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Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood

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Abstract

Background: Over-the-counter analgesic use during pregnancy, particularly acetaminophen, may be associated with negative developmental outcomes in children.

Objective: Estimate associations of prenatal and early-life exposure to acetaminophen in early childhood with cognitive, motor, and language skills in two birth cohorts.

Methods: The American Project Viva cohort (1217 mother-child pairs enrolled 1999-2002) assessed cognition at approximately 3 years using the Peabody Picture Vocabulary Test and the Wide Range Achievement of Visual Motor Abilities (WRAVMA). The Brazilian 2015 Pelotas Birth Cohort (3818 mother-child pairs) assessed cognition at 2 years using the INTERGROWTH-21st Neurodevelopment Assessment. We used linear regression to estimate associations of acetaminophen use during pregnancy (Project Viva and Pelotas) and infancy (Project Viva) with children's cognitive scores adjusted for maternal age, pre-pregnancy body mass index, education, parity, race/ethnicity, smoking and alcohol use during pregnancy, depression during pregnancy, antibiotic and ibuprofen use during pregnancy, household income, and child's sex.

Results: In Project Viva, exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy was associated with lower WRAVMA drawing scores (β −1.51, 95% CI −2.92, −0.10). However, in Pelotas, exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy was not associated with INTER-NDA motor scores (β 0.02; 95% CI −0.05, 0.09) and was associated with higher INTER-NDA total scores (β 0.08, 95% CI 0.01, 0.16). Other comparisons did not show evidence for any associations.

Conclusions: Inconsistencies and lack of specificity of the findings did not clarify the research question considering that we still have a large variability and uncertainty to define the risk or safety in the use of acetaminophen related to cognition in early childhood. More studies using better exposure assessment and better confounding variables are needed to clarify these associations.

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KEYWORDS

acetaminophen, cohort studies, infant, neurodevelopmental disorders, pregnancy

1 | BACKGROUND

Over-the-counter medications used to treat common pregnancy-related health problems such as pain are frequently used during pregnancy.[1,2] Acetaminophen is the most common analgesic used during pregnancy.[3]

Recent studies indicate the use of acetaminophen may be negatively associated with child development. These effects may be due to its mechanism of action via brain-derived neurotrophic factor (BDNF), as well as in neurotransmitter systems including serotonergic, dopaminergic, adrenergic, and endogenous endocannabinoids or cyclooxygenase-2.[4] BDNF seems to play a role in mediating external processes such as learning and memory.[5,6]

Long-term acetaminophen exposure during foetal life was associated with poorer gross motor development and communication skills at 3 years[7] and delayed motor milestones and communication problems at 18 months in the Norwegian MoBa cohort.[8] Language delay was observed in 30-month-old girls in the Swedish SELMA cohort.[9] In contrast, no associations of acetaminophen with developmental outcomes (mental and psychomotor) at 1 year were found in the Spanish INMA cohort.[10] The above studies were performed in high-income countries only. Also, there is limited research on the associations of acetaminophen use by the infant in the first year of life with later neurodevelopment.

Our goal was to estimate the associations of prenatal and infant exposure to acetaminophen with early childhood cognition using longitudinal data from children ages 2-3 years in Brazil and the United States.

Synopsis

Study question

To what extent is prenatal and early-life exposure to acetaminophen associated with negative cognitive, motor, and language skills during early childhood?

What is already known

Acetaminophen use during pregnancy may be related to negative developmental outcomes in children, but the evidence is not consistent in existing studies of preschool aged children.

What this study adds

We used two different instruments to evaluate cognition at two to three years of age in a US and a Brazilian cohort. The study explored domains of neurodevelopment that have not previously been studied extensively; however, most of the results were null and the few effects found do not provide strong evidence of a negative association of acetaminophen use with cognition in early childhood.

2 | METHODS

2.1 | Cohort selection

This study uses data from the Project Viva cohort in eastern Massachusetts, United States, and from the 2015 Pelotas Birth Cohort in southern Brazil. Project Viva is a prospective cohort study that recruited pregnant women between 1999 and 2002 from eight urban and suburban practices of Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. All women with single pregnancies, who had intention to remain in the geographical area, were fluent in English and presented by the 22nd week of gestation were eligible to enrol. Interested women were interviewed at the end of the 1st and 2nd trimesters of gestation, and mother-child pairs completed in-person visits in the first days after delivery and in early childhood [mean (SD) 3.3 (0.4) years]. In addition, mothers completed mailed questionnaires 12 months after delivery. Of 2128 live singleton births, this study includes the 1217 mother-child

pairs (57.2%) with information about exposure and outcomes in early childhood. Full details of study procedures can be found in the cohort profile paper.[11] Compared with the 1217 participants in this analysis, the 911 nonparticipants were somewhat less likely to have college-educated mothers (55.1% vs 71.6%) and to have annual household income exceeding $70 000 (54.1% vs 63.5%). The mean maternal age was slightly lower (31.0 vs 32.5 years). Acetaminophen use during pregnancy and gestational age at delivery were similar.

In Pelotas, we recruited pregnant women during antenatal care. This antenatal clinic study enrolled 73.8% of the mothers who subsequently delivered children included in the cohort. Pregnant women answered an initial assessment questionnaire before 16 weeks of gestation and were contacted again at 20 weeks (range 16-24 weeks of gestation) to answer the main assessment questionnaire. All women who gave birth in any of the five maternity hospitals of the city of Pelotas from 1 January to 31 December 2015, and lived in the urban area of the municipality, were invited to participate if they had not already enrolled prenatally. Mothers were interviewed at the hospitals, hours after delivery, using a standardised questionnaire that collected information on the socio-economic and demographic characteristics of the family, maternal reproductive history, pregnancy and delivery characteristics, prenatal medication use, life style, and morbidity. In total, 4275 livebirths were recruited, representing 98.7% of all births in the eligible population. This study used data from prenatal and perinatal components and 24-month follow-ups. The sample analysed includes 3818 mother-child pairs with information about the exposures (prenatal and perinatal) and outcomes at 2 years [mean (SD) 2.0 (0.06)]. More details of the study can be found in the cohort profile paper.[12] Compared with the 3818 participants in this analysis, the 457 nonparticipants were similar in almost all maternal characteristics. Nonparticipants were somewhat less likely to use any acetaminophen in 1st or 2nd trimester (50.0% vs 57.6%), and gestational age at delivery (mean 37.6 weeks vs 38.6 weeks) and birthweight (mean 3060 vs 3183 g) were slightly lower.

2.2 | Ethics approval

In Project Viva, mothers provided written informed consent at recruitment and at each postnatal visit. The Institutional Review Board of Harvard Pilgrim Health Care approved this study protocol. In Pelotas, the Federal University of Pelotas, School of Physical Education Ethics Committee, approved the study protocol at each follow-up visit. All mothers signed a consent form on behalf of themselves and their participating children before being interviewed.

2.3 | Main exposures

In Viva, exposure during pregnancy was defined as "any use in 1st or 2nd trimester" and "any use in 1st and 2nd trimester." In early and mid-pregnancy, mothers were asked to categorize their acetaminophen use *during this pregnancy* for the early pregnancy interview (median 9.9 weeks of gestation, corresponding to the 1st trimester) and *in the past 3 months* for the mid-pregnancy interview (median 27.9 weeks of gestation, corresponding to the 2nd trimester). Responses were categorised as: *never, 1-9 times, or 10 times or more*. The 1-year postpartum questionnaire collected data on the infant's acetaminophen use during the first year of life, categorised as: *never, 1-5 times, 6-10 times, or more than 10 times*. Each dose of acetaminophen was counted as a single administration time. Acetaminophen exposure during the first year was categorised for analysis as *less than 6 times or 6 times or more*.

In Pelotas, women were asked about any medication use during pregnancy at prenatal and perinatal interviews. Then, all drugs used were classified by trimester of use and number of days of use in each trimester. For the present analysis, the following acetaminophen exposures were used: *any use in 1st or 2nd trimester, any use in 1st and 2nd trimester, any use in 1st, 2nd, or 3rd trimester* and *any use in 1st, 2nd, and 3rd trimester*. The Pelotas cohort collected information about infant analgesic use at the 3- and 12-months follow-up interviews, but information was limited to use in the 15 days prior to the interview; therefore, we did not include infant use as an exposure in this analysis as it was not comparable to Project Viva's measures and did not accurate reflect exposure across infancy.

2.4 | Outcomes

Both studies evaluated cognitive development in early childhood, but assessments were done at around three years of age in Project Viva and at two years of age in Pelotas.

In Viva, trained research assistants evaluated children's cognition using the Peabody Picture Vocabulary Test (PPVT-III) and the Wide Range Achievement of Visual Motor Abilities (WRAVMA) either in the child's home or the research office. The PPVT is an age-standardised measure of receptive vocabulary for use in children and adults aged 2.5 years or older.[13] The WRAVMA consists of an age-normed test of visual-motor development. The instrument includes three tests of visual-motor development: visual-spatial (matching test), visual-motor (drawing test), and fine motor skills (pegboard test), which are used to generate a total standard score.[14] PPVT and WRAVMA scores are standardised to have a mean score of 100 and standard deviation of 15 for each population of interest. Higher scores indicate better development.

The Pelotas cohort evaluated children's cognitive development at a 24-month follow-up visit using the INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA).[15] The instrument was administered, mainly at the research clinic and sometimes in the child's home, by interviewers trained by neurodevelopment professionals. Retraining sessions were conducted every three months during the follow-up study. The INTER-NDA has been validated against the Bayley Scale for Infant Development III edition (BSID-III), with good agreement.[16,17] INTER-NDA consists of a combination of observed items as well as items reported by the mother.

It assesses cognitive, motor (fine and gross motor), and language skills (receptive and expressive) and combines them into a measure of total ability (overall results). INTER-NDA scores are z-scores age-standardized within sample to have a mean of 0 and a standard deviation of 1. Higher scores indicate better development.

2.5 | Covariates

In Viva, we derived covariates from a combination of questionnaires and interviews.[11] Data collected included maternal reported age at enrollment, race/ethnicity, education, household income, parity, alcohol intake during pregnancy, smoking status, ibuprofen use during pregnancy, and pre-pregnancy body mass index (BMI, kg/m^2 using mother's self-reported weight and height). We obtained information on antibiotic use from electronic medical records. Mothers provided information on depressive symptoms in mid-pregnancy using the Edinburgh Postpartum Depression Scale (EPDS) (range 0-30 with ≥13 indicating probable depression).[18] We calculated gestational age at birth using information from the last menstrual period, but if the early 2nd trimester ultrasound assessment differed from the calculated gestational age by more than 10 days, we used the ultrasound estimate of gestational age. We collected child sex and birthweight from medical records. We calculated sex-specific birthweight for gestational age z-scores using a US national reference.[19] On a 12-month questionnaire, mothers reported information on child's day care attendance, respiratory tract infections since birth (bronchiolitis, pneumonia, bronchitis, croup, or other respiratory tract infection), and use of ibuprofen ≥6 times in the first year of life. We collected maternal PPVT-III scores at the early childhood visit.

In Pelotas, the following maternal information was collected during hospital interviews: age, education level, self-reported skin colour, and family income (minimum wages). Parity (primipara), any smoking and alcohol intake during pregnancy, prenatal depressive/anxiety symptoms, any antibiotic use during pregnancy, and ibuprofen use during pregnancy were categorized as yes or no. We calculated pre-pregnancy BMI using self-reported weight and height. We recorded newborn sex at birth.

2.6 | Statistical analysis

We first describe both cohorts according to characteristics of mothers and children. We then used linear regression to evaluate the associations of acetaminophen use during pregnancy with children's cognitive scores. We performed unadjusted (model 1) and adjusted analyses (models 2 and 3) and presented effect estimates and 95% confidence intervals from each model. Model 2 was adjusted for maternal age, pre-pregnancy BMI, education, parity, race/ethnicity, smoking and alcohol intake during pregnancy, household income, and child's sex. Model 3 included the same variables from model 2, as well as antibiotic use during pregnancy, depression/anxiety during pregnancy (Pelotas) or depressive symptoms in mid-pregnancy (Viva), and ibuprofen use during pregnancy (same category as exposure). In Viva, we conducted models additionally adjusted for maternal PPVT-III score.

We also examined associations of acetaminophen use in the first year of life of the child with childhood development outcomes in Viva using unadjusted and adjusted linear regression. The first adjusted model (model 2) included maternal age, pre-pregnancy BMI, education, parity, race/ethnicity, smoking and alcohol intake during pregnancy and household income, and child's sex, gestational age, birthweight for gestational age z-score, and day care attendance. Model 3 kept the previous variables and added acetaminophen use during pregnancy (1st or 2nd trimester), respiratory tract infections in the first year, and ibuprofen use by the child in the first year (≥6 or <6 times).

We tested all exposure-outcome associations for multiplicative interaction with child sex. For exposures that presented sex interaction, we also analysed model 3 stratified by sex.

In addition, for Viva, we computed ordinal acetaminophen exposures. First, we assigned each frequency category a numerical value (acetaminophen use in 1st and 2nd trimester: never = 0, 1-9 times = 1, or ≥10 times = 2; acetaminophen use in infancy: never = 0, 1-5 times = 1, 6-10 times = 2, or >10 times = 3). Next, we computed the sum of early plus mid-pregnancy values (possible range 0-4). The effect estimates obtained for these ordinal exposures represent the change in outcome per category increase in acetaminophen.

We performed all statistical analyses using SAS version 9.4 (SAS Institute).

2.6.1 | Missing data

Of 2128 participants in Viva, we included 1217 in the analysis sample with any exposure and outcome data (1198 pregnancy exposure and 1041 infancy exposure) and excluded 911 with no outcome data in early 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 exposures and covariates. Next, among 1217, we ran all models weighted by the inverse of the probability of having early childhood outcomes. We also implemented IPW for all Pelotas models. We did not use multiple imputation because most covariates had <5% missing values. In Project Viva, all covariates had 0%-1% missing values except for depression during pregnancy (11% missing values). In Pelotas, all covariates had 0% missing values except for pre-pregnancy BMI (2.8%) and family income (5.6%).

3 | RESULTS

Compared with women enrolled in Viva, Pelotas participants were slightly younger [mean (SD) 27.1 (6.6) vs 32.5 (5.0) years], with higher pre-pregnancy BMI [25.8 (5.4) vs 24.6 (5.1) kg/m^2], lower levels of education and household income, and fewer women were white

(71.0% vs 73.5%). Smoking during pregnancy was higher in Pelotas (15.8% vs 9.9%), but any alcohol intake was much lower (7.3% vs 68.7%). Mothers from Pelotas were more likely to use antibiotics during pregnancy (43.7% vs 27.3%). In Pelotas, 11.4% self-reported depression or anxiety during pregnancy and in Viva 8.3% had probable depression during pregnancy. The mean (SD) child age at outcome in Viva was 3.3 (0.4) years and in the Pelotas cohort 2.0 (0.06) years (Table 1).

In Viva, any use of acetaminophen during 1st or 2nd trimester was reported by 69.9% of the mothers and any use in both trimesters (1st and 2nd trimesters) was reported by 41.3% of the mothers. During the first year of life, 67.4% of infants used acetaminophen ≥6 times (Table 1). The characteristics of Viva participants according to each exposure analysed are described in Table S1.

In Pelotas, 57.6% per cent of mothers reported any use of acetaminophen during 1st or 2nd trimester, 33.4% during both trimesters, 64.7% during 1st, 2nd, or 3rd trimester, and 20.3% during all trimesters (Table 1). The characteristics of the Pelotas participants according to each exposure are described in Table S2.

In both cohorts, women who used acetaminophen in the 1st or 2nd trimester (vs non-users) were less likely to be primipara and more likely to be white, depressed during pregnancy and to use antibiotics during pregnancy. However, in Viva, acetaminophen use was not associated with education (71.0% v. 74.0% college graduate) or household income (62.9% v. 65.5%>$70,000/year) whereas in Pelotas, acetaminophen use was associated with higher education level (32.6% v. 28.4% 12 + years) and higher household income (7.3% v. 5.4% minimum wages >10) (Tables S1 and S2). In both cohorts, higher education and income were associated with higher cognition scores.

Table 2 shows associations of acetaminophen use during pregnancy with early childhood cognitive outcomes in Viva and Pelotas. In Viva, exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy was associated with lower WRAVMA drawing scores. Unadjusted and adjusted results were similar (model 3: β −1.51, 95% CI −2.92, −0.10). The result was similar after additional adjustment for mother´s PPVT at 3 years. The ordinal acetaminophen exposure was also associated with lower WRVMA drawing scores (model 3: β −0.56 per category increase, 95% CI −1.13, 0.01). No other associations were found considering other categories of exposure to acetaminophen and other outcomes. There was no evidence of statistically significant interaction by child sex in Viva (data not shown).

In Pelotas, any use of acetaminophen in 1st and 2nd trimesters, or in all trimesters of pregnancy, was associated with higher INTER-NDA total scores. Unadjusted and adjusted results were similar (Table 2). In model 3, β (95% CI) was 0.08 (0.01, 0.16) for acetaminophen use in both the 1st and 2nd trimester and 0.10 (0.01, 0.18) for acetaminophen use in all trimesters. A few outcomes were more strongly associated with acetaminophen use among girls compared to boys (Table S3). For example, exposure to acetaminophen in the 1st or 2nd trimester was associated with higher INTER-NDA total scores among girls (β 0.13, 95% CI 0.04, 0.23) but was null among boys (β −0.01, 95% CI −0.10, 0.09). The mean (SD) and median (range) of the INTER-NDA total z-score was 0.10 (1.00) and 0.23 (−6.49 to 2.89) among girls and −0.09 (0.99) and 0.02 (−7.47 to 2.32) among boys.

In Viva, infancy exposure to acetaminophen in the first year of life, explored as an ordinal or a dichotomous variable, was not associated with any outcome (Table 3).

4 | COMMENT

4.1 | Principal findings

In this study, we evaluated associations of acetaminophen use during pregnancy in the US-based Project Viva cohort and in the Brazilian 2015 Pelotas Birth Cohort with cognitive outcomes at two to three years of age. We also explored associations of acetaminophen use during the first year of life among children from Viva.

Overall, results do not provide strong evidence for a relationship between acetaminophen intake during pregnancy and cognitive outcomes during the preschool years. While exposure to acetaminophen during both 1st and 2nd trimesters was associated with somewhat lower scores on one of the five outcomes in Viva, other exposure/outcome combinations were null. In Pelotas, a small protective effect was observed.

4.2 | Strengths of the study

Using tests that measured cognition and motor function, this study focused on domains of neurodevelopment that have not previously been studied extensively in relation to prenatal exposure to acetaminophen. Further, few studies have evaluated infancy exposure.

We used different instruments to measure cognitive development in Viva and Pelotas, although both cohorts measured the same domains (vocabulary and motor skills). We used the same analytic methods across cohorts and present results from two high-quality studies using data collected prospectively. Heterogeneity between studies can be explored as different structures of confounding, considering that one cohort was carried out in a developing country using a representative sample of a southern Brazilian city (Pelotas) and the other included participants from a developed country, the United States (Viva).

4.3 | Limitations of the data

This study should be interpreted in the context of several limitations. The first concerns the differences in the outcomes in Pelotas and Viva cohorts. Because we used different developmental tests at somewhat different ages, it is challenging to be sure about the consistency of the findings. The second is related to the differences in the exposures. For Viva, exposure for only the 1st and 2nd trimesters was available, while in Pelotas there was information on use

TABLE 1 Participant characteristics (mean and SD or N and %) among mother-child pairs in Project Viva and in 2015 Pelotas Birth Cohort

Project viva (N = 1217)		Pelotas cohort (N = 3818)	
Maternal characteristics		Maternal characteristics	
Age at enrollment (years)	32.5 (5.0)	Age at enrollment (years)	27.1 (6.6)
Pre-pregnancy BMI (kg/m^2)	24.6 (5.1)	Pre-pregnancy BMI (kg/m^2)	25.8 (5.4)
PPVT score at 3 years (points)	106.1 (14.6)		
Primipara, %		Primipara, %	
No	638 (52.4)	No	1897 (49.7)
Yes	579 (47.6)	Yes	1919 (50.3)
College degree or beyond, %		Education level, years, %	
No	345 (28.4)	0-4	322 (8.4)
Yes	871 (71.6)	5-8	986 (25.8)
		9-11	1332 (35.0)
		12+	1177 (30.8)
Race/ethnicity, %		Skin colour, %	
Black	144 (11.8)	White	2705 (71.0)
Hispanic	67 (5.5)	Black	600 (15.7)
White	894 (73.6)	Other	507 (13.3)
Other	111 (9.1)		
Smoking status, %		Smoked during pregnancy, %	
Never	839 (69.1)	No	3213 (84.2)
Former	255 (21.0)	Yes	603 (15.8)
During pregnancy	120 (9.9)		
Any alcohol intake during pregnancy, %		Any alcohol intake during pregnancy, %	
No	376 (31.3)	No	3537 (92.7)
Yes	826 (68.7)	Yes	278 (7.3)
Antibiotics during pregnancy, %		Antibiotics during pregnancy, %	
No	885 (72.7)	No	2148 (56.3)
Yes	332 (27.3)	Yes	1670 (43.7)
Depressed during pregnancy, %		Depression or anxiety during pregnancy, %	
No	979 (91.7)	No	3383 (88.6)
Yes	89 (8.3)	Yes	434 (11.4)
Household income>$70,000/year, %		Family income (minimum wages), %	
No	437 (36.5)	≤1	432 (12.0)
Yes	761 (63.5)	>1-3	1700 (47.2)
		>3-6	966 (26.8)
		>6-10	271 (7.5)
		>10	234 (6.5)
Ibuprofen 1st or 2nd trim, %		Ibuprofen 1st or 2nd trim, %	
No	966 (81.4)	No	7462 (97.7)
Yes	221 (18.6)	Yes	174 (2.3)
Pregnancy exposures		Pregnancy exposures	
Acetaminophen 1st or 2nd trim, %		Acetaminophen 1st or 2nd trim, %	
No	361 (30.1)	No	1620 (42.4)
Yes	837 (69.9)	Yes	2198 (57.6)
Acetaminophen 1st and 2nd trim, %		Acetaminophen 1st and 2nd trim, %	
No	692 (58.7)	No	2544 (66.6)

(Continues)

TABLE 1 (Continued)

Project viva (N = 1217)		Pelotas cohort (N = 3818)	
Yes	487 (41.3)	Yes	1274 (33.4)
		Acetaminophen 1st, 2nd, or 3rd trim, %	
		No	1348 (35.3)
		Yes	2470 (64.7)
		Acetaminophen 1st, 2nd, and 3rd trim, %	
		No	3044 (79.7)
		Yes	774 (20.3)
Child characteristics		Child characteristics	
Sex, %		Sex, %	
Male	607 (49.9)	Male	1936 (50.7)
Female	610 (50.1)	Female	1882 (49.3)
Gestational age (weeks)	39.5 (1.8)		
Birthweight (grams)	3501 (548)		
Attended daycare 1st year of life, %			
No	803 (76.7)		
Yes	244 (23.3)		
Any respiratory tract infections 1st year of life, %			
No	767 (73.3)		
Yes	280 (26.7)		
Ibuprofen ≥ 6 times 1st year of life, %			
No	610 (58.9)		
Yes	425 (41.1)		
Infancy exposure		Infancy exposure	
Acetaminophen ≥ 6 times 1st year of life, %		NA	
No	339 (32.6)		
Yes	702 (67.4)		
Early childhood		Early childhood	
Age, years	3.3 (0.4)	Age, years	2.0 (0.06)
Outcomes standardised to mean = 100; SD = 15	Mean (SD)	Outcomes z-scores mean = 0; SD = 1	Min-Max
PPVT-III	103.9 (14.3)	INTER-NDA total	−7.47, 2.89
WRAVMA total	102.3 (11.3)	INTER-NDA language	−4.25, 1.96
WRAVMA pegboard	98.4 (10.8)	INTER-NDA motor	−9.34, 1.43
WRAVMA drawing	99.3 (11.2)	INER-NDA cognitive	−4.25, 1.96
WRAVMA matching	107.9 (13.5)		

Abbreviations: BMI, body mass index; INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment; NA, not applicable; PPVT-III, Peabody Picture Vocabulary Test; WRAVMA, Wide Range Achievement of Visual Motor Abilities.

in all trimesters. In addition, the lack of information about dose and timing of the exposures and the possibility of under-reporting in self-reported questionnaires or interviews can limit our interpretation. However, considering that acetaminophen is an over-the-counter analgesic and that the information about its utilization is a challenge, we believe that our exposures are valid to explore the association.

Another limitation is the potential for confounding by indication.[20] However, we adjusted for variables related to health problems or medication use (depression, antibiotics, and ibuprofen) compatible with individuals taking analgesics, as a possible way to deal with this limitation. The inclusion of ibuprofen intake as covariate also is a proxy of mothers less healthy than those who used only acetaminophen.

We did not see substantial differences in estimates with adjustment for these potential markers of indication, but we recognize the possibility of, even with the adjustments, that the potential for confounding remains.

The tests we used to assess cognitive/motor function are validated among children aged two (INTER-NDA, Pelotas) and three years (PPVT and WRAVMA, Viva). However, we recognize that

TABLE 2 Associations of acetaminophen use during pregnancy in Project Viva (ordinal values 0-4 or dichotomous) and in 2015 Pelotas Birth Cohort (dichotomous) with early childhood cognitive outcomes

	Project Viva (N = 1198)		
Exposures/Outcomes (~3 y)	**Model 1 β (95% CI)**	**Model 2 β (95% CI)**	**Model 3 β (95% CI)**
Acetaminophen 1st or 2nd trim (70%)			
PPVT-III	0.88 (−1.06, 2.82)	0.50 (−1.27, 2.27)	0.79 (−0.99, 2.58)
WRAVMA total	−0.55 (−2.10, 0.99)	−0.53 (−2.03, 0.96)	−0.39 (−1.90, 1.13)
WRAVMA pegboard	−0.45 (−1.89, 0.99)	−0.32 (−1.77, 1.13)	−0.24 (−1.71, 1.22)
WRAVMA drawing	−1.18 (−2.71, 0.34)	−1.16 (−2.67, 0.35)	−1.05 (−2.58, 0.48)
WRAVMA matching	−0.13 (−1.98, 1.72)	−0.12 (−1.92, 1.68)	0.05 (−1.76, 1.86)
Acetaminophen 1st and 2nd trim (41%)			
PPVT-III	−0.20 (−2.00, 1.60)	−0.43 (−2.06, 1.20)	−0.33 (−1.97, 1.30)
WRAVMA total	−0.72 (−2.16, 0.73)	−0.61 (−2.00, 0.78)	−0.58 (−1.97, 0.82)
WRAVMA pegboard	−0.01 (−1.35, 1.33)	0.08 (−1.27, 1.42)	0.11 (−1.24, 1.46)
WRAVMA drawing	−1.62 (−3.03, −0.20)	−1.53 (−2.93, −0.13)	−1.51 (−2.92, −0.10)
WRAVMA matching	−0.48 (−2.20, 1.24)	−0.44 (−2.11, 1.23)	−0.35 (−2.02, 1.32)
Acetaminophen during pregnancy (per 1 category increase)			
PPVT-III	0.24 (−0.49, 0.96)	0.18 (−0.48, 0.84)	0.28 (−0.39, 0.96)
WRAVMA total	−0.27 (−0.85, 0.31)	−0.25 (−0.81, 0.32)	−0.20 (−0.77, 0.37)
WRAVMA pegboard	−0.13 (−0.66, 0.41)	−0.09 (−0.63, 0.46)	−0.07 (−0.63, 0.48)
WRAVMA drawing	−0.63 (−1.20, −0.06)	−0.61 (−1.17, −0.04)	−0.56 (−1.13, 0.01)
WRAVMA matching	−0.07 (−0.77, 0.62)	−0.05 (−0.73, 0.63)	0.00 (−0.68, 0.69)
	Pelotas Cohort (N = 3818)		
Exposures/Outcomes (~2 y)	**Model 1 β (95% CI)**	**Model 2 β (95% CI)**	**Model 3 β (95% CI)**
Acetaminophen 1st or 2nd trim (58%)			
INTER-NDA language	0.01 (−0.05, 0.08)	0.01 (−0.06, 0.07)	0.01 (−0.06, 0.07)
INTER-NDA total	0.06 (0.00, 0.13)	0.07 (0.00, 0.13)	0.06 (−0.01, 0.13)
INTER-NDA motor	0.04 (−0.03, 0.10)	0.03 (−0.03, 0.10)	0.04 (−0.03, 0.11)
INER-NDA cognitive	0.01 (−0.05, 0.08)	0.01 (−0.06, 0.07)	0.01 (−0.06, 0.07)
Acetaminophen 1st and 2nd trim (33%)			
INTER-NDA language	0.05 (−0.02, 0.12)	0.05 (−0.02, 0.12)	0.05 (−0.02, 0.12)
INTER-NDA total	0.08 (0.01, 0.15)	0.09 (0.02, 0.16)	0.08 (0.01, 0.16)
INTER-NDA motor	0.02 (−0.05, 0.09)	0.01 (−0.06, 0.08)	0.02 (−0.05, 0.09)
INER-NDA cognitive	0.05 (−0.02, 0.12)	0.05 (−0.02, 0.12)	0.05 (−0.02, 0.12)
Acetaminophen 1st, 2nd, or 3rd trim (65%)			
INTER-NDA language	−0.01 (−0.08, 0.06)	−0.02 (−0.08, 0.05)	−0.02 (−0.09, 0.05)
INTER-NDA total	0.05 (−0.02, 0.12)	0.05 (−0.02, 0.12)	0.04 (−0.03, 0.11)
INTER-NDA motor	0.03 (−0.04, 0.10)	0.03 (−0.04, 0.10)	0.03 (−0.04, 0.10)
INER-NDA cognitive	−0.01 (−0.08, 0.06)	−0.02 (−0.08, 0.05)	−0.02 (−0.09, 0.05)
Acetaminophen 1st, 2nd, and 3rd trim (20%)			
INTER-NDA language	0.06 (−0.02, 0.14)	0.06 (−0.02, 0.14)	0.06 (−0.02, 0.14)
INTER-NDA total	0.09 (0.01, 0.18)	0.10 (0.02, 0.18)	0.10 (0.01, 0.18)
INTER-NDA motor	0.07 (−0.01, 0.15)	0.07 (−0.02, 0.15)	0.07 (−0.01, 0.16)
INER-NDA cognitive	0.06 (−0.02, 0.14)	0.06 (−0.02, 0.14)	0.06 (−0.02, 0.14)

Notes: Model 1. Unadjusted.

Model 2. Adjusted for maternal age, pre-pregnancy BMI, education, parity, race/ethnicity, smoking and alcohol intake during pregnancy; household income and child´s sex.

Model 3. Model 2+ any antibiotics during pregnancy, depression/anxiety during pregnancy (Pelotas) or depressive symptoms in mid-pregnancy (Viva), and ibuprofen use during pregnancy (same category as exposure).

Abbreviations: INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment; PPVT-III, Peabody Picture Vocabulary Test; WRAVMA, Wide Range Achievement of Visual Motor Abilities.

TABLE 3 Associations of acetaminophen use during the first year of life (ordinal values 0-3 or dichotomous) with cognitive outcomes in early childhood in Project Viva (N = 1041)

	Model 1	Model 2	Model 3
Exposures/Outcomes (~3 y)	**β (95% CI)**		
Acetaminophen during the first year (≥6 vs <6 times)			
PPVT-III	2.10 (0.17, 4.03)	1.25 (−0.54, 3.04)	1.33 (−0.53, 3.19)
WRAVMA total	−0.55 (−2.11, 1.00)	−0.51 (−2.05, 1.03)	−0.33 (−1.92, 1.27)
WRAVMA pegboard	−0.80 (−2.28, 0.67)	−0.44 (−1.95, 1.07)	−0.26 (−1.82, 1.30)
WRAVMA drawing	0.62 (−0.90, 2.15)	0.48 (−1.05, 2.01)	0.65 (−0.94, 2.24)
WRAVMA matching	−0.99 (−2.86, 0.87)	−1.00 (−2.86, 0.85)	−0.95 (−2.87, 0.97)
Acetaminophen during the first year (per 1 category increase)			
WRAVMA total	0.90 (−0.06, 1.85)	0.47 (−0.41, 1.35)	0.51 (−0.41, 1.43)
WRAVMA pegboard	−0.75 (−1.52, 0.01)	−0.76 (−1.51, 0.00)	−0.71 (−1.49, 0.08)
WRAVMA drawing	−0.67 (−1.39, 0.06)	−0.53 (−1.27, 0.21)	−0.46 (−1.23, 0.31)
WRAVMA matching	−0.11 (−0.86, 0.65)	−0.16 (−0.91, 0.59)	−0.10 (−0.89, 0.69)

Note: Model 1. Unadjusted.

Model 2. Adjusted for maternal age, pre-pregnancy BMI, education, parity, race/ethnicity, smoking and alcohol intake during pregnancy; household income, child´s sex, gestational age, birthweight for gestational age z-score and day care attendance.

Model 3. Model 2+ acetaminophen use in the 1st *or* 2nd trimester and respiratory tract infection in the first year + ibuprofen used ≥6 times by the child in the first year.

Abbreviations: PPVT-III, Peabody Picture Vocabulary Test; WRAVMA, Wide Range Achievement of Visual Motor Abilities.

testing vocabulary in young children can be strongly depending on the education/training given by parents and that may not fully reflect the developing brain. Furthermore, we did not have information on cultural and family aspects beyond formal education, which may also be a limitation. However, we did adjust for maternal education.

We also observed some differences in baseline covariates between participants and those lost to follow-up, and therefore we implemented IPW. Results without IPW were very similar suggesting that loss to follow-up did not bias our analyses.

4.4 | Interpretation

There are different domains of neurodevelopment. We analysed cognitive outcomes in early childhood using PPVT, WRAVMA, and INTER-NDA. The literature is more consistent in finding an association of prenatal acetaminophen exposure with the behavioural outcomes (eg ADHD) than with the cognitive outcomes.[21,22]

Studies that have evaluated neurodevelopmental outcomes earlier in life are scarce. In the Norwegian MoBa cohort, children exposed to long-term use of acetaminophen (≥28 days) in foetal life had poorer gross motor development (β 0.24, 95% CI 0.12, 0.51) and communication (β 0.20, 95% CI 0.01, 0.39) at 3 years. Short-term exposure to acetaminophen (1-27 days) was also associated with poorer gross motor development (β 0.10, 95% CI 0.02, 0.19).[7]

Our study is partially in accordance with the reported findings. For Viva, we observed that use of acetaminophen during the 1st and 2nd trimesters of pregnancy was associated with lower scores in WRAVMA drawing domain, which evaluates visual-motor abilities. It may be that acetaminophen use in the first half of pregnancy especially affects visual-motor skills, or this may be a chance finding given that other associations were null.

For Pelotas, on the other hand, the use of acetaminophen during the 1st and 2nd trimesters, or in all trimesters, was associated with better performance in INTER-NDA overall score. However, we need to consider the possibility of residual confounding by uncontrolled family/social factors for this positive association, since education was positively associated with the exposure and the outcome. The effect size (of protection) we observed was very small; further studies addressing this topic using the same instrument are needed to understand the results. Furthermore, while results for boys were largely null, a protective effect was seen only among girls in Pelotas. Tovo-Rodrigues et al, reported sex-specific findings in an analysis of the 2004 Pelotas Birth Cohort data. In that study, the authors found an adverse association of acetaminophen exposure with hyperactivity/inattention as well as emotional problems in boys at 6 years of age.[23] Similar sex-specific findings were observed by Avella-Garcia et al, in which prenatal acetaminophen exposure was associated with a greater number of ASD symptoms in boys.[10] The mechanisms leading to differential effect in boys and girls are not well studied, or these differences might reflect chance findings.

Even with conflicting results, our data add information to an important and underexplored topic. The contradictory results may result from some uncontrolled confounding factor with different effect on Viva and Pelotas cohorts. If we had seen similar directions of effect in the two cohorts with different confounding structures, we would

have found that to be very strong evidence in favour of an influence of prenatal exposure to acetaminophen on child cognition. The fact that we did not observe similar results argues against such an influence.

We did not observe any relationships between acetaminophen use during infancy and outcomes in early childhood. Behavioural development involves a complex and dynamic set of genetically guided processes with constant interaction with the environment. The biological and functional aspects of the brain's fibre tracts and cortical and subcortical structures are still in development after birth.[24] However, pathways have not been elucidated, different mechanisms may lead to effects on cognition from exposures before and after birth.

4.5 | Conclusions

We analysed data from two cohorts with different socio-economic profiles to evaluate the relationship of prenatal exposure to acetaminophen with development in early childhood. We also explored, in Project Viva, the use of acetaminophen in the first year of life, a subject that has not to date been well explored. Results from Project Viva provide some support in line with findings from other cohorts, suggesting that acetaminophen exposure during pregnancy is associated with poorer developmental outcomes, such as visual-motor skills. However, most results from Pelotas were null or indicated a beneficial direction of effect. Given our results in combination with the existing literature, in which many results were null, the few effects found do not provide strong evidence of a negative association among acetaminophen use on cognition in early childhood.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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