen use as never, 1–9 times, or ≥10 times. The time referent was “during this pregnancy” for the early pregnancy interview (median 9.9 weeks of gestation) and “in the past 3 months” for the mid-pregnancy interview (median 27.9 weeks of gestation). We worded the questions as “Advil, Motrin, Nuprin, any other ibuprofen, or Alleve?” and “Tylenol or other acetaminophen, nonaspirin pain reliever?”. On the 1-year postpartum questionnaire, we asked mothers to categorize their infant’s acetaminophen and ibuprofen use during the first year of life as never, 1–5 times, 6–10 times, or >10 times. Each dose of acetaminophen or ibuprofen was counted as a single administration “time”. We also assessed aspirin intake but did not include it in this analysis because of very low exposure prevalence (3.9% used any in pregnancy, 0.3% used any in infancy).

Outcomes: Neurobehavoiural outcomes

In mid-childhood, one parent and one classroom teacher per child completed the Behavoiur Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ).[18] We did not record this information, but the parent was almost always the mother (the original Viva participant recruited during pregnancy). The BRIEF evaluates behavoiural executive function, assessing domains including planning and organization, working memory, inhibition of inappropriate impulses, emotional control, and ability to re-evaluate and shift problem solving approaches and is validated and standardised for use in children aged 5–18.[19] Trained Project Viva staff scored completed BRIEF questionnaires according to published guidelines to generate two index scores

(Metacognition [MI] and Behavoiural Regulation [BRI]), and one overall Global Executive Composite score (GEC), which combines the MI and BRI. The MI, BRI, and GEC scores were each standardised to mean 50, SD 10 using published reference data; higher scores represent greater problems.[19]

The SDQ assesses problem behavoiurs in four categories (hyperactivity, emotional problems, conduct problems, and peer problems) as well as prosocial behavoiur,[20] and has good agreement with the Child Behavoiur Checklist.[21,22] It is frequently used in research and clinical settings and is valid and reliable among children aged 4–16 years.[23] SDQ questionnaires were coded by trained Project Viva staff, yielding sub-scores in each behavoiural category and a measure of total behavoiural difficulties (possible range 0–40 with higher scores representing greater problems). Prosocial behavoiural scores remain separate, with higher scores indicating better function.

Potential covariates

We accessed information on participant demographics and health related behavoiurs from Project Viva questionnaires and interviews. Mothers reported their age, education, parity, pregnancy smoking status, and household income and their child's race/ethnicity. Mothers also reported their depressive symptoms in mid-pregnancy using the Edinburgh Postpartum Depression Scale (EPDS).[24] The EPDS has a possible range of 0–30 and ≥13 indicates probable depression.[25] We also assessed antidepressant and antibiotic use during pregnancy via information drawn from each woman's electronic medical record. We calculated gestational age by using the date of the last menstrual period, but if the early second-trimester ultrasound assessment differed from the calculated gestational age by more than 10 days, we used the ultrasound dating instead. We obtained infant sex, birthweight, and date of birth from medical records. We calculated sex-specific birthweight for gestational age z-scores using a US national reference.[26] On the 1-year postpartum questionnaire, mothers reported any diagnosis of a respiratory tract infection (bronchiolitis, pneumonia, bronchitis, croup, or other respiratory tract infection) by a health care professional since birth. At the mid-childhood study visits, mothers completed the Home Observation for Measurement of the Environment-Short Form (HOME-SF), a validated measure of emotional support and cognitive stimulation in the child's home.[27]

Statistical analysis

We first examined the associations between categorical exposures and neurobehavioural outcomes. After we verified a linear dose-response for each increasing exposure category (versus never) with each of the outcomes, we computed ordinal exposures by assigning each frequency category a numerical value (acetaminophen and ibuprofen use in early and mid-pregnancy: never = 0, 1–9 times = 1, or ≥10 times = 2; acetaminophen and ibuprofen use in infancy: never = 0, 1–5 times = 1, 6–10 times = 2, or >10 times = 3). After we verified that early and mid-pregnancy associations were similar, we computed the sum of early plus mid-pregnancy exposure categories (possible range 0–4). For example, if a participant reported using acetaminophen 1–9 times = 1 in early pregnancy and ≥10 times = 2 in mid-pregnancy, she would get a prenatal acetaminophen value of 3. The effect estimates obtained for these ordinal exposures represent the change in outcomes per category increase in acetaminophen

or ibuprofen. We also examined dichotomous prenatal exposures cut at the median (acetaminophen ≥10 versus <10 times and ibuprofen any versus never) and infant exposures cut at ≥6 versus <6 times. In addition, we examined prenatal acetaminophen as any versus never to use the same cutoff as ibuprofen.

We built multivariable linear regression models in which we first adjusted for potential confounders: maternal age, education, smoking during pregnancy, and parity, household income and HOME score, and child age, sex and race/ethnicity. We additionally adjusted infant exposures for gestational age, birthweight for gestational age z-score, and pregnancy acetaminophen or ibuprofen use. Next, to account for potential confounding by indication, we additionally adjusted for antibiotic use during pregnancy (pregnancy exposure models) and for respiratory tract infections during infancy (infancy exposure models), since infections are a common indication for these medications given their antipyretic properties, and hyperthermia is a fetal neuroteratogen.[28] The number of fever episodes would have been a better potential confounder than antibiotic use, but we did not have this variable available. We also included probable prenatal depression and antidepressant use during pregnancy (pregnancy exposure models) because headaches and aches and pains are common symptoms of depression[29] and maternal depression is associated with child behavoiurs.[30] Adding other potentially confounding variables, including maternal pre-pregnancy body mass index and alcohol consumption during pregnancy, did not materially change the observed results, so we did not include them in our final models.

Prior investigators have suggested that child sex may modify associations between acetaminophen exposure and behavoiural outcomes.[10] We assessed potential effect measure modification by re-running adjusted models stratified by sex and also computed interaction P-values. We also examined the joint acetaminophen-ibuprofen interaction by computing interaction P-values. In addition, we ran multivariable models adjusted for both acetaminophen and ibuprofen at the same time. To examine the extent to which prenatal and infant exposures might have an additive or multiplicative effect, we dichotomized prenatal and infant exposures and examined the effects within each of the 4 resulting strata and also computed interaction P-values. We also dichotomized prenatal acetaminophen and ibuprofen exposures (any versus never) and examined the effects within each of the 4 resulting strata and also computed interaction P-values.

Missing data

To account for missing data, we performed multiple imputation for all 2128 mother-child pairs in Project Viva. We then limited the analyses to the 1225 included participants and included the same sample size for all models. We used SAS (Proc MI) to impute 50 values for each missing observation and combined multivariable modeling estimates by using Proc MI ANALYZE in SAS version 9.4 (SAS Institute, Cary, NC). An alternative approach, including only participants with all covariate data (complete cases), yielded similar results (data not shown).

Of 2128 participants in Project Viva, we included 1225 in the analysis sample and excluded 903 with no outcome data in mid-childhood. To address the issue of missing outcome data, we implemented inverse probability weighting (IPW). First, among 2128, we predicted the

probability of missing outcomes, based on the following covariates (maternal age, education, smoking, parity, depression in mid-pregnancy, and antibiotic, antidepressant, acetaminophen, and ibuprofen use during pregnancy; household income and HOME score; and child sex, race/ethnicity, gestational age, birthweight for gestational age z-score, respiratory tract infections, and acetaminophen and ibuprofen during the first year). Next, among 1225, we ran all models weighted by the inverse of the probability of having mid-childhood outcomes.

Results

Mean (SD) maternal age at enrollment was 32.2 (5.2) years, 9.7% smoked during pregnancy, 68.9% were college graduates, 60.1% had household incomes >$70,000 per year and 64.5% of the children were white (Table 1). Although most mothers reported at least some acetaminophen use during pregnancy (69.8%), ibuprofen use during pregnancy was less common (18.4%). Ninety-five percent of children were given acetaminophen at least once in the first year of life; 66.9% of children were given ibuprofen at least once. Correlates of higher acetaminophen use during pregnancy included smoking during pregnancy, higher ibuprofen use during pregnancy, white child race/ethnicity, and higher child acetaminophen and ibuprofen in infancy (Table 1). As expected, those who took antibiotics in pregnancy and had a history of depression had higher acetaminophen use. In eTable 1 we show characteristics according to ibuprofen intake during pregnancy.

Mean (standard deviation) BRIEF GEC parent-rated score was 48.7 (9.1) and teacher-rated score was 51.2 (10.5); SDQ total difficulties parent-rated score was 6.6 (4.8) and teacher-rated score was 6.4 (5.8). Correlations between parent and teacher ratings on the same instrument were moderate (Spearman r=0.34 for the BRIEF GEC, and 0.45 for the SDQ), while within-rater correlations of BRIEF GEC with SDQ scores were higher (Spearman r=0.69 for parents, and 0.74 for teachers).

Unadjusted and confounder adjusted results were similar (Table 2). In multivariable models (Table 2, Model 2), we found that acetaminophen during pregnancy (per category increase) was associated with higher parent-rated scores (indicating greater problems) for both executive function and behaviour: BRIEF GEC (β 0.82 points; 95% CI 0.39, 1.26), BRIEF BRI (0.69; 0.26, 1.11), BRIEF MI (0.66; 0.24, 1.08) and SDQ (0.30; 0.08, 0.53). Patterns of association were similar for the teacher-rated outcomes (e.g. BRIEF GEC 0.68; 0.12, 1.24). After additional adjustment for probable depression and antidepressant and antibiotic use during pregnancy (Table 2, Model 4), results were similar.

We similarly found that ibuprofen intake during pregnancy (per category increase) was associated with higher parent-rated scores (indicating greater problems) on both the BRIEF and SDQ. For example, in multivariable models (Table 2, Model 2), effect estimates were: GEC (β 1.51 points; 95% CI 0.44, 2.59), BRIEF BRI (1.33; 0.27, 2.39), BRIEF MI (1.18; 0.15, 2.22) and SDQ (0.80; 0.25, 1.36). Patterns of association were similar for the teacher-rated outcomes. After adjustment for probable depression and antidepressant and antibiotic use during pregnancy (Table 2, Model 4), results were similar. There was no evidence of

interaction between acetaminophen and ibuprofen exposure. Also, inclusion of the other analgesic in multivariable models did not materially change the findings (results not shown).

Acetaminophen use during the first year of life was also associated with executive function and behavoiur problems in mid-childhood. In multivariable models (Table 3, Model 2), we found that acetaminophen intake during the first year of life (per category increase) was associated with higher parent-rated scores on the BRIEF GEC (β 0.96 points; 95% CI 0.40, 1.52), BRIEF BRI (0.68; 0.12, 1.24), BRIEF MI (0.95; 0.40, 1.49) and SDQ (0.63; 0.33, 0.92). After adjustment for prenatal acetaminophen intake and respiratory tract infections during the first year of life (Table 3, Model 4), results were slightly attenuated.

In multivariable models (Table 3, Model 2), ibuprofen (per category increase) was associated with higher parent-rated BRIEF GEC (β 0.73 points; 95% CI 0.24, 1.23) and SDQ (0.30; 0.05, 0.54). In Model 4, these results were 0.71; 0.21, 1.21 for BRIEF GEC and 0.27; 0.02, 0.52 for SDQ. Patterns of association were in a similar direction albeit weaker for teacher-rated scores.

There was no evidence of effect modification by child sex in observed associations with teacher scores, although in some cases parent reported outcomes showed stronger associations among girls compared with boys (eTable 2).

In eTable 3, we present the estimates for all covariates in the prenatal exposure models to compare the magnitude of effect sizes. Among 8-year-old boys and girls in Project Viva, their BRIEF GEC scores were 1.64 points higher if their mothers used acetaminophen ≥10 versus <10 times during pregnancy and were 1.56 points higher if their mothers used any ibuprofen during pregnancy. In the same adjusted models, the estimate for prenatal depression, a known risk factor for behavoiural problems,[28] was about 2.2 points and the estimate for smoking during pregnancy was about 1.4 points.

In eTable 4, we examined a 4-category exposure (low prenatal/low infant, low prenatal/high infant, high prenatal/low infant, high prenatal/high infant). Compared with low prenatal/low infant category, associations were strongest for high prenatal/high infant acetaminophen or ibuprofen intake, although interaction P-values were all non-significant. Prenatal and infant exposures appeared to have an additive, not a multiplicative effect.

In eTable 5, we examined a 4-category exposure (never acetaminophen/never ibuprofen, never acetaminophen/any ibuprofen, any acetaminophen/never ibuprofen, any acetaminophen/any ibuprofen). Compared with never acetaminophen/never ibuprofen category, associations were strongest for any acetaminophen/any ibuprofen intake, although interaction P-values were all non-significant. Effect estimates for acetaminophen alone, or ibuprofen alone, were generally similar to each other. Prenatal acetaminophen and ibuprofen exposures appeared to have an additive, not a multiplicative effect.

Discussion

Principal findings

In this prospective longitudinal study of over 1200 children, we found that acetaminophen and ibuprofen exposures during pregnancy or during infancy were associated with poorer executive function and behavoiurs among school-aged children. This analysis is in line with prior literature showing associations of prenatal acetaminophen intake with poorer neurodevelopmental outcomes in childhood. Further, it extends and strengthens the existing literature on this topic by examining ibuprofen in addition to acetaminophen, examining exposures during infancy as well as during pregnancy, including both teacher and parent assessments of executive function and behavoiurs, and considering potential confounding by indication by both maternal depression and prenatal/infant infections.

Strengths of the study

We believe this study has many strengths, including prospective data collection since early pregnancy; assessment of intake of both acetaminophen and ibuprofen at multiple timepoints; availability of several covariates to address confounding, including demographic characteristics and predictors of analgesic intake; research-standard outcomes assessed by both parents and classroom teachers; and a sample size that allowed precise estimates of effect.

Limitations of the data

This study also has several potential limitations. Although we captured analgesic intake within certain exposure frequencies, we did not have information on exact dose. Also, we assessed analgesic intake in early and mid-pregnancy only but not late pregnancy. Also, we did not assess maternal analgesic use during lactation, possibly leading to infant exposure and exposure misclassification. We were not able to adjust for all indications for analgesic use, which could have resulted in residual confounding by indication. We also observed some differences in baseline covariates between participants and those lost to follow-up and therefore we implemented IPW. Results with versus without IPW were very similar.

Interpretation

Our results are consistent with previous studies that reported associations of acetaminophen in pregnancy with greater childhood executive function and behavoiur problems.[5–9,14,32] Studies in Spain, New Zealand, United Kingdom, Denmark, and Norway have reported associations of prenatal acetaminophen use with offspring behavoiural problems, symptoms of attention deficit/hyperactivity disorder, and diagnosis with an autism spectrum disorder at school age. For example, using parent-reported SDQ scores, Thompson et al. observed that acetaminophen was a risk factor for total difficulties, emotional symptoms, and conduct problems at 7 years. At age 11, the association with the parent-reported emotional score persisted, whereas associations with the other parent-reported scores were weaker and confidence intervals contained 0.[7]

In the ALSPAC cohort in the UK, authors linked prenatal acetaminophen use to multiple behavoiural difficulties in children at age 7 years.[8] Among 7,796 mother-child pairs,

acetaminophen use at 18 and 32 weeks of gestation was associated with higher risk 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). Acetaminophen use at 32 weeks was also associated with higher risk 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). That study adjusted for possible indicators of acetaminophen use but did not examine exposure to ibuprofen. In addition, it did not examine acetaminophen and ibuprofen use by the child in infancy. Also, outcomes in that study were reported by mothers only (versus both mothers and teachers).

In the Brazilian 2004 Pelotas birth cohort, 6-year-old boys of mothers who used acetaminophen in pregnancy had higher odds of emotional (OR 1.47, 95% CI 1.07, 2.02) and hyperactivity (OR 1.42, CI 1.06, 1.92) problems, as assessed by parent reported SDQ scores.[10] At age 11 years, there was a small decrease in these associations (emotional OR 1.31, CI 0.99, 1.73 and hyperactivity OR 1.25, CI 0.95, 1.65) problems. However, among girls, associations were null for both outcomes at both ages. In our study, there was no evidence of effect modification by child sex based on teacher reported outcomes, although in some cases parent reported outcomes showed stronger associations among girls compared with boys. In comparison with our study, Pelotas used dichotomous outcomes based on parental report only.

In the Nurses' Health Study II cohort, Liew et al. found an association of prenatal acetaminophen use with childhood ADHD (OR 1.34, CI 1.05, 1.72).[31] The authors also examined two negative control exposure periods (about 4 years before and 4 years after the pregnancy). The associations of maternal acetaminophen use in the pre- and post-pregnancy exposure periods with ADHD were null, providing some evidence that observed associations are not explained by uncontrolled time-invariant factors.

To our knowledge, only one published study has examined associations of prenatal exposure to ibuprofen with neurodevelopmental outcomes. In a sibling-pair analysis among 2919 same-sex siblings in the Norwegian MoBA cohort, maternal prenatal ibuprofen exposure (≥28 days of use) was not associated with adverse psychomotor development (communication, fine and gross motor development), externalizing and internalizing behavoiur problems, or temperament (emotionality, activity, sociability and shyness) at 3 years of age.[32] Compared with our analysis, their exposure was considerably long (≥28 days), and children were younger at outcome assessment. Further, they used a sibling-control study design to adjust for familial and genetic factors.

Multiple mechanisms may underlie the associations we observed for acetaminophen and ibuprofen exposures and behavoiural problems in children. Acetaminophen and ibuprofen both cross the placenta. It has been suggested that acetaminophen interferes with neurotransmitter, endocrine, and immune systems, as well as with the regulation of brain-derived neurotrophic factor and cell oxidative stress, which are processes associated with brain development.[11,12,33–38] The fact that we found associations with both acetaminophen and ibuprofen might mean that relationships are more likely causal given that the two medications both cross the blood brain barrier and have similar analgesic and antipyretic effects despite their different mechanisms of action.

Alternatively, observed associations could be explained by unmeasured confounding. One particular concern is confounding by indication, namely that the reasons mothers, or children, take these medications might also be related to the studied outcomes. For example, febrile infections in pregnancy or infancy might be an indication for analgesic use, and either the infection itself or the resulting fever may affect neurodevelopment.[39] Similarly, mothers or children who are more bothered by minor discomforts may take these medications as analgesics and may be more likely to have behavoiural problems. We tried to address these possibilities by adjusting for a number of potential predictors of analgesic/antipyretic use, including depression and antidepressant and antibiotic use during pregnancy, and respiratory tract infections during infancy. Associations were not explained by these possible indicators of acetaminophen and ibuprofen use. As we did not measure all potential indications for use of these medications (e.g. migraines or rheumatologic conditions), residual confounding may remain, although we believe that the strong and consistent associations and lack of any notable attenuation with adjustment for measured confounders renders it less likely that the observed relationship is entirely explained by unmeasured confounding.

Both parents and teachers assessed children's executive function and behavoiurs. Parent and teacher ratings assess behavoiurs in different environments. In general, results were similar for both parent and teacher rated outcomes, although somewhat stronger for parent reports. This discrepancy may indicate that subtle executive function and behavoiur problems may differ by setting (home versus school) or may reflect greater confounding for parent reported outcomes. For example, it's possible that easily "irritated" mothers may be more likely take analgesics during pregnancy, give them to their children, and rate their children more poorly on the SDQ. We observed moderate inter-rater correlation between parent and teacher scores in our study population, which is consistent with patterns observed by other researchers and in normative population samples.[19,40]

In our study, prenatal acetaminophen results were similar based on parent versus teacher rated outcomes. However, prenatal ibuprofen results were slightly stronger for teacher versus parent rated outcomes. Based on parent rated outcomes, prenatal acetaminophen and ibuprofen results were similar. However, based on teacher rated outcomes, prenatal ibuprofen results were slightly stronger than acetaminophen. Infant acetaminophen and ibuprofen results were stronger for parent versus teacher rated outcomes. Also, patterns of association were similar in direction for infant acetaminophen versus ibuprofen, but stronger for acetaminophen. We are not sure why some of the results varied by reporter and acetaminophen versus ibuprofen. It could be evidence for confounding by indication (with slightly different indications for ibuprofen vs. acetaminophen), other confounding (different people choose to take one or the other) or evidence for real effect of both.

Conclusions

In conclusion, in this study, we found that prenatal and infant exposures to acetaminophen and ibuprofen were associated with mid-childhood executive function and behavoiur problems, and the associations were not explained by measured confounders. These findings highlight the need for further research on the mechanisms through which analgesics may act on the developing brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis

Study question

- To what extent are prenatal and early-life exposure to acetaminophen and ibuprofen associated with executive function and behavoiur in childhood?

What's already known

- Acetaminophen use during pregnancy may be related to neurobehavoiural problems in children, but little is known about effects of different analgesic types, dosage, and timing.

What this study adds

- We found that prenatal and infant exposures to acetaminophen and ibuprofen were associated with mid-childhood executive function and behavoiur problems, and the associations were not explained by measured confounders
- This study extends and strengthens the existing literature on this topic by examining ibuprofen in addition to acetaminophen and examining exposures during infancy as well as during pregnancy

Table 1.

Participant characteristics overall and according to category of acetaminophen intake during pregnancy, among 1225 mother-child pairs in the Project Viva cohort

		Category of acetaminophen intake during pregnancy			
	Overall	**0 (never)**	**1 (5 times)**	**2 (10 times)**	**3 and 4 (≥15 times)**
	n=1225	**370 (30.2%)**	**290 (23.7%)**	**340 (27.7%)**	**225 (18.4%)**
		Mean (SD) or %			
Maternal characteristics					
Age at enrollment (years)	32.2 (5.2)	31.7 (5.6)	32.1 (5.2)	32.4 (5.0)	32.7 (4.9)
Primipara, %	48.0	51.5	49.3	47.3	41.7
College degree or beyond, %	68.9	68.9	69.4	68.5	68.9
Smoking status, %					
Never	71.3	74.0	76.7	67.8	65.3
Former	19.0	17.2	15.0	22.9	21.1
During pregnancy	9.7	8.7	8.3	9.3	13.6
Antibiotics during pregnancy, %	28.5	23.2	29.4	27.8	37.0
Antidepressants during pregnancy, %	2.8	1.6	2.5	4.2	2.9
Depression in mid-pregnancy, %	9.5	8.3	8.4	10.7	11.1
Household income >$70,000/year, %	60.1	60.2	62.6	55.9	62.8
Pregnancy exposures					
Ibuprofen during pregnancy category, %					
0 (never)	81.6	88.4	83.4	78.7	72.2
1 (5 times)	15.5	8.8	15.5	19.1	21.3
2 (10 times)	2.5	2.5	0.8	1.9	5.5
3–4 (≥15 times)	0.4	0.3	0.3	0.3	0.9
Child characteristics					
Female sex, %	49.7	48.1	49.0	53.8	47.2
Gestational age (weeks)	39.5 (1.8)	39.6 (1.7)	39.5 (1.8)	39.6 (1.9)	39.2 (2.0)
Birthweight (grams)	3482 (566)	3458 (576)	3492 (528)	3511 (547)	3463 (619)
Birthweight/gestational age z-score	0.19 (0.97)	0.11 (1.03)	0.21 (0.91)	0.24 (0.91)	0.22 (0.99)
Race/ethnicity, %					
Black	16.0	18.0	15.7	16.1	12.9
Hispanic	4.4	4.6	3.4	5.7	3.0
White	64.5	55.7	66.1	65.8	74.8
Other	15.2	21.7	14.8	12.5	9.3
Infant exposures					
Acetaminophen during the first-year category, %					
0 (never)	4.9	7.5	4.7	3.9	2.3
1 (1–5 times)	29.8	36.2	31.1	27.8	20.8
2 (6–10 times)	24.4	23.9	22.2	26.1	25.2

	Overall	Category of acetaminophen intake during pregnancy			
		0 (never)	1 (5 times)	2 (10 times)	3 and 4 (≥15 times)
	n=1225	370 (30.2%)	290 (23.7%)	340 (27.7%)	225 (18.4%)
		Mean (SD) or %			
3 (>10 times)	40.9	32.4	42.1	42.2	51.6
Ibuprofen during the first-year category, %					
0 (never)	33.1	40.4	35.0	30.9	21.7
1 (1–5 times)	27.4	27.6	28.6	25.8	27.7
2 (6–10 times)	16.5	16.9	16.1	17.4	14.8
3 (>10 times)	23.1	15.1	20.3	25.8	35.9
Age (years) mid-childhood	7.9 (0.8)	7.9 (0.8)	7.9 (0.8)	7.9 (0.8)	7.9 (0.8)
HOME-SF score mid-childhood[a]	18.3 (2.2)	18.2 (2.2)	18.4 (2.3)	18.4 (2.2)	18.2 (2.3)
Mid-childhood outcomes					
Parent					
BRIEF Global Executive Composite[b]	48.7 (9.1)	47.8 (8.8)	48.2 (9.2)	49.5 (8.7)	49.6 (10.1)
Behavoiur Regulation Index	48.2 (8.8)	47.3 (8.3)	48.0 (9.2)	49.2 (8.7)	48.6 (9.3)
BRIEF Metacognition Index	48.4 (8.7)	47.8 (8.6)	48.0 (8.9)	48.9 (8.1)	49.4 (9.5)
SDQ Total Difficulties[c]	6.6 (4.8)	6.2 (4.6)	6.6 (5.1)	6.8 (4.7)	6.8 (4.7)
Prosocial	8.5 (1.7)	8.5 (1.7)	8.3 (1.8)	8.6 (1.6)	8.7 (1.6)
Teacher					
BRIEF Global Executive Composite[b]	51.2 (10.5)	50.4 (10.0)	50.8 (10.5)	52.0 (11.1)	51.6 (10.1)
Behavoiur Regulation Index	50.8 (10.2)	50.2 (10.1)	50.5 (10.0)	51.4 (10.3)	51.5 (10.2)
BRIEF Metacognition Index	51.2 (10.8)	50.4 (10.0)	50.9 (10.8)	52.2 (11.8)	51.6 (10.4)
SDQ Total Difficulties[c]	6.4 (5.8)	5.9 (5.7)	6.3 (5.6)	6.8 (6.3)	6.7 (5.7)
Prosocial	8.0 (2.2)	8.0 (2.1)	8.0 (2.2)	8.1 (2.2)	8.0 (2.2)

[a]The HOME-SF, or Home Observation for Measurement of the Environment (Short Form) assessment, used to measure emotional support and cognitive stimulation in the child's home; scale: 0–22, with higher scores representing greater support

[b]Behavoiur Rating Inventory of Executive Function (BRIEF) Index and Composite scores standardised to mean=50, standard deviation = 10 with higher scores representing greaterexecutive function problems. BRIEF Global Executive Composite score combines Metacognition Index and Behavoiur Regulation Index scores

[c]Strengths and Difficulties Questionnaire (SDQ) Total Difficulties scores have possible values of 0–40 with higher scores representing greater behavoiural problems

Table 2.

Associations of acetaminophen or ibuprofen during pregnancy (ordinal values 0–4 or dichotomous) with mid-childhood executive function and behavoiur, among 1225 mother-child pairs in the Project Viva cohort

	Parent rated outcomes			
	Model 1	**Model 2**	**Model 3**	**Model 4**
	β (95% confidence interval)			
Acetaminophen during pregnancy (per category)				
BRIEF Global Executive Composite	0.78 (0.34, 1.22)	0.82 (0.39, 1.26)	0.79 (0.35, 1.23)	0.76 (0.32, 1.20)
Behavoiur Regulation Index	0.60 (0.17, 1.03)	0.69 (0.26, 1.11)	0.64 (0.21, 1.07)	0.61 (0.18, 1.04)
BRIEF Metacognition Index	0.66 (0.24, 1.08)	0.66 (0.24, 1.08)	0.65 (0.23, 1.07)	0.62 (0.20, 1.04)
SDQ Total Difficulties	0.25 (0.02, 0.48)	0.30 (0.08, 0.53)	0.27 (0.04, 0.49)	0.24 (0.02, 0.46)
Prosocial	0.06 (−0.02, 0.14)	0.05 (−0.02, 0.13)	0.06 (−0.02, 0.14)	0.06 (−0.02, 0.14)
Ibuprofen during pregnancy (per category)				
BRIEF Global Executive Composite	1.87 (0.77, 2.96)	1.51 (0.44, 2.59)	1.47 (0.39, 2.54)	1.49 (0.42, 2.57)
Behavoiur Regulation Index	1.51 (0.44, 2.57)	1.33 (0.27, 2.39)	1.27 (0.21, 2.32)	1.28 (0.23, 2.34)
BRIEF Metacognition Index	1.64 (0.58, 2.70)	1.18 (0.15, 2.22)	1.16 (0.12, 2.20)	1.18 (0.14, 2.22)
SDQ Total Difficulties	1.02 (0.44, 1.60)	0.80 (0.25, 1.36)	0.76 (0.20, 1.31)	0.77 (0.22, 1.32)
Prosocial	−0.07 (−0.27, 0.14)	−0.02 (−0.21, 0.18)	−0.01 (−0.21, 0.18)	−0.02 (−0.21, 0.18)
Acetaminophen during pregnancy (≥10 versus <10 times)				
BRIEF Global Executive Composite	1.77 (0.71, 2.83)	1.77 (0.73, 2.81)	1.72 (0.68, 2.76)	1.64 (0.59, 2.68)
Behavoiur Regulation Index	1.50 (0.48, 2.53)	1.61 (0.59, 2.62)	1.54 (0.52, 2.55)	1.45 (0.44, 2.47)
BRIEF Metacognition Index	1.43 (0.42, 2.45)	1.39 (0.39, 2.39)	1.36 (0.36, 2.37)	1.29 (0.29, 2.30)
SDQ Total Difficulties	0.56 (−0.01, 1.12)	0.61 (0.08, 1.14)	0.55 (0.02, 1.08)	0.48 (−0.05, 1.01)
Prosocial	0.21 (0.02, 0.40)	0.19 (0.00, 0.37)	0.19 (0.01, 0.38)	0.21 (0.02, 0.39)
Acetaminophen during pregnancy (any versus never)				
BRIEF Global Executive Composite	1.54 (0.38, 2.69)	1.74 (0.61, 2.86)	1.66 (0.53, 2.79)	1.60 (0.47, 2.73)
Behavoiur Regulation Index	1.57 (0.45, 2.68)	1.82 (0.72, 2.92)	1.72 (0.62, 2.82)	1.66 (0.56, 2.76)
BRIEF Metacognition Index	1.11 (−0.01, 2.23)	1.25 (0.16, 2.34)	1.22 (0.12, 2.32)	1.17 (0.07, 2.26)
SDQ Total Difficulties	0.68 (0.07, 1.30)	0.88 (0.30, 1.46)	0.80 (0.22, 1.38)	0.75 (0.17, 1.32)
Prosocial	0.03 (−0.18, 0.24)	−0.02 (−0.22, 0.19)	−0.01 (−0.21, 0.19)	0.00 (−0.21, 0.20)
Ibuprofen during pregnancy (any versus never)				
BRIEF Global Executive Composite	1.94 (0.54, 3.34)	1.55 (0.18, 2.91)	1.52 (0.15, 2.88)	1.56 (0.19, 2.92)
Behavoiur Regulation Index	1.58 (0.23, 2.93)	1.39 (0.06, 2.72)	1.35 (0.02, 2.68)	1.38 (0.05, 2.71)
BRIEF Metacognition Index	1.72 (0.37, 3.06)	1.19 (−0.13, 2.50)	1.17 (−0.14, 2.49)	1.21 (−0.11, 2.52)
SDQ Total Difficulties	1.04 (0.30, 1.78)	0.81 (0.12, 1.51)	0.79 (0.09, 1.48)	0.81 (0.12, 1.50)
Prosocial	−0.06 (−0.31, 0.20)	0.00 (−0.24, 0.25)	0.00 (−0.24, 0.25)	0.00 (−0.25, 0.24)
	Teacher rated outcomes			
Acetaminophen during pregnancy (per category)				
BRIEF Global Executive Composite	0.58 (−0.02, 1.17)	0.68 (0.12, 1.24)	0.64 (0.08, 1.19)	0.62 (0.05, 1.18)
Behavoiur Regulation Index	0.51 (−0.06, 1.09)	0.68 (0.12, 1.24)	0.64 (0.08, 1.20)	0.62 (0.06, 1.18)
BRIEF Metacognition Index	0.55 (−0.05, 1.16)	0.60 (0.03, 1.17)	0.56 (−0.01, 1.13)	0.55 (−0.02, 1.12)
SDQ Total Difficulties	0.29 (−0.02, 0.61)	0.39 (0.08, 0.69)	0.36 (0.05, 0.66)	0.35 (0.05, 0.65)

	Parent rated outcomes			
	Model 1	**Model 2**	**Model 3**	**Model 4**
	β (95% confidence interval)			
Prosocial	0.00 (−0.12, 0.12)	−0.04 (−0.16, 0.08)	−0.04 (−0.16, 0.08)	−0.04 (−0.16, 0.08)
Ibuprofen during pregnancy (per category)				
BRIEF Global Executive Composite	2.03 (0.53, 3.52)	1.61 (0.19, 3.03)	1.55 (0.12, 2.97)	1.53 (0.10, 2.96)
Behavoiur Regulation Index	2.19 (0.70, 3.68)	1.91 (0.46, 3.37)	1.85 (0.40, 3.30)	1.82 (0.37, 3.28)
BRIEF Metacognition Index	1.78 (0.27, 3.29)	1.33 (−0.11, 2.76)	1.28 (−0.16, 2.71)	1.26 (−0.17, 2.70)
SDQ Total Difficulties	1.38 (0.55, 2.22)	1.32 (0.51, 2.13)	1.28 (0.47, 2.09)	1.25 (0.44, 2.05)
Prosocial	−0.48 (−0.79,−0.18)	−0.50 (−0.80,−0.20)	−0.50 (−0.79,−0.20)	−0.49 (−0.79,−0.19)
Acetaminophen during pregnancy (≥10 versus <10 times)				
BRIEF Global Executive Composite	1.37 (−0.05, 2.78)	1.53 (0.22, 2.85)	1.46 (0.15, 2.77)	1.41 (0.10, 2.73)
Behavoiur Regulation Index	1.17 (−0.19, 2.53)	1.45 (0.14, 2.75)	1.38 (0.08, 2.68)	1.32 (0.02, 2.63)
BRIEF Metacognition Index	1.31 (−0.16, 2.77)	1.39 (0.04, 2.74)	1.33 (−0.02, 2.68)	1.29 (−0.06, 2.65)
SDQ Total Difficulties	0.65 (−0.10, 1.41)	0.84 (0.12, 1.57)	0.80 (0.08, 1.52)	0.79 (0.06, 1.51)
Prosocial	0.05 (−0.24, 0.34)	−0.04 (−0.32, 0.24)	−0.03 (−0.31, 0.25)	−0.03 (−0.32, 0.25)
Acetaminophen during pregnancy (any versus never)				
BRIEF Global Executive Composite	1.27 (−0.21, 2.75)	1.57 (0.17, 2.97)	1.47 (0.08, 2.86)	1.44 (0.05, 2.83)
Behavoiur Regulation Index	1.03 (−0.44, 2.50)	1.45 (0.02, 2.88)	1.35 (−0.07, 2.76)	1.32 (−0.10, 2.73)
BRIEF Metacognition Index	1.25 (−0.26, 2.76)	1.46 (0.03, 2.88)	1.37 (−0.05, 2.79)	1.35 (−0.07, 2.77)
SDQ Total Difficulties	0.69 (−0.12, 1.51)	0.94 (0.17, 1.72)	0.88 (0.11, 1.65)	0.88 (0.11, 1.65)
Prosocial	0.03 (−0.27, 0.33)	−0.05 (−0.35, 0.24)	−0.05 (−0.35, 0.25)	−0.05 (−0.35, 0.25)
Ibuprofen during pregnancy (any versus never)				
BRIEF Global Executive Composite	2.40 (0.57, 4.22)	1.94 (0.22, 3.66)	1.90 (0.18, 3.62)	1.89 (0.15, 3.62)
Behavoiur Regulation Index	2.67 (0.88, 4.45)	2.39 (0.66, 4.13)	2.36 (0.63, 4.09)	2.32 (0.59, 4.06)
BRIEF Metacognition Index	2.05 (0.18, 3.93)	1.54 (−0.23, 3.31)	1.51 (−0.26, 3.28)	1.50 (−0.28, 3.27)
SDQ Total Difficulties	1.63 (0.61, 2.65)	1.58 (0.59, 2.56)	1.55 (0.57, 2.53)	1.50 (0.53, 2.48)
Prosocial	−0.52 (−0.89,−0.15)	−0.53 (−0.90,−0.17)	−0.53 (−0.89,−0.17)	−0.52 (−0.89,−0.16)

Model 1. Unadjusted

Model 2. Adjusted for maternal age, education, smoking, and parity; household income and HOME score; and child age, sex and race/ethnicity

Model 3. Model 2 + antibiotics during pregnancy

Model 4. Model 3 + antidepressants during pregnancy and EPDS ≥13 in mid-pregnancy

Table 3.

Associations of acetaminophen or ibuprofen during the first year of life (ordinal values 0–3 or dichotomous) with mid-childhood executive function and behavoiur, among 1225 mother-child pairs in the Project Viva cohort

	Parent rated outcomes			
	Model 1	**Model 2**	**Model 3**	**Model 4**
	β (95% confidence interval)			
Acetaminophen during the first year (per category)				
BRIEF Global Executive Composite	0.91 (0.33, 1.48)	0.96 (0.40, 1.52)	0.81 (0.24, 1.39)	0.84 (0.25, 1.42)
Behavoiur Regulation Index	0.63 (0.06, 1.20)	0.68 (0.12, 1.24)	0.55 (−0.02, 1.13)	0.53 (−0.06, 1.12)
BRIEF Metacognition Index	0.91 (0.35, 1.48)	0.95 (0.40, 1.49)	0.83 (0.28, 1.39)	0.88 (0.31, 1.44)
SDQ Total Difficulties	0.57 (0.25, 0.88)	0.63 (0.33, 0.92)	0.58 (0.29, 0.88)	0.58 (0.28, 0.88)
Prosocial	0.00 (−0.11, 0.10)	0.00 (−0.11, 0.10)	−0.01 (−0.12, 0.09)	−0.01 (−0.12, 0.09)
Ibuprofen during the first year (per category)				
BRIEF Global Executive Composite	0.64 (0.15, 1.13)	0.73 (0.24, 1.23)	0.70 (0.20, 1.19)	0.71 (0.21, 1.21)
Behavoiur Regulation Index	0.41 (−0.06, 0.89)	0.52 (0.04, 1.00)	0.49 (0.01, 0.97)	0.47 (−0.02, 0.95)
BRIEF Metacognition Index	0.69 (0.21, 1.17)	0.75 (0.27, 1.23)	0.72 (0.24, 1.20)	0.76 (0.27, 1.24)
SDQ Total Difficulties	0.24 (−0.03, 0.50)	0.30 (0.05, 0.54)	0.28 (0.03, 0.53)	0.27 (0.02, 0.52)
Prosocial	0.02 (−0.06, 0.11)	0.01 (−0.08, 0.09)	0.01 (−0.08, 0.09)	0.01 (−0.08, 0.10)
Acetaminophen during the first year (≥6 versus <6 times)				
BRIEF Global Executive Composite	1.79 (0.62, 2.96)	1.93 (0.79, 3.08)	1.65 (0.49, 2.81)	1.69 (0.51, 2.87)
Behavoiur Regulation Index	1.43 (0.29, 2.57)	1.54 (0.40, 2.68)	1.30 (0.14, 2.46)	1.26 (0.08, 2.45)
BRIEF Metacognition Index	1.70 (0.56, 2.83)	1.82 (0.71, 2.92)	1.60 (0.48, 2.72)	1.67 (0.54, 2.81)
SDQ Total Difficulties	1.13 (0.51, 1.75)	1.28 (0.69, 1.87)	1.20 (0.60, 1.80)	1.19 (0.58, 1.80)
Prosocial	−0.05 (−0.27, 0.17)	−0.06 (−0.27, 0.15)	−0.08 (−0.30, 0.13)	−0.09 (−0.31, 0.13)
Ibuprofen during the first year (≥6 versus <6 times)				
BRIEF Global Executive Composite	1.33 (0.18, 2.48)	1.43 (0.29, 2.56)	1.38 (0.25, 2.51)	1.40 (0.25, 2.55)
Behavoiur Regulation Index	0.98 (−0.13, 2.10)	1.13 (0.02, 2.23)	1.08 (−0.02, 2.19)	1.03 (−0.09, 2.16)
BRIEF Metacognition Index	1.37 (0.26, 2.48)	1.42 (0.34, 2.51)	1.39 (0.30, 2.48)	1.46 (0.35, 2.57)
SDQ Total Difficulties	0.51 (−0.12, 1.15)	0.60 (0.02, 1.18)	0.57 (0.00, 1.15)	0.55 (−0.04, 1.14)
Prosocial	0.01 (−0.19, 0.21)	−0.02 (−0.21, 0.18)	−0.02 (−0.21, 0.18)	−0.02 (−0.22, 0.18)
	Teacher rated outcomes			
Acetaminophen during the first year (per category)				
BRIEF Global Executive Composite	0.41 (−0.34, 1.16)	0.66 (−0.04, 1.36)	0.53 (−0.17, 1.23)	0.54 (−0.17, 1.24)
Behavoiur Regulation Index	0.45 (−0.28, 1.17)	0.69 (−0.03, 1.40)	0.56 (−0.16, 1.28)	0.57 (−0.17, 1.31)
BRIEF Metacognition Index	0.35 (−0.44, 1.14)	0.57 (−0.16, 1.31)	0.46 (−0.27, 1.20)	0.46 (−0.28, 1.20)
SDQ Total Difficulties	0.25 (−0.16, 0.65)	0.29 (−0.09, 0.68)	0.22 (−0.17, 0.61)	0.21 (−0.18, 0.61)
Prosocial	0.10 (−0.06, 0.26)	0.10 (−0.06, 0.26)	0.11 (−0.05, 0.27)	0.11 (−0.06, 0.27)
Ibuprofen during the first year (per category)				
BRIEF Global Executive Composite	0.09 (−0.57, 0.75)	0.42 (−0.22, 1.05)	0.38 (−0.25, 1.01)	0.38 (−0.26, 1.02)
Behavoiur Regulation Index	0.17 (−0.45, 0.79)	0.50 (−0.10, 1.09)	0.45 (−0.14, 1.04)	0.45 (−0.14, 1.05)
BRIEF Metacognition Index	0.05 (−0.63, 0.73)	0.34 (−0.33, 1.01)	0.31 (−0.36, 0.97)	0.30 (−0.37, 0.98)

	Parent rated outcomes			
	Model 1	**Model 2**	**Model 3**	**Model 4**
	β (95% confidence interval)			
SDQ Total Difficulties	0.11 (−0.22, 0.45)	0.18 (−0.14, 0.51)	0.15 (−0.17, 0.47)	0.15 (−0.18, 0.47)
Prosocial	−0.01 (−0.13, 0.11)	−0.04 (−0.17, 0.08)	−0.03 (−0.16, 0.09)	−0.04 (−0.16, 0.08)
Acetaminophen during the first year (≥6 versus <6 times)				
BRIEF Global Executive Composite	0.78 (−0.64, 2.19)	1.32 (−0.03, 2.68)	1.08 (−0.27, 2.43)	1.09 (−0.26, 2.45)
Behavoiur Regulation Index	0.78 (−0.68, 2.23)	1.28 (−0.18, 2.75)	1.04 (−0.44, 2.52)	1.05 (−0.46, 2.55)
BRIEF Metacognition Index	0.69 (−0.77, 2.16)	1.21 (−0.16, 2.58)	1.00 (−0.38, 2.37)	1.00 (−0.38, 2.38)
SDQ Total Difficulties	0.48 (−0.35, 1.31)	0.64 (−0.16, 1.43)	0.49 (−0.30, 1.29)	0.48 (−0.32, 1.29)
Prosocial	0.13 (−0.19, 0.45)	0.12 (−0.20, 0.43)	0.14 (−0.18, 0.45)	0.12 (−0.20, 0.45)
Ibuprofen during the first year (≥6 versus <6 times)				
BRIEF Global Executive Composite	0.32 (−1.20, 1.84)	0.97 (−0.48, 2.43)	0.92 (−0.53, 2.37)	0.92 (−0.54, 2.38)
Behavoiur Regulation Index	0.35 (−1.10, 1.80)	0.96 (−0.42, 2.34)	0.90 (−0.47, 2.26)	0.90 (−0.48, 2.28)
BRIEF Metacognition Index	0.33 (−1.24, 1.90)	0.93 (−0.60, 2.47)	0.89 (−0.64, 2.42)	0.89 (−0.65, 2.43)
SDQ Total Difficulties	0.32 (−0.46, 1.11)	0.48 (−0.27, 1.24)	0.44 (−0.31, 1.19)	0.43 (−0.34, 1.19)
Prosocial	0.03 (−0.25, 0.31)	−0.05 (−0.33, 0.24)	−0.03 (−0.31, 0.25)	−0.05 (−0.33, 0.24)

Model 1. Unadjusted

Model 2. Adjusted for maternal age, education, smoking, and parity; household income and HOME score; and child age, sex, race/ethnicity, gestational age and birthweight for gestational age z-score

Model 3. Model 2 additionally adjusted for maternal pregnancy acetaminophen or ibuprofen (same analgesic as exposure)

Model 4. Model 3 additionally adjusted for respiratory tract infections first year of life