Received: 30 June 2019 | Revised: 26 November 2019 | Accepted: 22 December 2019

DOI: 10.1111/ppe.12649

Paediatric and Perinatal Epidemiology WILEY

SPECIAL ISSUE:
ACETAMINOPHEN-NEURODEVELOPMENT

Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development

Luciana Tovo-Rodrigues[1] | Marina Xavier Carpena[1] | Thais Martins-Silva[1] | Iná S. Santos[1,2] | Luciana Anselmi[1] | Aluísio J. D. Barros[1] | Fernando C. Barros[1] | Andréa D. Bertoldi[1] | Alicia Matijasevich[3]

[1]Postgraduate Program in Epidemiology, Universidade Federal de Pelotas, Pelotas, Brazil

[2]Postgraduate Program Pediatrics Child Health, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil

[3]Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de São Paulo, SP, Brazil

Correspondence
Luciana Tovo-Rodrigues, Postgraduate Program in Epidemiology – Universidade Federal de Pelotas, Pelotas, Rio Grande do Sul, Brazil.
Email: luciana.tovo@gmail.com

Funding information
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil, Grant/Award Number: Finance Code 001; World Health Organization; Ministério da Saúde; National Support Program for Centers of Excellence; Children's Pastorate; Brazilian National Research Council Technological Development

Abstract

Background: Several studies have reported that there is an association between developmental and emotional/behavioural problems in children exposed to acetaminophen during foetal development. However, few studies have focused on development and behavioural outcomes in early life.

Objectives: To test the association between prenatal exposure to acetaminophen and low neurodevelopmental performance at 24 months and behavioural/emotional problems at 48 months of life.

Methods: We used data from the 2004 Pelotas Birth Cohort, a population-based longitudinal prospective study. Neurodevelopment was evaluated at 24 months using Battelle's Developmental Inventory (BDI) (n = 3737). We assessed global function as well as each domain (personal-social, adaptative, motor, cognitive, and communication). Behavioural/emotional problems were assessed at 48 months using the Child Behaviour Checklist (CBCL) (n = 3624). We used the CBCL total, externalising, and internalising symptomatology and individual subscales (withdrawn, somatic complaints, anxious/depressed, social problems, cognitive problems, attention problems, aggressive behaviour, and rule-breaking behaviour). Acetaminophen use during pregnancy was retrospectively assessed at the perinatal follow-up. Poisson regression and multiple linear regression analyses were used to test the association, adjusting for several family and maternal sociodemographic and health factors, medication use during pregnancy, and the sex of the child.

Results: Acetaminophen exposure during prenatal development was not associated with low neurodevelopmental performance at 24 months assessed using the BDI or to emotional and behavioural problems assessed at 48 months using the CBCL in the adjusted models.

Conclusions: We cannot confirm the existence of an association between acetaminophen used during pregnancy and low neurodevelopmental performance at 24 months and emotional/behavioural problems at 48 months of life based on the present results.

KEYWORDS

acetaminophen, child development, developmental, neurodevelopmental disorders, pregnancy, psychology

1 | BACKGROUND

Acetaminophen is one of the most frequently used medications during pregnancy worldwide. Although it is considered safe when administered within its therapeutic range in adults,[1,2] its risk during pregnancy remains unclear. Significant attention has been afforded to the association between exposure to acetaminophen during foetal life and increased risk of attention deficit/hyperactivity disorder (ADHD)[3] and autism spectrum disorder (ASD) in childhood.[4] Our previous results from the 2004 Pelotas Birth Cohort, based on the Strength and Difficulties Questionnaire (SDQ), showed that the use of acetaminophen during pregnancy increased the odds of emotional and hyperactivity/inattention problems at 6 years of age in boys, while a nominal effect was observed at 11 years.[5]

Evidence indicates that it is pharmacologically active within the central nervous system[6] and it is able to cross the placental[7] and blood brain barriers.[6] Interference with serotonergic and cannabinoid pathways has been reported.[6,8] The potential mechanisms linking acetaminophen to psychiatric problems include excess toxic N-acetyl-p-benzoquinone imine formation, oxidative stress- and inflammation-induced immune dysregulation, altered brain-derived neurotropic factor levels, endocrine disruption, inhibition of prostaglandin synthesis, and cannabinoid receptor[9] and anti-androgenic effects.[10,11]

Attention deficit/hyperactivity disorder and autism spectrum disorder are classified as neurodevelopmental disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[12] where it is stated that affected individuals may exhibit difficulties from birth onward and that the neurological cause arises during gestation or at birth,[13,14] which is supported by genomic findings.[15,16] Thus, it is possible that the impairment in neurodevelopment caused by acetaminophen emerges earlier in life in domains related to the mentioned disorders or in other domains. The rationale to study these traits is that if acetaminophen plays a role in neurodevelopment, its effect may be stronger in the early stages than it may be later in life.

To date, the effect of acetaminophen exposure during the pre-gestational age on neurodevelopment during early life has been explored by the Norwegian Mother and Child Cohort Study (MoBa),[17,18] Infancia y Medio Ambiente (INMA) Spanish prospective birth cohort,[19] and Swedish Environmental Longitudinal, Mother and child, Asthma and allergy cohort (SELMA).[20] Poorer gross motor development and communication skills, delays in the motor and walking milestones, externalising behaviour, internalising behaviour, attainment and communication problems, higher activity levels, and language delay were associated with acetaminophen exposure in prenatal life.[17,18,20]

Synopsis

Study question

Is acetaminophen exposure during pregnancy associated with neurodevelopment and emotional/behavioural problems in infancy and early childhood?

What is already known

Acetaminophen use during pregnancy has been associated with attention deficit and hyperactivity disorders and autism. The findings regarding development in early life are inconsistent.

What this study adds

We used data from the 2004 Pelotas Birth Cohort to investigate the potential role of acetaminophen exposure during pregnancy in low neurodevelopmental performance at 24 months (including motor, cognitive, communication, adaptative, and personal-social areas) and behavioural/emotional problems at 48 months, evaluating withdrawal, somatic symptoms, social behaviour, attention, anxiety, rule-breaking behaviour, and aggressive symptoms, and considering both internalising and externalising symptomatology. The data cannot confirm the existence of an association between acetaminophen used during pregnancy and offspring evaluated outcomes.

In this study, we aimed to evaluate the effect of acetaminophen exposure during prenatal development on neurodevelopmental performance at 24 months and emotional/behavioural problems at 48 months of life in the children from the 2004 Pelotas Birth Cohort (Brazil).

2 | METHODS

2.1 | Study design

This was a prospective longitudinal study that used data from the 2004 Pelotas Birth Cohort, Brazil. The birth cohort was carried out between January and December 2004. Eligible mothers were those living in the urban area of Pelotas or in Jardim América. They were interviewed within 24 hours after delivery. A total of 4231 children

were recruited to the study. The mothers were inquired about the socio-economic conditions of the family, life style, gestational history, and birth conditions. The newborn was measured and had its gestational age assessed. The same children were re-visited at 3, 12, 24, and 48 months and at 6 and 11 years of age. The current study used data from the 24- and 48-month assessments for outcome definition and perinatal assessment to evaluate pregnancy exposure to acetaminophen and covariates.[21,22]

2.2 | Exposure

Maternal use of medication during pregnancy was retrospectively assessed using a standardised questionnaire applied at the perinatal evaluation. The following question was asked: "Did you use any medications during pregnancy?". Mothers who provided a positive answer were asked to report the names of all medications used during pregnancy, as well as the period of use. The use of acetaminophen was defined as at least once during pregnancy, regardless of the dose used.[5]

2.3 | Missing data

The 2004 Pelotas Birth Cohort assessed 4231 children at the perinatal stage, and the follow-up rates were 93.4% and 91.8% at 24 and 48 months, respectively.[21,22] Twelve children with a Battelle's Developmental Inventory (BDI) developmental score of <50 were excluded from the analysis because they presented severe mental deficit due to problems such as cerebral palsy and Down syndrome. The same criterion was used in a previous paper from our group.[23] Thus, for this study, we initially included 4219 children. The percentage of missing observations for acetaminophen exposure, BDI at 24 months, and the Child Behaviour Checklist (CBCL) at 48 months was 3.3%, 8.9%, and 11.4%, respectively. Of 4219 children in the initial sample, we included 3737 (88.3%) and 3,624 (85.7%) in the analysis sample in the 24- and 48-month follow-ups, respectively. To address the issue of missing outcome data, we implemented inverse probability weighting (IPW). First, we predicted the probability of missing outcomes based on the exposure and covariates of the perinatal follow-up. Next, among the 3737 and 3624 individuals of each outcome we ran all models weighted by the inverse of the probability of having each outcome separately.

2.4 | Outcomes

2.4.1 | Low neurodevelopmental performance

The screening version of BDI was used to assess the children's development at 24 months of age. This is a standardised tool largely used for such evaluation and includes several domains: personal, social, adaptative, fine and gross motor, communication, and cognitive.[24]The assessments were performed at the child's home, in the presence of the mother or caregiver, by interviewers trained by a paediatrician specialised in child development. For this study, the BDI scores were dichotomised to define a low performance group using the 10th percentile as the cut-off point (separately for boys and girls), as performed in a previous study.[23] Low performance (belonging to the first decile) was not associated with sex given how the classification was implemented.

2.4.2 | Emotional and behavioural problems

Child behavioural/emotional problems were assessed at 48 months using the CBCL.[25] The version for individuals aged 4-18 years, which comprises 118 behavioural and emotional items, was used. This version has been validated for the Brazilian population.[26,27] A psychologist (LA) trained interviewers and supervised the application of the test among the children's mothers. In cases of absent mothers, the assessment was not conducted. A profile of childhood psychological problems provided scores on eight empirically derived scales: withdrawn, somatic complaints, anxious/depressed, social problems, cognitive problems, attention problems, aggressive behaviour, and rule-breaking behaviour. Data from these scales were summed to provide an overall score (total problems) and were also grouped in two broad dimensions (internalising and externalising problems). We identified clinical groups using a *t* score > 63 in the CBCL total, externalising, or internalising scales, and >70 points in the individual symptomatology scales, in accordance with the CBCL manual.[28]

2.5 | Statistical analysis

We first described the outcomes (low neurodevelopment performance assessed by the BDI and total emotional/behavioural Problems assessed by the CBCL) according to the following covariates of interest: information on family Wealth Index Quotient (WIQ) in the month prior to delivery, maternal schooling, age, skin colour, marital status, parity, smoking during pregnancy, alcohol consumption during pregnancy, mood symptoms during pregnancy, pre-gestational body mass index (BMI), prenatal care (number of antenatal care appointments attended during pregnancy), infectious diseases during pregnancy, high blood pressure and diabetes mellitus diagnosis during pregnancy, and child sex were considered as potential confounders. To minimise the confounding effect of other nonsteroidal analgesic use during pregnancy, we also adjusted the regression models for this information. The same strategy was previously employed.[5] The choice of covariates included in the regression analysis was based on a theoretical model, in which the potential associated factors with both acetaminophen use and neurodevelopmental and mental health variables were used. The differences in the distribution of covariates were assessed using Pearson chi-square tests. Crude and adjusted analyses were carried out using Poisson regression adjusted for robust variance. The

effect estimates are presented as relative risk (RR) and respective 95% confidence intervals (CIs). Effect modification by child sex was tested for all outcomes. All analyses were conducted using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

2.6 | Sensitivity analysis

Additional analyses were conducted to assess the robustness of the findings. We performed crude and adjusted linear regression to assess whether acetaminophen use during pregnancy was associated with the symptoms in our sample. For this analysis, the outcomes were considered as continuous variables, and the results are presented as the beta coefficient (β) and the 95% CI.

2.7 | Ethical approval

The 2004 Pelotas Cohort was approved by the Federal University of Pelotas Medical School Research Ethics Committee. Mothers were fully informed of all follow-up procedures, the general objectives, the voluntary condition of their participation, their right to not participate, their right to not answer specific questions, and their right to confidentiality of the information provided.

3 | RESULTS

At 24 months, a total of 3727 children had valid information for acetaminophen exposure and BDI, and at 48 months, the number of children with valid information for exposure and CBCL was 3624. The use of acetaminophen was reported by 27.8% (n = 1060) of the mothers included in this study.

The sample included in this study comprised mostly girls (52.0% and 51.9% at 24- and 48 months respectively), children whose mothers, by the delivery time, reported being of white skin colour (62.0% and 61.9%), having a partner (84.1% and 84.3%), having pre-gestational BMI between 18.5 at 24 kg/m^2 (60.6% and 60.9%), having no mood symptoms (75.4% and 75.6%), no infections (58.8% and 59.0%), no smoking (72.8% and 72.9%), no alcoholic beverage consumption (96.7% and 96.6%), no hypertension (76.2% and 75.8%), no diabetes (97.1% and 97.0%), and no other analgesics use (79.4% and 79.3%), during pregnancy. The mean number of antenatal care appointments was 8.2 at 24 months and 8.3 at 48 months. The prevalence of maternal age younger than 25 years was 45.3% at both follow-ups and of lower education (5-8 years) was 41.2% and 41.7% at 24 and 48 months, respectively. Being primiparous was reported by 39.4% and 39.2% of participants, respectively (Table 1).

Low performance on the BDI was associated with poorest family WIQ, reported black skin colour, lower education, higher parity, maternal mood symptoms, hypertension, and smoking during pregnancy (Table 1). The CBCL total problems' scale was associated with male sex, poorest family WIQ, skin colour other than white or black, lower education, higher parity, single motherhood, pre-gestational BMI < 18.5 kg/m^2, presence of mood symptoms, infections, smoking, alcoholic beverage consumption, and use of other analgesics during pregnancy (Table 1).

Belonging to the richest family WIQ, maternal schooling longer than 12 years, no single motherhood, and using other analgesics during pregnancy were positively associated with the use of acetaminophen during pregnancy (Table S1). Further, skin colour other than white, higher parity (3 or more), and smoking were negatively associated with use of acetaminophen (Table S1).

Considering the BDI, in the crude models, the use of acetaminophen at least once during pregnancy led to a decreased risk of offspring low performance on the motor and cognitive area domains (RR, 0.70; 95% CI, 0.54, 0.89 and RR, 0.87; 95% CI, 0.78, 0.96, respectively). After adjustment for confounders, the RR approached the unit, and no association was observed. There was no interaction effect between sex and acetaminophen exposure during foetal life for all evaluated BDI domains (Table 2).

For the CBCL, in the crude model, the use of acetaminophen at least once during pregnancy was associated with a decreased risk of offspring externalising problems (RR 0.88; 95% CI 0.78, 0.99). After adjustment, the estimates varied from RR 0.75 (95% CI 0.28, 2.01) in the attention domain to RR 1.95 (95% CI 0.95, 4.03) in the anxiety domain. There was no effect modification regarding sex for any CBCL outcome (Table 3).

Overall, the sensitivity analyses were consistent with the binary regression, and no association was observed between acetaminophen use during pregnancy and offspring BDI and CBCL scores in the fully adjusted models (Tables S2 and S3). The only association observed concerned the BDI cognitive domain, which showed a protective effect when the trait was evaluated as a continuous outcome, consistent with the direction observed when the variable was treated as a binary outcome.

4 | COMMENT

4.1 | Principal findings

In this study, we explored the association between maternal use of acetaminophen during pregnancy and offspring neurodevelopment at 24 months and behavioural/emotional problems at 48 months. This study does not confirm the existence of a risk effect of acetaminophen used during pregnancy on offspring low neurodevelopmental performance at 24 months and emotional/behavioural problems at 48 months of life.

4.2 | Strengths of the study

This study added important new information regarding the association of acetaminophen exposure with outcomes in early life, which

TABLE 1 Sample description considering the outcomes evaluated at both 24 and 48 months of age and their characterisation according to the covariates included in the study

	24 months (N = 3737)		48 months (N = 3624)	
		Low performance on BDI		Emotional and behavioural problems
	N (%)	N (%)	N (%)	N (%)
Child sex				
Male	1942 (52.0)	210 (10.8)	1881 (51.9)	436 (23.2)
Female	1795 (48.0)	186 (10.4)	1743 (48.1)	353 (20.3)
Family WIQ				
1 (poorest)	721 (19.3)	133 (18.5)	696 (19.2)	219 (31.5)
2	770 (20.6)	115 (14.9)	753 (20.8)	193 (25.6)
3	747 (20.0)	67 (9.0)	732 (20.2)	155 (21.2)
4	749 (20.0)	42 (5.6)	726 (20.0)	149 (20.5)
5 (richest)	750 (20.1)	39 (5.2)	717 (19.8)	73 (10.2)
Mother's skin colour				
White	2292 (62.0)	196 (8.6)	2220 (61.9)	387 (17.4)
Black	612 (16.6)	94 (15.4)	600 (16.8)	159 (26.5)
Other	790 (21.4)	100 (12.7)	764 (21.3)	225 (29.5)
Mother's age (years)				
<25	1690 (45.2)	187 (11.1)	1642 (45.3)	420 (25.6)
25-29	869 (23.3)	88 (10.1)	824 (22.8)	175 (21.2)
30-34	776 (20.8)	71 (9.2)	765 (21.1)	131 (17.1)
>35	400 (10.7)	49 (12.3)	391 (10.8)	63 (16.1)
Mother's schooling (years)				
0-4	564 (15.3)	111 (19.7)	537 (15.0)	165 (30.7)
5-8	1526 (41.2)	188 (12.3)	1500 (41.7)	394 (26.3)
9-12	1239 (33.5)	69 (5.6)	1194 (33.3)	189 (15.8)
>12	370 (10.0)	26 (7.0)	357 (10.0)	32 (9.0)
Parity (number of children)				
1 (first child)	1472 (39.4)	124 (8.4)	1422 (39.2)	302 (21.2)
2	994 (26.6)	86 (8.7)	971 (26.8)	174 (17.9)
3 or more	1270 (34.0)	185 (14.6)	1230 (34.0)	312 (25.4)
Being single mother				
No	3144 (84.1)	325 (10.3)	3055 (84.3)	628 (20.6)
Yes	593 (15.9)	71 (12.0)	569 (15.7)	161 (28.3)
Pre-gestational BMI(kg/m^2)				
<18.5	160 (4.7)	20 (12.5)	151 (4.5)	47 (31.1)
18.5-24	2073 (60.6)	195 (9.4)	2028 (60.9)	420 (20.7)
25-29	804 (23.5)	78 (9.7)	776 (23.3)	151 (19.5)
30 or more	384 (11.2)	46 (12.0)	376 (11.3)	90 (23.9)
Mood symptoms during pregnancy				
No	2816 (75.4)	265 (9.4)	2737 (75.6)	494 (18.1)
Yes	920 (24.6)	131 (14.2)	885 (24.4)	294 (33.2)
Infectious diseases during pregnancy				
No	2194 (58.8)	229 (10.4)	2133 (59.0)	407 (19.1)
Yes	1534 (41.2)	164 (10.7)	1483 (41.0)	381 (25.7)
Smoking during pregnancy				
No	2721 (72.8)	259 (9.5)	2642 (72.9)	472 (17.9)
Yes	1016 (27.2)	137 (13.5)	982 (27.1)	317 (32.3)
Alcohol consumption during pregnancy				
No	3614 (96.7)	380 (10.5)	3501 (96.6)	750 (21.4)
Yes	123 (3.3)	16 (13.0)	123 (3.4)	39 (31.7)
Other analgesic used during pregnancy				
No	2949 (79.4)	305 (10.3)	2857 (79.3)	601 (21.0)
Yes	767 (20.6)	89 (11.4)	746 (20.7)	188 (24.8)
Hypertension during pregnancy				
No	2843 (76.2)	281 (9.9)	2741 (75.8)	578 (21.1)
Yes	886 (23.8)	113 (12.8)	876 (24.2)	209 (23.9)

Abbreviation: WIQ, Wealth Index Quotient.

contributes to the current interpretation of the topic. Our study focused on a relatively unexplored outcome in two different ages in a cohort from a middle-income country. We used data from a large population-based birth cohort in Brazil focused on mental health and development, with a high follow-up rate with evaluation at various time points throughout childhood, which is scarce in the literature. We adjusted the models for several variables important for both neurodevelopment and emotional and behavioural outcomes that may also influence the use of acetaminophen. We adjusted the model for the use of other types of nonsteroidal analgesics in order to exclude the effect of other medications on the outcome. The cohort included high-quality information regarding the confounders, and we assessed the role of acetaminophen independently of potential maternal and child confounders. These points can be considered as strengths of our study.

4.3 | Limitations of the data

The results should be interpreted considering certain limitations. The first limitation refers to the retrospective gathering of data on medication use during pregnancy, which may have resulted in difficulty recalling acetaminophen use. Besides the retrospective framing of the assessment of acetaminophen use during pregnancy, another limitation that may have involved a memory issue is related to the broad question used to assess it that may have led to under-reporting of acetaminophen use. Thus, the low prevalence of acetaminophen use observed in this study may be due to under-reporting. Therefore, we

were not able to address the dose response or the effect of a specific time window of exposure to better explore the association.

In addition, our analysis may not have had sufficient power to identify a significant association. Considering that under-reporting of the use of acetaminophen may be a limitation of the exposure definition in our study, we expect that the effect sizes observed in the association analyses were underestimated. We also observed some differences in the baseline covariates between participants included and those lost to follow-up, and therefore, we implemented IPW. The results without IPW were very similar, suggesting that losses to follow-up did not bias our analyses.

Confounding by indication may also have hampered the results, since indication information was not collected at the perinatal interview. Although we cannot exclude the possibility of residual confounding, we adjusted the analysis for variables that are related to the use of acetaminophen (ie the presence of infection during pregnancy, pre-gestational BMI, mood symptoms, high blood pressure diagnosis, and the use of other analgesics), which may have helped overcome this limitation. The self-report nature of the pregnancy health data, however, inserts some imprecision to the adjustment, and we cannot exclude confounding by indication in the present study. Finally, it is possible that postnatal exposure to acetaminophen by the toddlers may play a role in neurodevelopment. However, we were not able to assess it.

TABLE 2 Association between the use of acetaminophen during pregnancy and offspring's low neurodevelopmental performance outcomes (binary traits) as assessed by Battelle's Development Inventory at 24 months in the 2004 Pelotas Birth Cohort, Brazil

	Any use of acetaminophen during pregnancy
	RR (95% CI)
Low performance in BDI	
Model 1	0.83 (0.65, 1.06)
Model 2	1.04 (0.81, 1.32)
Model 3	1.00 (0.78, 1.28)
Social-personal area	
Model 1	0.90 (0.72, 1.13)
Model 2	1.03 (0.82, 1.29)
Model 3	1.00 (0.80, 1.25)
Adaptative area	
Model 1	0.89 (0.75, 1.06)
Model 2	0.90 (0.75, 1.08)
Model 3	0.91 (0.76, 1.08)
Motor area	
Model 1	0.70 (0.54, 0.89)
Model 2	0.92 (0.72, 1.17)
Model 3	0.91 (0.71, 1.16)
Communication area	
Model 1	0.91 (0.73, 1.13)
Model 2	1.04 (0.84, 1.30)
Model 3	1.04 (0.84, 1.30)
Cognitive area	
Model 1	0.87 (0.78, 0.96)
Model 2	0.93 (0.84, 1.03)
Model 3	0.92 (0.83, 1.02)

Note: For all domains, the reference category is the one whose individual outcome variables symptoms are below the considered cut-off point and those who were not exposed to acetaminophen during prenatal life.

The low performance group includes individuals belonging to the first decile. RR: relative risk; CI 95%: 95% confidence interval.

Model 1: unadjusted.

Model 2: adjusted for family wealth index; mother's skin colour; mother's age; mother's schooling; single mothers; parity; pre-pregnancy BMI; tobacco and alcohol use; and prenatal care (number of antenatal care appointments attended during pregnancy) during pregnancy.

Model 3: fully adjusted model (Model 2+ mood symptoms; infectious diseases; high blood pressure and gestational diabetes and treatment received during pregnancy; use of other analgesics during pregnancy; and child sex).

4.4 | Interpretation

The studies evaluating the association between acetaminophen use during pregnancy and neurodevelopment in infancy and early childhood have reported conflicting results. Importantly, in contrast to our study, all the three cohorts to date have collected acetaminophen use information during prenatal assessments. The inconsistencies across studies may have resulted from the acetaminophen use data classification as well as from the outcome scales used and age of assessment differences.

Poorer gross motor development score, communication skill score, and delayed walking score as assessed by the Ages and Stages Questionnaire (ASQ) at 3 years were associated with longer exposure (≥28 days) to acetaminophen during prenatal development in a sibling-controlled analysis in the MoBa cohort.[17,18] In the same cohort, using propensity score matching analysis, long-term acetaminophen exposure during pregnancy was associated with delayed walking and communication problems as assessed by ASQ at 18 months.[18] Shorter term use (<28 days) was only associated with poorer gross motor at 3 years of age.[17] No association was observed at 18 months.[18] Our results, which are based on the assessment of acetaminophen use at least once during pregnancy, were not able to confirm the risk effect of acetaminophen exposure during foetal life on neurodevelopment scale performance (low performance total, social-personal, adaptative, motor, communication, and cognitive areas). Although we observed an association between acetaminophen use and offspring motor and the cognitive domains in the crude analyses and for the cognitive domain in the sensitivity full-adjusted analysis, the direction of the association was the opposite to that found for the MoBA cohort.

In the SELMA cohort, including data of 754 Swedish mother-child pairs, a greater number of acetaminophen tablets ingested

TABLE 3 Association between the use of acetaminophen during pregnancy and offspring emotional and behavioural problem outcomes (binary traits) as assessed by the Child Behaviour Checklist at 48 mo in the 2004 Pelotas Birth Cohort, Brazil

CBCL total, broad-band, and specific scales	RR (95% CI)
Total Emotional/behavioural problems	
Model 1	0.90 (0.77, 1.05)
Model 2	1.05 (0.90, 1.27)
Model 3	0.99 (0.85, 1.16)
Internalising problems	
Model 1	0.87 (0.65, 1.16)
Model 2	1.07 (0.79, 1.45)
Model 3	1.00 (0.75, 1.35)
Externalising problems	
Model 1	0.88 (0.78, 0.99)
Model 2	1.00 (0.89, 1.14)
Model 3	0.97 (0.86, 1.10)
Withdrawn-depressed	
Model 1	1.05 (0.56, 2.00)
Model 2	1.36 (0.69, 2.67)
Model 3	1.31 (0.68, 2.53)
Somatic complaints	
Model 1	1.47 (0.62, 3.49)
Model 2	1.84 (0.70, 4.83)
Model 3	1.47 (0.58, 3.72)
Social problems	
Model 1	0.94 (0.40, 2.22)
Model 2	1.55 (0.62, 3.91)
Model 3	1.56 (0.64, 3.83)
Anxious-depressed	
Model 1	1.47 (0.73, 2.97)
Model 2	1.97 (1.00, 4.24)
Model 3	1.95 (0.95, 4.03)
Thought problems	
Model 1	0.83 (0.40, 1.76)
Model 2	0.95 (0.44, 2.08)
Model 3	0.89 (0.41, 1.91)
Attention problems	
Model 1	0.54 (0.21, 1.41)
Model 2	0.83 (0.30, 2.28)
Model 3	0.75 (0.28, 2.01)
Rule-breaking behaviour	
Model 1	0.84 (0.61, 1.17)
Model 2	1.12 (0.81, 1.55)
Model 3	1.09 (0.79, 1.52)
Aggressive behaviour	
Model 1	0.88 (0.68, 1.14)
Model 2	1.02 (0.78, 1.32)
Model 3	0.98 (0.75, 1.27)

Note: For all domains, the reference category is the one whose individual's outcome variables symptoms are above the considered cut-off point and those who were not exposed to acetaminophen during the prenatal life.

The cut-off point used to categorise the variables total emotional and behavioural problems as well as the broad-band scales (externalising and internalising problems) was 63 points. For all the specific scales, the cut-off point was 70.

Model 1: unadjusted.

Model 2: adjusted for family wealth index; mother's skin colour; mother's age; mother's schooling; single mothers; parity; pre-pregnancy BMI; tobacco and alcohol use; and prenatal care (number of antenatal care appointments attended during pregnancy) during pregnancy.

Model 3: fully adjusted model (Model 2+ mood symptoms; infectious diseases; high blood pressure and gestational diabetes and treatment received during pregnancy; use of other analgesics during pregnancy; and child sex).

Abbreviations: CI, confidence interval; RR, relative risk.

during pregnancy (>6) was associated with greater language delay (the use of fewer than 50 words assessed by nurse evaluation and parental questionnaire on language use) in 30-month-old girls but not in boys.[20] In our study, although the effect estimates for the communication area point towards a risk, the CI was large. Similar to our results, Avella-Garcia et al[19] using the INMA cohort data did not find an association between the use of acetaminophen at least once during pregnancy and offspring mental and psychomotor developmental scores at 1 year of age using the developmental outcomes of the Bayley Scales of Infant Development.[19] Considering our findings and those of the previous studies, it is possible that long-term exposure to acetaminophen may play a role in neurodevelopmental low performance; however, we were not able to examine this.

Internalising and externalising symptoms are key indicators of psychopathology across the lifespan. The presence of these symptoms in childhood and adolescence increases the risk of psychiatric diagnoses in adulthood.[29] Internalising symptoms include anxiety, sadness, social withdrawal, and fearfulness while externalising symptoms include overactivity, poor impulse control, non-compliance, and aggression.[25,30,31] In our study, we did not find evidence corroborating a risk effect of acetaminophen exposure during pregnancy on internalising or externalising problems. In general, large variation was observed in the association estimates, including null effects, divergence in the association directions, and wide CI. The only cohort in which the CBCL instrument was used was the MoBa. The results regarding internalisation and externalisation problems were conflicting when comparing the children at 1.5 and 3 years of age. Children exposed to prenatal acetaminophen for more than 28 days had greater extent of externalising and internalising symptomatology at 3 years of age.[17] However, no

association between long-term acetaminophen use during pregnancy and externalising and internalising symptoms at 18 months of age was observed.[18]

The mechanisms underlying the association between acetaminophen use and outcomes related to mental health and neurodevelopment remain to be elucidated. The inconsistences regarding the internalising and externalising domains and other behavioural issues are of note. In our previous study, exploring the same cohort, we found an association with the emotional and hyperactivity/inattention domains in boys at 6 years of age, while a smaller estimate was observed at 11 years.[5] Some differences between the two studies need to be stressed. The instrument used to assess the outcomes differed and explored different constructs. The CBCL is more widely used for diagnostic purposes and has higher sensitivity for detecting mental health problems. Conversely, the SDQ is an instrument used for screening, which could explain at least partially the differences in the results. The BDI is more useful for detection of severe mental issues, but a direct comparison with this instrument is not possible. Another important topic is related to a possible age-specific effect of acetaminophen acting on specific neurodevelopmental pathways. Inconsistencies involving the age were observed in the MoBa cohort and in the study by Thompson et al.[32] Further studies exploring the association across ages are important to elucidate the potential role of acetaminophen use throughout life. Although we found a positive result in our previous study, we were not able to confirm an association using earlier life outcomes.

5 | CONCLUSIONS

In conclusion, we cannot confirm the existence of a risk effect of acetaminophen use during pregnancy on low neurodevelopmental performance at 24 months and emotional/behavioural problems at 48 months of life based on the present study results, in contrast to previous reports of confirmed risk in the literature. Such differences indicate the need to better characterise the potential mechanism of action of acetaminophen because it remains largely unknown. Further longitudinal studies with well-collected information related to acetaminophen use, such as detailed dose and frequency of use, are required to address these associations. Further studies focusing on determinants of acetaminophen use are also needed for proper adjustment of confounders.

ACKNOWLEDGEMENTS

This article is based on data from the study "Pelotas Birth Cohort, 2004" conducted by Postgraduate Program in Epidemiology at Universidade Federal de Pelotas, with the collaboration of the Brazilian Public Health Association (ABRASCO). The World Health Organization, National Support Program for Centers of Excellence (PRONEX), Brazilian National Research Council Technological Development (CNPq), Brazilian Ministry of Health, and Children's Pastorate supported previous phases of the study until 2009. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001. LTR, MXC, ISS, ADB, AB, FCB, and AM are supported by CNPq.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Luciana Tovo-Rodrigues https://orcid.org/0000-0002-8732-6059
Andréa D. Bertoldi https://orcid.org/0000-0002-4680-3197

REFERENCES

1. Toussaint K, Yang XC, Zielinski MA, et al. What do we (not) know about how paracetamol (acetaminophen) works? *J Clin Pharm Ther*. 2010;35(6):617-638.
2. Ghanem CI, Perez MJ, Manautou JE, Mottino AD. Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacol Res*. 2016;109:119-131.
3. Gou X, Wang Y, Tang Y, et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. *Aust N Z J Psychiatry*. 2019;53(3):195-206. Epub 2019/01/19.
4. Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: a systematic review, meta-analysis, and meta-regression analysis of cohort studies. *Am J Epidemiol*. 2018;187(8):1817-1827.
5. Tovo-Rodrigues L, Schneider BC, Martins-Silva T, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. *BMC Psychiatry*. 2018;18(1):368.
6. Kumpulainen E, Kokki H, Halonen T, Heikkinen M, Savolainen J, Laisalmi M. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics*. 2007;119(4):766-771.
7. Nitsche JF, Patil AS, Langman LJ, et al. Transplacental passage of acetaminophen in term pregnancy. *Am J Perinatol*. 2017;34(6):541-543.
8. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol*. 2006;531(1–3):280-281.
9. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav*. 2018;101:125-147.
10. Kristensen DM, Lesne L, Le Fol V, et al. Paracetamol (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis. *Int J Androl*. 2012;35(3):377-384.
11. van den Driesche S, Macdonald J, Anderson RA, et al. Prolonged exposure to acetaminophen reduces testosterone production by the human fetal testis in a xenograft model. *Sci Transl Med*. 2015;7(288):288ra80-288ra80.
12. Association AP. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub. 2013.
13. Doernberg E, Hollander E. Neurodevelopmental disorders (ASD and ADHD): DSM-5, ICD-10, and ICD-11. *CNS Spectr*. 2016;21(4):295-299.
14. Van Herwegen J, Riby D. Neurodevelopmental disorders : research challenges and solutions. 2015; Available from: http://public.eblib.com/choice/publicfullrecord.aspx?p=1883789.
15. Grove J, Ripke S, Als TD, et al. Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet*. 2019;51(3):431-444.

16. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet*. 2019;51(1):63-75.
17. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol*. 2013;42(6):1702-1713.
18. Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MM, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. *Int J Epidemiol*. 2016;45(6):1998-2008.
19. Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. *Int J Epidemiol*. 2016;45(6):1987-1996.
20. Bornehag CG, Reichenberg A, Hallerback MU, et al. Prenatal exposure to acetaminophen and children's language development at 30 months. *Eur Psychiatry*. 2018;51:98-103.
21. Santos IS, Barros AJ, Matijasevich A, Domingues MR, Barros FC, Victora CG. Cohort profile: the 2004 Pelotas (Brazil) birth cohort study. *Int J Epidemiol*. 2011;40(6):1461-1468.
22. Santos IS, Barros AJ, Matijasevich A, et al. Cohort Profile Update: 2004 Pelotas (Brazil) Birth Cohort Study. Body composition, mental health and genetic assessment at the 6 years follow-up. *Int J Epidemiol*. 2014;43(5):1437-a-f.
23. Barros AJ, Matijasevich A, Santos IS, Halpern R. Child development in a birth cohort: effect of child stimulation is stronger in less educated mothers. *Int J Epidemiol*. 2010;39(1):285-294.
24. Newborg J, Stock JR, Wnek L, Guidabaldi J, Svinicki J. *Battelle Developmental Inventory*. Itasca, IL: Riverside Publishing; 1988.
25. Achenbach TM. *Integrative guide for the 1991 CBCL/4-18, YSR, and TRF profiles*. Department of Psychiatry: University of Vermont; 1991.
26. Bordin IA, Rocha MM, Paula CS, et al. Child Behavior Checklist (CBCL), Youth Self-Report (YSR) and Teacher's Report Form(TRF): an overview of the development of the original and Brazilian versions. *Cadernos de Saude Publica*. 2013;29(1):13-28.
27. Bordin IAS. Validação da versão brasileira do Child Behavior Checklist ou Inventário de Comportamentos da Infância e Adolescência: dados preliminares. 1992.
28. Achenbach TM, Edelbrock CS. Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monogr Soc Res Child Dev*. 1981;46(1):1-82.
29. Cicchetti D, Toth SL, eds. *Internalizing and externalizing expressions of dysfunction*. Hillsdale, NJ: Erlbaum; 1991.
30. Woodman AC, Mailick MR, Greenberg JS. Trajectories of internalizing and externalizing symptoms among adults with autism spectrum disorders. *Dev Psychopathol*. 2016;28(2):565-581.
31. Werry JS, Quay HC. The prevalence of behavior symptoms in younger elementary school children. *Am J Orthopsychiatry*. 1971;41(1):136-143.
32. Thompson JM, Waldie KE, Wall CR, Murphy R, Mitchell EA. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PloS one*. 2014;9(9):e108210.

SUPPORTING INFORMATION

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

How to cite this article: Tovo-Rodrigues L, Carpena MX, Martins-Silva T, et al. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. *Paediatr Perinat Epidemiol*. 2020;34:278–286. https://doi.org/10.1111/ppe.12649