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Maternal Acetaminophen Use during Pregnancy and Childhood Behavioral Problems: Discrepancies between Mother and Teacher Reported Outcomes

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Abstract

Background: Maternal acetaminophen use during pregnancy is common and has been associated with childhood behavioral problems among offspring, specifically hyperactivity and conduct problems.

Objective: Assessments of child behavior in many previous studies have relied on maternal or parent report. Acknowledging that results of behavioral assessments vary between informants, we examined the association between maternal acetaminophen use during pregnancy and behavior problems in childhood based on mother and teacher-report.

Methods: A longitudinal study of 560 mother-child pairs with data on illnesses and medication use during pregnancy and neurodevelopmental assessments during childhood was conducted. Acetaminophen use during pregnancy was captured using a standardized maternal interview, completed one year after delivery on average. Measures of childhood (6–12 years of age) behavior were obtained via mother and teacher-report, using the Child Behavior Checklist and Teacher Report Form. Linear and log-binomial models were used to calculate adjusted mean differences (MD) and risk ratios (RR), respectively, and 95% confidence intervals (CI) for internalizing, externalizing, and total behavior problems comparing acetaminophen users to non-users. Stabilized inverse probability weights were used to account for loss to follow-up and adjustments for indication were made.

Results: Approximately 60% (n=354) of women reported use of acetaminophen during pregnancy. Acetaminophen use during pregnancy was associated with an increase in total behavior problem score and risk of clinical behavior problems according to mother-report (MD 2.2, 95% CI 0.3, 4.1; RR 1.93, 95% CI 0.99, 3.76) but not according to teacher-report. Weighting to account for participation did not alter results, while adjustment for indications of acetaminophen use greatly attenuated the associations with mother-reported total behavior problem score and risk of clinical behavior problems (MD 0.1, 95% CI −2.1, 2.3; RR 1.31, 95% CI 0.67, 2.58).

Conclusions: Acetaminophen use during pregnancy was weakly associated with mother-reported behavior problems, and not associated with teacher-reported problems.

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Keywords

acetaminophen; neurodevelopment; prenatal; externalizing; internalizing; behavior

Background

Acetaminophen is one of the most commonly used medications during pregnancy with an estimated 65% of pregnant women in the United States using it at least once.[1] Acetaminophen, an analgesic and antipyretic, is considered an appropriate treatment for headache, fever, and aches and pains during pregnancy.[2] While acetaminophen use in pregnancy has generally not been linked with adverse birth outcomes,[3] there is accruing evidence that prenatal exposure is associated with increased risks of adverse neurodevelopmental outcomes among offspring, particularly attention problems, hyperactivity and conduct problems.[4–11] With many studies suggesting an adverse effect of such a commonly used medication,[12] the focus has shifted to potential biases that might explain these observed associations. The methodologic challenges faced in examining prenatal exposures in relation to childhood neurodevelopment are numerous and include selection bias due to biased retention of participants, dependent misclassification due to maternal report of both exposure and outcome, unmeasured confounding, and lack of specificity and consistency in outcome definitions.[13–15]

The impact of unmeasured confounding on these observed associations has been the most widely investigated using methods such as analyses of negative control exposure windows before and after pregnancy[4,16] and partner's acetaminophen use,[4,11] and sibling-design studies.[10] Based on results from these approaches, confounding alone does not appear to account for the observed associations,[18] although concerns around confounding still exist.[19] There has been less attention given to selection bias due to differential loss to follow up or cohort attrition, with one study employing analytic methods such as weighting.[9]

The role of dependent misclassification has been more challenging to quantify. Dependent error arises in many of these studies due to maternal report of both the exposure and outcome where individual variation in reporting accuracy may occur due to biologic or social reasons.[20] While most studies to date are vulnerable to dependent misclassification,[4–6,8–10,17] some studies have used teachers or psychometrists for behavioral assessments[7,9,21] or registry recorded diagnoses[6,11] to address this potential bias.

The objective of this study is to assess associations between prenatal exposure to acetaminophen and measures of behavioral assessment in childhood and how they differ based on mother and teacher assessments of behavior using an instrument allowing for systematic comparison.

Methods

Data used in this analysis were originally collected as part of a study of risk factors for and sequelae of a craniofacial malformation, hemifacial microsomia. Cases of hemifacial microsomia born between 1996 and 2002 were ascertained from 26 craniofacial centers

across the United States and Canada. Controls were non-malformed children that were matched to cases on birth year and pediatric practice or practices within the same zip code. Mothers of cases and controls were interviewed within 4 years of delivery using a standardized interview to collect information on demographics, reproductive history, diet, illnesses and medication use during pregnancy. Mothers were re-contacted when their child reached 5–6 years of age and invited to participate in the follow-up portion of the study. A battery of neurodevelopmental tests were subsequently administered when children were 6–12 years old. This analysis includes the cohort of 560 singleton control children, or those without a structural malformation, with data on maternal exposures during pregnancy, collected on average 12 months after delivery (interquartile range: 3 – 20 months) and at least one neurodevelopmental assessment in childhood. The controls are expected to represent the general pediatric population. This study was approved by the Institutional Review Board (IRB) at Boston University.

Exposure: Maternal Acetaminophen Use

Data on maternal acetaminophen use were collected using a standardized interview administered after delivery and prior to childhood neurodevelopmental assessments. Mothers were asked about medication use during the six month period beginning one month prior to their last menstrual period through the fifth month of pregnancy at two separate points in the interview. Women were specifically asked about medications used for the treatment of selected indications including upper respiratory infection (cold, flu, and bronchitis), headaches (migraine, sinus, and other), pain or injury, and fever. They were also separately asked about the use of any cough/cold or flu medications and pain and fever drugs. Information on the indication, timing of use, frequency of use, duration, and dose were collected for all medications. If available, women were asked to use the product bottle or package to confirm the exact medication formulation or use a provided medication identification booklet to assist in recall. Although exposure after the fifth month of pregnancy was not explicitly asked about, information on use that extended into this time frame was captured through questions on frequency and duration. All medications, which included over-the-counter and prescription products, were classified using the Slone Drug Dictionary.[22] Women were considered exposed to acetaminophen if they reported taking single component acetaminophen or any combination product containing acetaminophen (e.g. Dayquil®). We categorized acetaminophen use in pregnancy as ‘any’ or ‘none’. We further categorized use based on duration of acetaminophen use during pregnancy, with short-term use defined as < 28 days and long-term use defined as ≥ 28 days (consecutive or non-consecutive) as has been done in previous studies.[10,17]

Outcome: Behavioral Assessment

The Child Behavior Checklist (CBCL) and the Teacher-Report Form (TRF) are easy to administer instruments that are used to assess common child behavior problems. These tests are part of the Achenbach System of Empirically Based Assessment (ASEBA) and allow for systematic comparison of child behavior across informants.[23] Respondents are provided with a list of items and rate each as not true, sometimes true, or often true. Responses to specific items are tallied to provide measures of three composite or ‘broadband’ scales, including externalizing behavior problems (e.g. hyperactive, noncompliant, disruptive),

internalizing behavior problems (e.g. shy, withdrawn, despondent), and total behavior problems. Scores are also derived for specific behavior problem or 'syndrome' scales, including anxious/depressed, withdrawn/depressed, somatic, social, thought, attention, rule-breaking, and aggressive. Higher scores indicate worse behavior. T-scores with a mean value of 50 and standard deviation of 10 are calculated for each scale. The broadband scores can be dichotomized based on a deviant cut point (T > 60), which is equivalent to a 1 SD increase, to reflect scores in the borderline clinical and clinical range. We chose to include the borderline clinical scores, in addition to the clinical scores, since a prior publication of these data showed only 4–7% of this non-clinic population met criteria for the clinical range.[24] The CBCL and TRF have well-established reliability and validity.[23] Sensitivity of the CBCL total problem score in assessing the need for mental health services is estimated to be 78%, while specificity is 67%.[25] For ADHD specific behaviors, parent report has a high sensitivity, while teacher report has a high specificity.[26] Of the 560 children included in this analysis, 556 had a completed CBCL assessment and 494 had a completed TRF assessment.

Statistical Analysis

The distribution of demographic and pregnancy characteristics by any acetaminophen use during pregnancy were calculated among participants in the childhood sample. Unadjusted and adjusted mean differences (MD) and 95% confidence intervals (CI) for the broadband scales and syndrome scales were calculated using linear regression models. Children of mothers reporting no acetaminophen use during pregnancy served as the reference group. For the dichotomized outcomes using deviant cut points (T-scores ≥ 60), we used log-binomial regression models with a Poisson distribution to calculate unadjusted and adjusted risk ratios (RR). Covariates in the adjusted models were selected *a priori* and included maternal age (continuous), race, education, marital status, parity, drinking and smoking during early pregnancy. To account for cohort attrition between the delivery interview and childhood assessment, models were weighted using stabilized inverse probability weights (SIPW). First, inverse probability weights were calculated by fitting a logistic regression model predicting participation using the following covariates: maternal age and paternal age at delivery, maternal race, marital status, maternal education, alcohol drinking, smoking, parity, gravidity, pre-pregnancy body mass index, planned pregnancy, acetaminophen use, headache, and infant sex. To avoid the influence of extreme weights, stabilized weights, which divide the predicted probability of participation by the proportion of mothers that participated instead of 1, were created.[27] Lastly, models were adjusted for four indication categories: headache, fever, pain, and upper respiratory infection without fever, including allergy. Medicated depression and anxiety was also considered as a potential confounder, but adjustment did not alter associations and was therefore not included in the models.

Sensitivity Analyses

We performed several sensitivity analyses to assess the robustness of our findings. We excluded women reporting only occasional use of acetaminophen (n=94), defined as a frequency of use in the following categories; once per month, occasionally, or 1–6 times during pregnancy. Secondly, we excluded women who were unable to confirm the exact product used through the bottle or booklet (n=57). In a third analysis, to examine associations with single component acetaminophen, women who used multi-component

acetaminophen products (n=105) were excluded. We performed another sensitivity analysis restricted to participants that completed the pregnancy interview within two years of delivery (n=448, 80%). We also restricted the analysis to children with both a completed CBCL and TRF to allow for comparison between the same set of participants (n=489). Lastly, we examined maternal use of ibuprofen, another pain medication that is largely acquired without prescription, which was not associated with childhood behavioral outcomes in some previous studies.[8,10]

Results

Of the 826 mother-child dyads that were eligible for the follow-up study, 560 (68%) were included in this analysis. Participating mothers were more likely to be white non-Hispanic and have higher levels of education than non-participants. They were also slightly more likely to be acetaminophen users (Table 1). Among participants, 63.2% (n=354) of mothers reported acetaminophen use during pregnancy. Acetaminophen users were more likely to be white non-Hispanic compared to non-users (84.2% vs. 60.7%). Users were also more likely to have higher levels of education, be married, drink alcohol in early pregnancy, and have other children. As expected, mothers reporting acetaminophen use were also more likely to report headaches, upper respiratory tract infections, fever, and pain during pregnancy (Table 1).

There was no association between any acetaminophen use during pregnancy and teacher-reported behavioral outcomes during childhood (MD −0.4, 95% CI −2.2, 1.4 [TRF total problems]), while any use was associated with mother-reported behavioral problems (MD 2.2, 95% CI 0.3, 4.1 [CBCL total problems]). Utilizing SIPW to account for differences in characteristics of participants and non-participants at the childhood follow-up, estimates were essentially unchanged, while adjustment for indications attenuated associations with mother-reported outcomes (MD 0.1, 95% CI −2.1, 2.3 [CBCL total problems]). The MD was similar for both internalizing and externalizing broadband scales (Table 2). After SIPW and adjustment for indication, acetaminophen use during pregnancy was not strongly associated with any syndrome scales, although the MD for anxious/depressed behavior on the CBCL was slightly elevated (Table 3).

We examined mother's duration of use as short-term (<28 days) or long-term (≥28 days). Approximately three-fourths of mothers that reported any acetaminophen use during pregnancy were short-term users (n=253, 73%). Compared to short-term users, long-term users were more likely to report pain (22% vs. 15%) and upper respiratory infections (75% vs. 68%). Total behavior problems were associated with short and long term use based on mother-report but MDs remained close to the null for teacher-reported problems. Similar to the primary analysis, weighting did not alter results, while adjustment for indication shifted estimates downwards. Adjustment for indication had the greatest impact on CBCL outcomes for long-term use, reducing mean differences in T-scores to −0.5 for externalizing problems and to 0.1 for total problems (Table 4).

Using a dichotomous outcome measure, up to 12.9% and 12.7% of children were classified as borderline clinical or clinical on a broadband scales using the TRF and CBCL,

respectively. Again, elevated risk ratios for acetaminophen use and behavior problems on the CBCL were attenuated after adjustment for indication (RRs 1.26 and 1.31 for externalizing and total problems, respectively).

Sensitivity Analyses

Approximately a quarter of mothers reporting acetaminophen use during pregnancy were occasional users. Removing these women from analyses shifted mean differences downward slightly, with the exception of externalizing behavior on the CBCL, which increased from MD 0.3 (95% CI −1.7, 2.4) to MD 0.6 (95% CI −1.6, 2.8). Restrictions to acetaminophen exposure confirmed through bottle or booklet and single component acetaminophen resulted in similar findings as the primary analysis. Analyses restricted to the 80% of participants that completed the pregnancy interview within two years of delivery showed a stronger associations between acetaminophen use and mother-reported outcomes. Analyses restricted to children with both a completed CBCL and TRF yielded results similar to the primary analysis. Lastly, among the 560 mothers included in this study, 52 (9.3%) reported use of ibuprofen, nearly half of which were also acetaminophen users (n=21). Use of ibuprofen during pregnancy was not associated with higher scores on either the TRF or CBCL. (Table 6)

Comment

Principal findings—The primary aim of this analysis was to examine the association between acetaminophen use during pregnancy and behavioral outcomes in offspring according to two separate informants, namely mother and teacher, using an assessment tool allowing for a systematic comparison. Associations between acetaminophen use during pregnancy and childhood behavior scores were stronger when using mother-report of the outcome than teacher-report. Associations between acetaminophen use during pregnancy and childhood behavior problems according to teacher-report were generally null. This finding is similar to one other study that obtained executive function measures using an instrument designed for both parent- and teacher-report, which demonstrated acetaminophen use was associated with poorer scores when parent-rated compared to when teacher-rated. The discrepancy in findings according to reporter raises the possibility of dependent misclassification because exposure is reported by the mother. Of note, associations for mother-reported outcomes were attenuated after controlling for illness (also mother-reported), but no confounding of the teacher-reported outcomes was observed.

Strengths of the study

Strengths of our analysis include weighting to account for loss to follow up and adjustment for common indications of acetaminophen use, which were collected on all participants. Weighting did not appreciably change the results, while adjustment for indication, including headache, upper respiratory infection, fever, and pain, weakened these observations. Adjustment for many potential confounders, including fever and infection/inflammation, has also attenuated results in another study.[6] Other strengths include detailed exposure assessment, albeit retrospective, and the use of a reliable and valid behavior assessment tool.

Limitations of the data

While our study generated interesting findings regarding the role of informant in the association between acetaminophen and behavioral problems, some limitations should be noted. First, the data used in this analysis were originally collected to investigate pregnancy and reproductive risk factors for a malformation. Therefore, acetaminophen exposure was based on a retrospective, self-report measure that focused specifically on the first 5 months of pregnancy. While we did not ask specifically about use initiated in late pregnancy, we were able to capture use extending into this period through questions on duration and frequency. Approximately 60% of women in our study reported acetaminophen use during pregnancy, which is similar to the exposure prevalence of acetaminophen use in many birth cohorts in which data were collected prospectively.[4–6,10] The interval between maternal interview and delivery was as long as three years for some participants, but it was within two years of delivery for 80% of the sample. Accuracy of medication reporting is presumed to be better for women with shorter intervals; the stronger associations for such women between acetaminophen use and mother-reported outcomes might be considered a more valid estimate of effect. However, we continued to observe no association for teacher-reported outcomes, raising the possibility that dependent misclassification may be most apparent in women with short interview intervals. Secondly, we lacked data on some potential confounders, particularly those related to maternal stress, IQ, and behavioral problems.

Interpretation

In clinical practice, it is known that child functioning can vary between contexts and interactions and therefore a multi-informant assessment is necessary to obtain a complete picture of childhood behavior. One informant is not necessarily more accurate, but the parallel assessments allow for identification of consistencies and inconsistencies which are important in determining diagnoses and treatment.[28] Our study utilized a continuous outcome measure in a non-clinic sample and examined mean differences across the distribution of T-scores, which represents the entire spectrum of child behavior, and does not align with a specific or standardized diagnosis. Using a one standard deviation cutoff to include the borderline and clinical range of scores,[23] up to 13% of our sample fell within this range, which is in line with an expected 16% assuming a normal distribution of this non-clinic based sample. Conclusions using the dichotomous outcome measure were somewhat stronger compared to the continuous outcome results, showing that any acetaminophen use was associated with a 30% increased risk of externalizing and total behavior problems for mother-reported outcomes, even after adjustment for indication, however associationsfor teacher-reported problems remained essentially null. These findings are comparable in magnitude to other studies using a dichotomous outcome measure of total difficulties on the parent-reported SDQ.[4,6,8] Upon examination of specific syndrome scales, mean differences for acetaminophen use were only elevated for anxious/depressed behavior reported on the CBCL. In contrast to other studies, we did not observe increases in attention-related behavior problems on the continuous scale according to mother or teacher-report, but did observe an increase in mother-reported borderline/clinical externalizing behavior.

The possibility that associations between acetaminophen use during pregnancy and mother-reported behavior problems observed in our study might stem from misclassification is

worth considering. Dependent misclassification of exposure and outcome arises when collection of these variables relies on the same reporter, i.e. maternal report of exposure and outcome.[20] Maternal personality traits, such as social desirability or negative affect, may lead to systematic over- or under-reporting of both exposure and outcome. Studies that have examined discrepancies between parent and teacher reports on childhood behavior have identified parental stress[29] and socioeconomic indicators [30] as important predictors of discrepancies. Such discrepancies in reporting are known to be greater among non-clinical populations, with higher scores generally recorded on the CBCL than the TRF.[31] With respect to ADHD specifically, discrepancies are due to parents observing different ADHD behaviors, some observations of which are valid and some biased.[32] Specific maternal personality traits, such as extraversion, less conscientiousness, and impulsivity, have also been associated with acetaminophen use during pregnancy.[33] If such specific personality traits also lead to systematic over-reporting or under-reporting of exposure and outcome, bias due to the dependent misclassification would result. Our findings, in conjunction with a prior study,[9] demonstrate that measures of association obtained from epidemiologic studies examining acetaminophen use and child behavior can be influenced by the informant reporting the outcomes.

In our study, indication categories of headache, upper respiratory infection, fever, and pain, were more strongly associated with mother-reported behavioral outcomes than teacher-reported ones. In a prior analysis of these data examining upper respiratory infection and behavioral outcomes, we showed stronger associations with CBCL scores than TRF scores. [24] That reported indication is more strongly associated with mother-reported than teacher-reported outcomes is consistent with dependent misclassification, although the role of dependent error when relying on the same reporter for confounder information as well is less clear.

Several studies of prenatal acetaminophen exposure and attention and hyperactivity behaviors have used informants other than mothers or parents. One of the first studies used psychometrists to conduct assessments of child behavior and observed no association between acetaminophen use and attention scores.[21] More recently, a Spanish study using teacher report of ADHD symptomatology reported an increased association between acetaminophen use during pregnancy and total ADHD symptom scores (IRR 1.25, 95% CI 0.93, 1.69).[7] Registry based studies have reported acetaminophen associated increases in risk of 12% for ADHD and 37% for hyperkinetic disorder, respectively.[6,11] The aforementioned studies all relied on maternal report of acetaminophen. It is worth noting that registry-based diagnoses might also be vulnerable to maternal reporting bias, if maternal personality traits influence seeking evaluation of their child.

While the role of maternal personality and psychiatric morbidities as it relates to the potential for dependent misclassification mechanisms has not been elucidated, there has been much more focus on these variables as they relate to confounding. For example in studies using negative control exposures, such as postnatal use or partner's use, if no association is reported for the negative control exposure, the estimates for prenatal exposures are concluded to be unconfounded.[4] Similarly, if associations are observed with the negative control exposure, unmeasured or residual confounding of maternal pregnancy exposures and

outcome is suspected. Alternatively, associations observed between postnatal acetaminophen use and childhood behavior could be a result of dependent misclassification. Medications used for similar indications might be subject to the same pattern of bias. Our results for ibuprofen use do not support a dependent misclassification mechanism, since we did not observe an increase in behavior problems according to either mother or teacher-report, although these findings were based on 52 exposed mothers. Additionally, compared to acetaminophen users, ibuprofen users were more likely to be smokers (19% vs. 14%) and also had a different pattern of medication use with a median use of 3 times compared to 7 times, indicating that the profile of ibuprofen users is different, as may be their propensity for over- or under-reporting exposure and outcome measures. Our ibuprofen findings were consistent with two previous reports in which NSAID use was associated with smaller or no associations with childhood behaviors [8,10] Interestingly, a study dating back to the mid-1970s when aspirin use was more common and accepted than acetaminophen use, showed aspirin was associated with decrements in attention, but acetaminophen was not.[21]

Conclusions

In conclusion, acetaminophen use during pregnancy was weakly associated with mother-reported behavior problems, and not associated with teacher-reported problems. Given the multi-informant assessment required to actually diagnose conditions such as ADHD, future studies aimed at investigating this association should employ rigorous assessments to improve sensitivity and specificity of exposure and outcome measurements.

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Synopsis

Study question:

Does maternal use of acetaminophen during pregnancy affect measures of childhood behavior, specifically internalizing and externalizing problems, according to mother or teacher-report?

What's already known:

Prenatal exposure to acetaminophen has previously been linked with increased risks of childhood behavior problems, specifically hyperactivity, conduct problems, and attention problems, in many epidemiologic studies.

What this study adds:

Associations between maternal acetaminophen use during pregnancy and behavior problems during childhood among offspring may differ depending on the informant completing the behavior assessment. Maternal use of acetaminophen during pregnancy was associated with childhood behavioral problems according to mother-report only and attenuated by adjustment for indication.

Social Media Quote

Observed associations between prenatal acetaminophen exposure and childhood behavior problems were informant dependent, with associations observed with mother-reported measures of behavior but not with teacher-reported measures of behavior.

Samantha Parker: @SamParkerPhD

Martha Werler: @MarthaWerler

Table 1.

Characteristics of Eligible Controls, Participants at Childhood Behavioral Assessment, and by Acetaminophen Use during Pregnancy.

	Eligible Controls n=826		**Childhood Respondents n=560**					
			Total		**Acetaminophen Users (n=354)**		**Non-Users (n=206)**	
Race/Ethnicity	n	%	n	%	n	%	n	%
White, non-Hispanic	540	65.4	423	75.5	298	84.2	125	60.7
Black, non-Hispanic	161	19.5	67	12.0	25	7.1	42	20.4
Hispanic	87	10.5	48	8.6	22	6.2	26	12.6
Other	38	4.6	22	3.9	9	2.5	13	6.3
Age at conception								
≤25	260	31.5	140	25.0	78	22.0	62	30.1
26–34	441	53.4	326	58.2	213	60.2	113	54.9
≥35	125	15.1	94	16.8	63	17.8	31	15.0
Education								
≤12 years	323	39.1	170	30.4	95	26.8	75	36.4
13–15 years	186	22.5	133	23.8	90	25.4	43	20.9
≥16 years	316	38.3	256	45.7	169	47.7	87	42.2
Marital status								
Married	722	87.4	498	88.9	320	90.4	178	86.4
Single/Divorced	104	12.6	62	11.1	34	9.6	28	13.6
Body Mass Index								
< 18.5	30	3.6	19	3.4	12	3.4	7	3.4
18.5–24.9	509	61.6	350	62.9	226	63.8	124	60.2
25–29.9	165	20.0	115	20.5	71	20.1	44	21.4
≥30	98	11.9	68	12.1	44	12.4	24	11.7
Missing	24	2.9	8	1.4	1	0.0	7	3.4
Alcohol drinking	241	29.2	190	33.9	129	36.4	61	29.6
Smoking	114	13.8	77	13.8	51	14.4	26	12.6
Parity								
0	358	43.3	245	43.8	144	40.7	101	49.0
1	291	35.2	196	35.0	127	35.9	69	33.5
2+	177	21.4	119	21.3	83	23.4	36	17.5
Infant Sex								
Male	423	51.2	279	49.8	176	49.7	103	50.0
Female	403	48.8	281	50.2	178	50.3	103	50.0

	Eligible Controls n=826		Childhood Respondents n=560					
			Total		Acetaminophen Users (n=354)		Non-Users (n=206)	
Indication								
Headache	460	55.7	318	56.8	266	75.1	52	25.2
Upper respiratory infection without fever	406	49.2	294	52.5	202	57.1	92	44.7
Fever	73	8.8	55	9.8	46	13.0	9	4.4
Pain	112	13.6	81	14.5	60	16.9	21	10.2
Medicated Depression and/or Anxiety	28	3.4	21	3.8	18	5.1	3	1.5
Acetaminophen								
Any	487	59.0	354	63.2				
None	339	41.0	206	36.8				

Table 2.

Adjusted and Weighted Mean Differences for the Acetaminophen Use during Pregnancy and Behavioral Outcome Broadband Scales, Childhood Assessment, Teacher and Mother Report, T-Scores

	Mean Differences and 95% Confidence Intervals		
	Adjusted[a]	**SIPW**[b]	**Indication Adjusted**[c]
Teacher Report Form	n=493	n=493	n=493
Internalizing	−0.1 (−1.8, 1.5)	−0.3 (−2.0, 1.3)	−1.0 (−3.0, 0.9)
Externalizing	0.4 (−1.2, 1.9)	0.2 (−1.4, 1.7)	−0.4 (−2.2, 1.4)
Total Problems	−0.4 (−2.2, 1.4)	−0.5 (−2.3, 1.3)	−1.1 (−3.2, 1.0)
Child Behavior Checklist	n=555	n=555	n=555
Internalizing	2.5 (0.8, 4.3)	2.3 (−0.5, 4.1)	0.2 (−1.9, 2.2)
Externalizing	1.9 (0.1, 3.7)	2.0 (−0.2, 3.7)	0.3 (−1.7, 2.4)
Total Problems	2.2 (0.3, 4.1)	2.3 (−0.4, 4.2)	0.1 (−2.1, 2.3)

[a] adjusted for maternal age, race, education, marital status, smoking, drinking, and parity

[b] weighted by SIPW (stabilized inverse probability weights), c-statistic 0.73, weights range from 0.47–3.8

[c] additionally adjusted for indication/illness (headache, upper respiratory infection, fever, pain)

Table 3.

Adjusted and Weighted Mean Differences for the Acetaminophen Use during Pregnancy and Behavioral Outcome Syndrome Scales, Childhood Assessment, Teacher and Mother Report, T-Scores

	Mean Differences and 95% Confidence Intervals		
	Adjusted[a]	**SIPW**[b]	**Indication Adjusted**[c]
Teacher Report Form	n=493	n=493	n=493
Anxious/Depressed	−0.3 (−1.3, 0.7)	−0.4 (−1.3, 0.6)	−0.9 (−2.0, 0.2)
Withdrawn/Depressed	−0.4 (−1.2, 0.5)	−0.4 (−1.2, 0.5)	−0.8 (−1.8, 0.2)
Somatic Complaints	0.2 (−0.7, 1.2)	0.1 (−0.8, 1.1)	−0.3 (−1.4, 0.8)
Social Problems	−0.5 (−1.5, 0.4)	−0.6 (−1.6, 0.4)	−1.1 (−2.2, 0.0)
Thought Problems	0.1 (−0.9, 1.1)	−0.2 (−1.1, −.8)	−0.6 (−1.8, 0.5)
Attention Problems	−0.4 (−1.4, 0.7)	−0.4 (−1.4, 0.7)	−0.7 (−1.9, 0.5)
Rule-Breaking Behavior	0.1 (−0.8, 1.1)	0.0 (−0.9, 1.0)	−0.4 (−1.6, 0.7)
Aggressive Behavior	0.3 (−0.7, 1.3)	0.2 (−0.9, 1.2)	−0.3 (−1.5, 0.9)
Child Behavior Checklist	n=555	n=555	n=555
Anxious/Depressed	1.9 (−0.9, 2.9)	1.6 (0.6, 2.6)	0.6 (−0.6, 1.8)
Withdrawn/Depressed	0.5 (−0.3, 1.3)	0.4 (−0.5, 1.3)	−0.4 (−1.4, 0.6)
Somatic Complaints	1.2 (0.2, 2.2)	0.9 (−0.1, 1.9)	0.1 (−1.3, 1.1)
Social Problems	0.3 (−0.6, 1.1)	0.2 (−0.6, 1.1)	−0.3 (−1.4, 0.7)
Thought Problems	0.7 (−0.3, 1.7)	0.7 (−0.3, 1.7)	−0.1 (−1.3, 1.1)
Attention Problems	0.0 (−1.0, 1.0)	0.1 (0.9, 1.1)	−0.9 (−2.0, 0.2)
Rule-Breaking Behavior	0.9 (0.1, 1.8)	0.8 (−0.1, 1.6)	−0.1 (−1.0, 0.9)
Aggressive Behavior	1.1 (0.1, 2.1)	1.0 (0.0, 2.0)	0.1 (−1.1, 1.3)

[a] adjusted for maternal age, race, education, marital status, smoking, drinking, and parity

[b] weighted by SIPW (stabilized inverse probability weights), c-statistic 0.73, weights range from 0.47–3.8

[c] additionally adjusted for indication/illness (headache, upper respiratory infection, fever, pain)

Table 4.

Adjusted and Weighted Mean Differences for Frequency of Acetaminophen Use during Pregnancy and Behavioral Outcomes, Childhood Assessment, Teacher and Mother Report, T-Scores

	Mean Differences and 95% Confidence Intervals					
	Short-Term (< 28 Uses) n=253			Long-Term (≥ 28 Uses) n=94		
	Adjusted[a]	SIPW[b]	Indication Adjusted[c]	Adjusted[a]	SIPW[b]	Indication Adjusted[c]
Teacher Report Form						
Internalizing	0.1 (−1.7, 1.9)	−0.1 (−1.9, 1.7)	−0.8 (−2.9, 1.2)	−0.9 (−1.7, 1.9)	−1.1 (−3.6, 1.3)	−2.0 (−4.7, 0.7)
Externalizing	0.2 (−1.5, 1.8)	0.0 (−1.7, 1.7)	−0.5 (−2.4, 1.4)	1.0 (−1.2, 3.2)	0.7 (−1.6, 3.0)	0.0 (−2.5, 2.5)
Total Problems	−0.2 (−2.1, 1.7)	−0.2 (−2.2, 1.7)	−0.8 (−3.0, 1.4)	−0.9 (−3.5, 1.6)	−1.3 (−4.0, 1.4)	−2.1 (−5.0, 0.8)
Child Behavior Checklist						
Internalizing	2.2 (0.3, 4.0)	2.1 (0.2, 3.9)	0.1 (−2.0, 2.2)	3.2 (0.7, 5.7)	2.8 (0.2, 5.4)	0.3 (−2.5, 3.1)
Externalizing	2.1 (0.2, 3.9)	2.1 (0.2, 4.0)	0.6 (−1.6, 2.7)	1.6 (−0.9, 4.1)	1.6 (−1.0, 4.2)	−0.5 (−3.3, 2.4)
Total Problems	2.0 (0.0, 4.0)	2.2 (0.1, 4.2)	0.1 (−2.2, 2.4)	2.8 (0.1, 5.5)	2.8 (0.0, 5.6)	0.1 (−3.0, 3.1)

[a] adjusted for maternal age, race, education, marital status, smoking, drinking, and parity

[b] weighted by SIPW (stabilized inverse probability weights), c-statistic 0.73, weights range from 0.47–3.8

[c] additionally adjusted for indication (headache, upper respiratory infection, fever, pain)

Table 5.

Adjusted and Weighted Risk Ratios for Acetaminophen Use During Pregnancy and Clinical Behavioral Outcomes, Childhood Assessment

	Percent in Clinical Range[a]	Risk Ratios and 95% Confidence Intervals		
	n (%)	Adjusted[b]	SIPW[c]	Indication Adjusted[d]
Teacher Report Form				
Internalizing	57 (10.2)	0.80 (0.44, 1.45)	1.08 (0.62, 1.88)	0.86 (0.48, 1.56)
Externalizing	54 (9.6)	1.00 (0.56, 1.78)	0.99 (0.59, 1.67)	0.90 (0.50, 1.62)
Total Problems	72 (12.9)	0.82 (0.48, 1.43)	1.03 (0.65, 1.64)	0.84 (0.48, 1.47)
Missing TRF	66			
Child Behavior Checklist				
Internalizing	71 (12.7)	1.52 (0.85, 2.70)	1.46 (0.93, 2.31)	1.04 (0.61, 1.81)
Externalizing	68 (12.1)	1.60 (0.91, 2.81)	1.61 (0.96, 2.69)	1.26 (0.71, 2.22)
Total Problems	63 (11.3)	1.93 (0.99, 3.76)	1.77 (1.03, 3.06)	1.31 (0.67, 2.58)
Missing CBCL	4			

[a] number and percentage of subjects meeting clinical definition for behavioral problems using a t-score cutoff of 60

[b] adjusted for maternal age, race, education, marital status, smoking, drinking, and parity

[c] weighted by SIPW (stabilized inverse probability weights), c-statistic 0.73, weights range from 0.47–3.8

[d] additionally adjusted for indication (headache, upper respiratory infection, fever, pain)

Table 6.

Sensitivity Analyses. Adjusted and Weighted Mean Differences for Acetaminophen Use and Behavioral Outcomes.

	Mean Differences and 95% Confidence Intervals						
	Primary Analysis	**Removing Occasional Users[a]**	**Confirmed Use by Bottle or Booklet[b]**	**Single Component Acetaminophen[c]**	**Pregnancy interview completed within 2 years[d]**	**Completed CBCL and TRF**	**Ibuprofen Exposure[e]**
Teacher Report Form	n=493	n=408	n=444	n=399	n=394	n=489	n=493
Internalizing	−1.0 (−3.0, 0.9)	−1.9 (−4.1, 0.2)	−0.8 (−2.8, 1.3)	−0.7 (−2.9, 1.4)	−1.5 (−3.7, 0.8)	−0.9 (−2.8, 1.1)	−2.6 (−5.5, 0.3)
Externalizing	−0.4 (−2.2, 1.4)	−0.4 (−2.4, 1.5)	−0.2 (−2.2, 1.7)	−0.7 (−2.6, 1.2)	0.1 (−2.0, 2.1)	−0.4 (−2.2, 1.5)	−1.0 (−3.7, 1.7)
Total Problems	−1.1 (−3.2, 1.0)	−1.9 (−4.2, 0.4)	−0.9 (−3.2, 1.3)	−1.4 (−3.7, 0.8)	−1.1 (−3.6, 1.3)	−1.0 (−3.1, 1.1)	−1.5 (−4.7, 1.6)
Child Behavior Checklist	n=555	n=461	n=498	n=450	n=445	n=489	n=555
Internalizing	0.2 (−1.9, 2.2)	0.1 (−2.1, 2.3)	0.3 (−1.8, 2.5)	0.1 (−2.0, 2.2)	0.9 (−1.4, 3.2)	0.1 (−2.1, 2.3)	−1.8 (−4.7, 1.2)
Externalizing	0.3 (−1.7, 2.4)	0.6 (−1.6, 2.8)	−0.2 (−2.4, 2.2)	0.0 (−2.2, 2.2)	0.7 (−1.6, 3.0)	0.0 (−2.1, 2.2)	−1.0 (−4.0, 1.9
Total Problems	0.1 (−2.1, 2.3)	0.1 (−2.3, 2.4)	−0.1 (−2.4, 2.2)	−0.2 (−2.6, 2.2)	1.1 (−1.5, 3.4)	−0.3 (−2.6, 2.0)	−0.4 (−3.6, 2.8)

All models adjusted for maternal age, race, education, marital status, smoking, drinking, parity, and indication (headache, URI, fever, pain) and weighted by stabilized inverse probability weights.

[a] Occasional use defined as frequency of once per month, occasionally, or 1–6 times during pregnancy; 260 exposed and 206 unexposed

[b] Restricted to confirmed, by bottle or booklet, exposures 297 exposed and 206 unexposed

[c] Restricted to single component acetaminophen, 249 exposed and 206 unexposed

[d] Restricted to pregnancy interviews completed within two years of delivery, 288 exposed, 160 unexposed

[e] 52 exposed to ibuprofen