International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	THE IMPACT OF PRENATAL EXPOSURE TO PARACETAMOL ON THE OCCURRENCE OF NEURODEVELOPMENTAL DISORDERS IN CHILDHOOD: A LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4411
RECEIVED	11 October 2025
ACCEPTED	23 December 2025
PUBLISHED	30 December 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

THE IMPACT OF PRENATAL EXPOSURE TO PARACETAMOL ON THE OCCURRENCE OF NEURODEVELOPMENTAL DISORDERS IN CHILDHOOD: A LITERATURE REVIEW

Aleksandra Miśta *(Corresponding Author, Email: o.urbanska99@gmail.com)*
Provincial Specialist Hospital in Wrocław, Wrocław, Poland
ORCID ID: 0009-0007-1389-2596

Paweł Harbut
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0001-0405-4407

Aleksander Białoń
University Hospital in Krakow, Kraków, Poland
ORCID ID: 0009-0007-4447-7619

Dominika Walczak
4th Military Clinical Hospital with Polyclinic in Wrocław, Wrocław, Poland
ORCID ID: 0009-0007-1629-871X

Weronika Ewa Nowak
Jan Mikulicz-Radecki University Clinical Hospital, Wrocław, Poland
ORCID ID: 0009-0006-8445-2072

Adrian Kruk
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0001-1749-6159

Katarzyna Jakubowska
4th Military Clinical Hospital with Polyclinic in Wrocław, Wrocław, Poland
ORCID ID: 0009-0006-6542-8309

Aleksandra Dorosz
Lower Silesian Center of Oncology, Pulmonology, and Hematology in Wrocław, Wrocław, Poland
ORCID ID: 0009-0001-4956-5702

Igor Gawłowski
5th Military Clinical Hospital with Polyclinic in Kraków, Kraków, Poland
ORCID ID: 0009-0007-8895-4237

Lidia Jurczenko
4th Military Clinical Hospital in Wrocław, Wrocław, Poland
ORCID ID: 0009-0005-5075-629X

ABSTRACT

Background: In recent years, several large cohort studies have drawn attention to a possible association between maternal paracetamol use during pregnancy and the occurrence of neurodevelopmental disorders. Given the complex etiology of these conditions and the fact that acetaminophen is considered the only safe analgesic and antipyretic during pregnancy, these publications have generated both concern and controversy.
Methods: This paper is based on studies published in PubMed. The reviewed literature includes publications from 2000 to 2025, primarily involving large cohorts (typically at least 100 participants) and accounting for potential confounding factors. The search terms used were "paracetamol," "acetaminophen," "neurodevelopmental disorders," "autism," and "ADHD." Based on these criteria, 41 articles were selected for analysis.
Results: Cohort studies demonstrated a slight increase in the risk of neurodevelopmental disorders associated with prenatal acetaminophen exposure. However, a causal relationship has not been established.
Conclusions: Paracetamol may have an adverse effect on fetal nervous system development; therefore, its use during pregnancy should be limited to cases with clear medical indication and in accordance with the product's prescribing information.

KEYWORDS

Paracetamol, Acetaminophen, Neurodevelopmental Disorders, Autism, ADHD

CITATION

Aleksandra Miśta, Paweł Harbut, Aleksander Białoń, Dominika Walczak, Weronika Ewa Nowak, Adrian Kruk, Katarzyna Jakubowska, Aleksandra Dorosz, Igor Gawłowski, Lidia Jurczenko. (2025). The Impact of Prenatal Exposure to Paracetamol on the Occurrence of Neurodevelopmental Disorders in Childhood: A Literature Review. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4411

Introduction:

Paracetamol is considered by the U.S. Food and Drug Administration (FDA) to be a safe medication for use during pregnancy and is classified as a Category B drug (animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in human studies). [41] It is an over-the-counter medication and the only analgesic and antipyretic approved for managing high fever or pain in pregnant women. Some sources report that up to every second pregnant woman uses paracetamol during pregnancy. Paracetamol use has also been associated with promoting the closure of the patent ductus arteriosus (PDA), making it one of the most frequently administered drugs in neonatal intensive care units—with some reports ranking it as the third most commonly used medication. [1]

Despite the widespread knowledge regarding the adverse effects, pharmacokinetics, and mechanism of action of paracetamol, recent studies have drawn attention to a potential association between maternal paracetamol use during pregnancy and the occurrence of neurodevelopmental disorders (such as autism spectrum disorder, ADHD, and emotional or behavioral disorders). [2]

Numerous studies report statistical correlations between acetaminophen exposure and increased rates of autism or ADHD; however, these findings do not establish a causal relationship. [3] The non-selective inhibition of peripheral cyclooxygenase and interference with cannabinoid receptors are proposed mechanisms of acetaminophen action that make such an association biologically possible. [1] It has been suggested that paracetamol may induce apoptosis and oxidative stress in the fetal brain, and may also indirectly affect the synthesis of hormones, such as testosterone. [3] Furthermore, animal studies have demonstrated degenerative and necrotic changes in the respiratory, reproductive, and nervous systems. [1]

In 2021, an international consortium of scientists and clinicians issued a statement recommending that paracetamol be used during pregnancy only when absolutely necessary and medically justified. In addition to the scientific community, the potential impact of acetaminophen on human neurodevelopment has also

attracted political attention. Recent statements by the President of the United States have once again drawn global focus to the issue of the origins of neurodevelopmental disorders and the possible influence of analgesic treatment on their development. [4]

The present paper aims to review the current body of literature to provide a comprehensive overview of paracetamol use during pregnancy in the context of neurodevelopmental disorders in the offspring. It also seeks to evaluate the influence of additional modifying factors that may contribute to the occurrence of conditions such as autism spectrum disorder and may be indirectly related to analgesic use during pregnancy, including maternal fever, infections, and chronic diseases. An important aspect discussed in the reviewed studies is the method used to assess acetaminophen exposure (maternal self-report versus meconium concentration analysis), as well as the potential impact of confounding factors, such as genetic predispositions. [3]

2. Biological Mechanisms of Potential Paracetamol Effects

2.1 Pharmacokinetics and Placental Transfer

Paracetamol belongs to the group of organic compounds and is a hydroxyl derivative of acetanilide (which itself is an acetyl derivative of aniline). It is absorbed from the gastrointestinal tract through passive diffusion. [5] The onset of action occurs approximately 30 minutes after oral administration, with a duration of up to 4 hours and a plasma half-life of about 2 hours. The drug is metabolized in the liver via two main pathways. The first, accounting for approximately 95% of total metabolism, involves conjugation with glucuronic acid or sulfate groups. The remaining 5% of acetaminophen metabolism proceeds via the cytochrome P450 enzyme system, leading to the formation of toxic metabolites. [6]Although paracetamol is considered relatively safe when administered at therapeutic doses, excessive or prolonged use may result in severe hepatic and renal damage. [7] Paracetamol readily crosses the placental barrier. According to the product characteristics, it has not been shown to cause congenital malformations in the fetus; however, the summary of product characteristics recommends caution due to the uncertain effects of the drug on fetal neurodevelopment. Acetaminophen is also excreted into breast milk in trace amounts. [6]

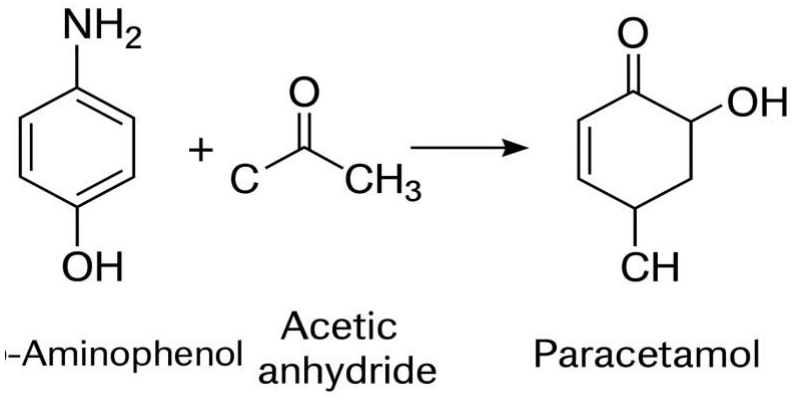

Fig. 1. *Simplified schematic of paracetamol synthesis.*

2.2 Effects on Brain Function and Neurochemistry

Several animal studies have investigated the potential impact of acetaminophen on neurotransmission and brain function. Research conducted on mice has demonstrated altered monoaminergic metabolism in the hypothalamus, cerebellum, medulla, and spinal cord following prenatal exposure to paracetamol. Moreover, acetaminophen administration on postnatal days 3 and 10 resulted in reduced habituation patterns—specifically, decreased locomotor and exploratory activity—observed in two-month-old mice. [8] Some studies have also reported that paracetamol affects the brain's endocannabinoid system, primarily through the CB1 receptor. [9] This system plays a crucial role in regulating mood, pain, appetite, and the metabolism of lipids and glucose. The pharmacological action of paracetamol involves inhibition of anandamide reuptake and activation of CB1 receptors via its active metabolite, *N-arachidonoylphenolamine* (AM404). [10] An experiment on mice demonstrated that a global CB1 antagonist attenuated the antiallodynic effects of acetaminophen in a postoperative pain model induced by surgical incision. The study confirmed CB1 receptor activation by paracetamol in both sexes, across two mouse strains, and following two routes of administration (intraperitoneal and oral). [9] Another experiment suggested that acetaminophen may also exert its effects on

the endocannabinoid system through vanilloid receptors (TRPV1), thereby questioning the exclusive role of CB1 receptors. The TRPV1 receptor is activated by AM404, triggering analgesic effects. Diminished AM404 activity was observed in TRPV1 knockout mice, while animals pretreated with selective CB1 inhibitors did not respond to acetaminophen administration. These findings indicate the involvement of both receptor types in acetaminophen activation within the central nervous system. [11] Additionally, the results suggest that acetaminophen exerts its analgesic effects partly through descending serotonergic pathways in the spinal cord. [12] The endocannabinoid system is therefore believed to contribute to acetaminophen's modulation of acute and chronic pain as well as its influence on pain threshold. [5]

As mentioned in the previous section, an important aspect to consider is the influence of paracetamol on serotonergic neurotransmission. Serotonin plays a crucial role in human pain perception, primarily through modulation of nociceptive transmission within the spinal cord. The bulbospinal serotonergic pathways appear to be involved in the analgesic effects of paracetamol or its metabolites; however, this mechanism requires further investigation. [11] Another experimental study in mice suggested the involvement of both the serotonergic and opioid systems in the induction and maintenance of paracetamol's pharmacological effects. Following acetaminophen administration, laboratory animals exhibited approximately a 30% reduction in both μ-opioid and 5-HT2 receptor density after a 7-day treatment period (with two doses of paracetamol administered per day). [13]

The analgesic effect of paracetamol through serotonergic pathways has been confirmed in studies involving the co-administration of acetaminophen with 5-HT3 receptor antagonists, such as tropisetron and granisetron. This combination resulted in the abolition of APAP-induced analgesia. [14]

Another experiment demonstrated that administration of APAP on the 10th postnatal day in mice led to a reduction in brain-derived neurotrophic factor (BDNF) levels compared to the control group. BDNF supports axonal growth, neuronal survival, synapse formation, and cell migration. [15]

2.3 Possible mechanism of neurotoxicity and oxidative stress.

Influence of paracetamol's actions in human organism was examined in many aspects. The mechanisms by which it damages the kidneys, liver, and potentially the nervous system are complex. Among these, notable pathways include oxidative stress, inflammatory responses, apoptosis, and ferroptosis, first described in 2012. Ferroptosis is characterized by iron-dependent accumulation of reactive oxygen species derived from lipid peroxidation. The principal cell-damaging mechanisms in ferroptosis include disturbances in iron metabolism, impaired antioxidant capacity, accumulation of lipid hydroperoxides, and mitochondrial dysfunction. [7]

The mechanism of hepatocyte injury involves the initiation of mitochondrial oxidative stress and fragmentation of mitochondrial DNA. Reactive oxygen species derived from complex I and III of the electron transport chain also play a significant, albeit not fully understood, role in hepatocyte damage. The details of hepatocyte injury remain unclear. [16] Beyond the effects of ROS, this damage encompasses inflammatory cascades and apoptosis. [17]

The current research focuses on the mechanisms underlying the potential neurotoxicity of paracetamol. A cited study in mice indicates that prenatal exposure to acetaminophen resulted in offspring exhibiting deviations such as impaired nest-finding ability, stereotypical behaviors, and increased vertical exploration. [18] Similar to hepatocytes, neuronal damage may be associated with reactive oxygen species-mediated lipid peroxidation within cells. Another study in experimental animals demonstrated impairments in cognitive function, exploratory behavior, and social interactions in offspring whose mothers were administered paracetamol from the first day of pregnancy. [8] In one study, RNA sequencing was employed for an unbiased exploration of potential mechanisms of acetaminophen neurotoxicity. Experimental animals were subjected to behavioral tests, including the open field test, elevated plus maze, and a 5-choice reaction time task. Despite accounting for sex differences, no significant differences were observed between the control and paracetamol-treated groups. [19]

In another mouse study, paracetamol exposure was associated with DNA damage induced by oxidative stress, as well as excessive activation of the immune system. [15]

Despite numerous studies in human cohorts—accounting for confounding factors such as chronic pain, maternal characteristics, advanced maternal age, and fever—as well as experimental animal studies, the precise mechanism underlying paracetamol neurotoxicity has not been definitively established. [19]

2.4. Individual Differences: Genetics, Metabolism, and Environmental Factors

Despite its reputation as a safe drug, paracetamol can behave differently in the body due to various individual patient factors. In elderly individuals or those with impaired liver or kidney function, acetaminophen metabolism is slower, increasing the risk of acute toxicity. The biotransformation of APAP can also be influenced by other substances, such as salicylates, MAO inhibitors, or alcohol, with chronic alcohol consumption increasing the risk of hepatotoxicity. [6] Acetaminophen metabolism is also affected by genetic factors and chronic diseases. An experiment in rabbits demonstrated statistically significant differences in the half-life of paracetamol between animals with experimentally induced diabetes and healthy controls. The study indicated that disturbances in carbohydrate metabolism could prolong the elimination time of acetaminophen. Additionally, an increase in clearance and volume of distribution was observed in diseased individuals. The experiment also revealed variations in APAP metabolism according to circadian rhythms. [5]

3. Review of Epidemiological Studies

Contemporary research has long focused on potential causes of neurodevelopmental disorders, such as ADHD, autism spectrum disorders, and emotional or behavioral problems. In one cohort study, the association between prenatal exposure to paracetamol and the occurrence of attention-deficit/hyperactivity disorder (ADHD) was investigated. Exposure to acetaminophen was assessed by measuring its concentration in neonatal meconium (odds ratio [OR] 2.43; 95% CI 1.41–4.21). ADHD diagnoses were made prospectively when the children were 6–7 years old. Detection of paracetamol in meconium was associated with an increased likelihood of developing ADHD. Among 345 children, acetaminophen was detected in the meconium of 199, and 33 were diagnosed with ADHD. The study demonstrated a dose–response relationship, with each doubling of the paracetamol dose associated with a 10% increase in the odds of ADHD. [3]

Another large cohort study followed approximately 2.5 million children in Sweden from 1997 to 2019. The study investigated the association between prenatal paracetamol exposure and the development of neurodevelopmental disorders such as ADHD and autism. Diagnoses in children were verified using International Classification of Diseases (ICD) codes from the National Patient Register, as well as the Prescribed Drug Register, which confirmed the use of ADHD medications such as methylphenidate or atomoxetine. Paracetamol use was recorded prospectively based on prenatal records and prescription data. The study controlled for confounding factors, both genetic and environmental, by analyzing siblings from the same biological parents. Multiple sensitivity analyses were also performed to validate the findings. Among the study population, 7.49% of children were prenatally exposed to paracetamol. Exposure was more frequent among children whose parents had lower socioeconomic status, higher body mass index in early pregnancy, smoked during pregnancy, or had diagnosed psychiatric or neurodevelopmental conditions, as well as in children with indications for paracetamol use and concurrent use of related medications.

The results demonstrated a slight increase in the risk of autism following prenatal paracetamol exposure (the 10-year risk of autism was 0.09% higher among children exposed to acetaminophen compared with those unexposed). However, in analyses comparing exposed children with their siblings, no association was found between APAP use and the occurrence of autism (HR 0.98, 95% CI 0.93–1.04), ADHD (HR 0.98, 95% CI 0.94–1.02), or intellectual disability (HR 1.01, 95% CI 0.92–1.10). [4]

In another cohort study involving 996 mothers and children, researchers at Johns Hopkins University in Boston assessed the presence of paracetamol and its metabolites in cord blood samples collected immediately after birth. The study controlled for variables including maternal age, ethnicity, stress, alcohol and drug use, education, body mass index (BMI), fever during pregnancy, and others. The results indicated that children in the high acetaminophen exposure group were 2.14–3.62 times more likely to be diagnosed with autism spectrum disorders and 2.26–2.86 times more likely to be diagnosed with ADHD. [20]

Another sibling-based study examined the association between acetaminophen use for more than 28 days and neurodevelopmental disorders. However, results from sibling comparisons did not support these associations. [21]

In another large study, six major European cohorts were evaluated: the Avon Longitudinal Study of Parents and Children (ALSPAC), DNBC, Gene and Environment: Prospective Study on Infancy in Italy (GASPII), Generation R Study, INMA (comprising four subcohorts), and the Mother–Child Cohort in Crete (RHEA) (Methods S1). Mother–child pairs were assessed between 1992 and 2008. Approximately 73,000 children were included for whom data on prenatal paracetamol exposure were available and for whom at least one early childhood symptom of ASD or ADHD was recorded. The results showed that prenatal acetaminophen use was associated with a 19% increased risk of autism compared with unexposed children

(OR = 1.19; 95% CI: 1.07–1.33), with these disorders more frequently diagnosed in boys. For ADHD, the risk increased by 21%, with a similar increase observed in both male and female children. Additional factors were identified: children with ASD symptoms were more likely to be born to younger mothers with lower educational attainment, alcohol-related problems, or poor mental health during pregnancy. In the case of ADHD, there was a tendency for affected children to be born to primiparous mothers who smoked and also experienced mental health challenges during pregnancy. [22]

A retrospective cohort study was also conducted to evaluate the association between prenatal paracetamol exposure and early childhood language development. The study initially included 532 children and their mothers. Paracetamol use was documented at approximately 10–14, 16–18, 22–24, 28–30, and 34–36 weeks of gestation, as well as within 24 hours after birth, based on detailed maternal interviews regarding medication use, including dosage and indication. This allowed identification of active acetaminophen use. Children's language abilities were assessed using the CDI questionnaire at 26.5–28.5 months of age and the SLAS at 36–38 months. The study controlled for variables including parental education, maternal age, parity, household income, first-trimester tobacco and alcohol use, whether English was the participant's native language, child's age at assessment, and number of older siblings. Additionally, average perceived stress (PSS) and the Edinburgh Postnatal Depression Scale (EPDS) were considered. Paracetamol use during the second and third trimesters was associated with reduced vocabulary size and complexity, regardless of the assessment tool used. No such effects were observed for paracetamol use during the first trimester. [23]

Another study focused not only on the potential occurrence of neurodevelopmental disorders following acetaminophen exposure but also on emotional difficulties in children. Brazilian researchers prospectively assessed a cohort of 4,231 newborns born in Pelotas. The children were subsequently followed up at ages 3, 12, 24, 48, and 72 months, and 11 years. Paracetamol use was determined based on maternal interviews regarding medications taken during pregnancy. Children's symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ), which evaluates 25 psychological attributes divided into five scales: inattention/hyperactivity, conduct problems, emotional symptoms, peer relationship problems, and prosocial behavior. The study accounted for variables including the National Economic Index, sex, maternal education, maternal skin color, parity, maternal smoking during pregnancy, alcohol consumption, maternal BMI, infections during pregnancy, and use of NSAIDs during pregnancy. After adjusting for these factors, emotional problems were observed (OR = 1.47; 95% CI: 1.07–2.02), as well as inattention and hyperactivity in boys. These associations were not observed in girls. [24]

A long-term cohort study conducted in the United Kingdom, involving several thousand pregnant women, reported a slight increase in the risk of behavioral problems, conduct disorders, and difficult temperaments in children, primarily during the preschool years, after adjusting for confounding variables. [25]

Numerous meta-analyses and literature reviews have also assessed the association between paracetamol use during pregnancy and an increased risk of neurodevelopmental disorders. In one such review, databases were analyzed to link acetaminophen use, the occurrence of irregular breathing during pregnancy, and a subsequent ADHD diagnosis. The literature also supported correlations between prenatal APAP exposure and language impairments as well as psychomotor delays. [26]

Another meta-analysis proposed a bold hypothesis suggesting that oxidative stress combined with acetaminophen use may underlie the pathology of autism spectrum disorders (ASD). This implies that in susceptible individuals, paracetamol use could act as a trigger for ASD development. [27]

The Polish Society of Gynecologists and Obstetricians also issued a statement on this topic. They cited two large studies, one of which, conducted in Sweden, was mentioned earlier. The second study was conducted in Japan. Initially, researchers reported a slight increase in the risk of ASD (HR = 1.06); however, after analysis of the control group, this value decreased to HR = 0.68. The initial analysis contained errors in classification, inappropriate selection of the study group, and failure to account for confounding factors. [28]

In another meta-analysis, 46 studies were evaluated. Of these, 27 reported an association between prenatal paracetamol exposure and neurodevelopmental disorders, 9 found no significant association, and 4 reported a negative association. The analysis was conducted using the Scientific Literature Navigation Guide. [29]

Table 1. Summary of Selected Cohort Studies

Area of the research	Amount of examined children	Affliction	Increase risk of NDD	Disturbing factors (amount)	References
Quebec, Canada	345 children	ADHD	2,5x [OR], 2,43; 95% CI, 1,41-4,21	Counted (1)	[3]
Sweden	2 480 797 children	ADHD ASD Intellectual disability	0,09x for ASD After analysis of siblings:lack of risk for **ASD** HR, 0,98 [95% CI, 0,93-1,04] **ADHD** (HR, 0,98 [95% CI, 0,94-1,02] **ID** HR, 1,01 [95% CI, 0,92-1,10]	Counted multiple: economic status,, illnesses, apearence of NDD in family, drugs and alcohol during pregnancy and others	[4]
Boston, USA	996 pair of mother and child	ADHD ASD	**ADHD** II tercile [OR 2,26; 95% CI: 1,40–3,69] III tercyl [OR 2,86; 95% CI: 1,77–4,67] **ASD** II tercile [OR 2,14; 95% CI: 0,93–5,13}] III tercyl [OR 3,62; 95% CI: 1,62–8,60]	Counted multiple: age of mother, ethnic origin, stress, taking drugs and alcohol, education, Body Mass Index (BMI), fever during pregnancy and others	[20]
Norway	26 613 children 12 902 families	ADHD	Exposition to paracetamol: **Under 28 days** - Lack of risk **Over 28 days** - Increase of risk (aHR) = 2,02 (95%(CI) = 1,17–3,25) Control of siblings do not confirm the connection	Counted: analysis of siblings	[21]
6 european cohorts	73 881 pair of mother and child	ASD ADHD	19% for **ASD** OR=1,19; 95% CI: 1,07–1,33 21% for **ADHD** OR=1,21, 95% CI 1,07–1,36	Counted: age of mother, BMI drugs and alcohol, psychiatric disease during pregnancy, fever, infections and others	[22]
Illinois, USA	532 pair of mother and child	Language functions	Nonsignificant growth for II and III trimester	Counted: education of parents, age of mother, amount of births, salary, smoking and alcohol during I trimester and others.	[23]
Pelotas, Brazil	4231 children	NDD Emotional Disorders	Increase risk of emotional problems OR = 1,47; 95% CI: 1,07–2,02	Counted: sex, education, skin colour of mother, number of births, smoking and alcohol during pregnancy, BMI, infections and others.	[24]
Avon, Great Britain	12 418 pregnant women	Behavioural problems Character Disorder	Insignificant increase of risk of behavioural problems and character disorders.	Counted: diseases of mother, current health condition, lifestyle, social conditions and others	[25]

4. Types of Neurodevelopmental Disorders Examined in the Context of Paracetamol Exposure

4.1. Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a highly complex etiology. Among the mechanisms implicated in its pathogenesis are oxidative stress and impaired mitochondrial autophagy. [30] Electroencephalography (EEG) studies have demonstrated reduced functional connectivity in individuals with ADHD, particularly within the alpha, theta, and delta frequency bands, contributing to symptoms primarily in the emotional and behavioral domains. Two brain regions were found to be most prominently involved: the left fusiform gyrus and the left rostral anterior cingulate cortex. [31] Genetic factors play a significant role in the pathogenesis of ADHD. One study investigating the genetic basis of neurodevelopmental disorders identified similar variants of dopaminergic genes in children with ADHD. The same study also emphasized the importance of environmental factors such as maternal stress during pregnancy, pregnancy complications, low socioeconomic status, and maternal medication use during gestation in the development of neurodevelopmental disorders, including ADHD. [32] Representative symptoms of ADHD include inattention, hyperactivity, and impulsivity. Additional characteristic features comprise excessive talkativeness, restlessness, carelessness, and avoidance of tasks requiring sustained mental effort. Diagnosis requires the presence of at least six features as specified in the DSM-5 criteria. [33]

An increasing number of studies link attention-deficit/hyperactivity disorder (ADHD) with oxidative stress and subsequent mitochondrial dysfunction. Due to the involvement of high-energy-demand systems—such as the central nervous system, gastrointestinal tract, and musculoskeletal system—the etiology of ADHD has been associated with disrupted cellular metabolism. The oxidative stress that underlies this disruption may originate as early as during maternal pregnancy, subsequently activating in the fetus and triggering a cascade of inflammatory responses, increased mitochondrial production of reactive oxygen species (ROS), neuroinflammation, and neuronal damage. These processes may ultimately contribute to the development of neurodevelopmental disorders. [15]

4.2. Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is characterized by two core diagnostic domains: (1) deficits in social communication and social interaction, and (2) restricted, repetitive patterns of behavior, interests, or activities. [33] Furthermore, symptoms must be present from early infancy and must limit or impair social functioning. [34] As in the case of ADHD, the etiology and pathogenesis of ASD are highly complex. Autism has been associated with mitochondrial dysfunctions. Mitochondria are essential for neuronal migration, and aberrant localization or delayed migration of neurons often leads to abnormal cortical stratification. [30] Genetic factors may also play a role—for example, the loss of fragile X messenger ribonucleoprotein (FMRP) results in Fragile X syndrome, a severe form of autism spectrum disorder. [35] However, most ASD cases appear to follow a polygenic inheritance pattern, indicating that no single gene is solely responsible for the disorder.

Among environmental factors implicated in the development of ASD are prenatal exposure to air pollution, low birth weight, advanced parental age, viral infections during pregnancy, prematurity, multiple gestation, maternal autoimmune diseases, and prenatal stress. [36], [37]

Genetic factors underlying ASD and ADHD frequently overlap. One study identified 17 loci shared between autism and ADHD. Similar to attention-deficit/hyperactivity disorder, autism may be linked to oxidative stress and consequent mitochondrial pathology. Developmental neurotoxins that induce oxidative stress have been associated with both disorders. Up to 80% of individuals with autism display markers of mitochondrial abnormalities, such as altered mitochondrial-to-nuclear DNA ratios. Structural alterations in mitochondrial DNA and deficiencies in electron transport chain proteins have also been demonstrated. [15]

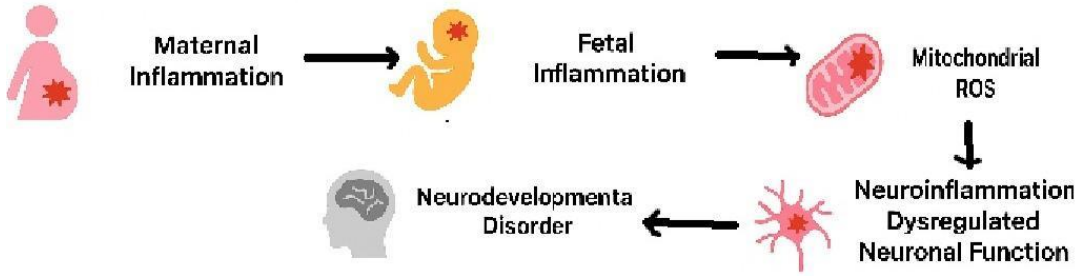

Fig. 2. *Potential mechanism of neurodevelopmental disorders.*

4.3. Other Potential Consequences of Prenatal Exposure to Paracetamol

Due to its potential effects on the central nervous system, paracetamol may also influence other aspects of cognitive and emotional functioning in children.

Cohort studies, after adjusting for confounding variables, have indicated possible adverse effects of acetaminophen exposure on language development, emotional regulation, and behavioral outcomes. Specifically, prenatal exposure to paracetamol has been associated with reduced language abilities, increased incidence of emotional difficulties, problems with attention and concentration, behavioral disturbances, and the presence of difficult temperament traits in children. [23–25]

5. Factors Modifying the Risk of Paracetamol Exposure

Contemporary scientific literature highlights the complex etiology of neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). The occurrence of these conditions is most likely associated with a combination of genetic predisposition and environmental influences. When considering the potential impact of paracetamol on the development of neurodevelopmental disorders, several modifying factors must be taken into account. One important factor is maternal infection during pregnancy — prenatal exposure to influenza, cytomegalovirus, or rubella has been shown to correlate with an increased risk of autism in offspring. These infections are frequently accompanied by fever, which may lead pregnant women to use paracetamol — currently the only antipyretic medication considered safe during pregnancy. Advanced parental age may also modulate the risk of neurodevelopmental disorders. With increasing paternal age, the accumulation of *de novo* mutations in the germline becomes more likely, while maternal age is associated with a higher prevalence of autoimmune conditions. Additionally, older parents may have increased use of analgesic medications due to the presence of chronic or degenerative diseases. [37], [4]

The dose and duration of paracetamol exposure also appear to influence the likelihood of neurodevelopmental disorders. One cohort study demonstrated that acetaminophen use for less than seven days was associated with a relatively small risk of attention-deficit/hyperactivity disorder (ADHD) in offspring. However, exposure exceeding 29 days was linked to a (HR) of 2.20 (95% CI: 1.50–3.24), regardless of the indication for its use. This association was also observed in fathers who used paracetamol prior to conception. [38]

A separate study assessing paracetamol metabolite concentrations in neonatal meconium categorized exposure into three quantitative levels. For the lowest exposure level, the risk to the fetus did not differ significantly from that observed in unexposed pregnancies. In contrast, the highest level of prenatal acetaminophen exposure was associated with a fourfold increase in the risk of developing ADHD. [3]

The most critical period for exposure to teratogenic substances during pregnancy is between days 14 and 56, corresponding to the phase of organogenesis. Drug intake during this window carries the greatest risk of inducing structural malformations. The perinatal period may also present risks, as certain substances can influence uterine contractility or exacerbate bleeding during labor. [39]

The nervous system develops continuously throughout pregnancy, beginning around day 20, when the primordial structures of the brain and spinal cord become visible. The fifth week represents the peak period of neural development, encompassing the formation of the pituitary gland and the establishment of spinal

synapses. Subsequent months involve the progressive enrichment of the nervous system through the addition of new neurons and glial cells. During the third trimester, the already advanced brain architecture undergoes functional refinement, including processes such as differentiation, learning, memory formation, acquisition of habits and preferences, and the emergence of primary emotions. [40] A cohort study evaluating language development in children suggested that the second and third trimesters of pregnancy constitute the most vulnerable periods for the potential neurodevelopmental effects of acetaminophen exposure. [23]

6. Discussion

At present, numerous researchers are investigating the potential causes of neurodevelopmental disorders, with particular attention given to the possible role of acetaminophen (paracetamol)—the most commonly used medication during pregnancy—in the etiology of ADHD, ASD, and other neurological dysfunctions.

A growing body of evidence suggests an association between prenatal paracetamol exposure and later neurodevelopmental abnormalities. When confounding variables are not accounted for, the relationship between acetaminophen exposure and the development of ADHD or autism appears relatively straightforward. [3] Furthermore, concerns have been raised regarding the drug's broad impact on various brain systems and functions. Animal studies have demonstrated significant effects of acetaminophen on both the endocannabinoid and serotonergic systems. [9], [11], [13]

In addition, experiments involving APAP exposure have shown that animals display deficits in environmental adaptation and behavioral regulation, such as difficulty locating their nests and exhibiting stereotypic or abnormal behaviors. [8], [18] Several studies and experimental findings also emphasize potential mechanisms of acetaminophen-induced neurotoxicity, including oxidative stress, DNA damage, immune system overactivation, and mitochondrial dysfunction. [7], [15–17]

Some cohort studies have reported only minor differences between control groups (unexposed to paracetamol) and exposed groups in terms of the incidence of neurodevelopmental disorders. Other studies have emphasized the significant contribution of confounding factors, such as genetic predisposition (many sibling-comparison studies have challenged the causal role of acetaminophen), advanced parental age, and maternal conditions during pregnancy, including fever and chronic illnesses. The aforementioned studies suggest that the presence of acetaminophen exposure may be coincidental or clinically insignificant in the pathogenesis of neurodevelopmental disorders. Instead, they propose that the underlying causes of ADHD and ASD may be related to other factors that are indirectly associated with acetaminophen use. [4], [37] Notably, studies reporting a strong association between acetaminophen exposure and the development of neurodevelopmental or neurodegenerative abnormalities often failed to account for critical confounders, such as environmental influences, pregnancy complications, or maternal comorbidities. Furthermore, even in analyses that adjusted for confounding variables, the increased risk linked to acetaminophen use was rarely of clinical or statistical significance. [3], [21], [25]

Some studies also rely on indirect or insufficiently reliable measures of paracetamol exposure, such as prescription records or medical documentation. These data sources do not allow for accurate estimation of the actual dose ingested or even confirmation of whether the medication was truly consumed, given that paracetamol is readily available over the counter and is commonly used without prescription. [4], [22–24]

Considering the critical importance of fetal exposure to potentially harmful agents, it is essential to conduct further research that accounts for as many confounding factors as possible. Future studies should also aim to employ more precise and standardized methods for quantifying acetaminophen exposure, thereby improving the reliability and interpretability of results.

7. Conclusions

Paracetamol remains an essential medication for the management of fever and pain in pregnant women. However, current evidence does not provide a definitive answer as to whether the drug constitutes a causal factor in the development of neurodevelopmental disorders in children. At present, the medical literature does not confirm a cause-and-effect relationship between prenatal acetaminophen exposure and the subsequent occurrence of autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD) in offspring. Nonetheless, both human cohort studies and animal experiments have reported certain correlations between acetaminophen exposure and an increased risk of neurodevelopmental abnormalities. These findings indicate that paracetamol should be used with caution during pregnancy, and only when clinically necessary, in strict accordance with the product characteristics and medical recommendations.

REFERENCES

1. Patel R, Sushko K, van den Anker J, Samiee-Zafarghandy S. Long-term safety of prenatal and neonatal exposure to paracetamol: a systematic review. *Int J Environ Res Public Health.* 2022 Feb 14;19(4):2128. doi:10.3390/ijerph19042128. PMID: 35206317; PMCID: PMC8871754.
2. Bauer AZ, Swan SH, Kriebel D, Liew Z, Taylor HS, Bornehag CG, et al. Paracetamol use during pregnancy: a call for precautionary action. *Nat Rev Endocrinol.* 2021 Dec;17(12):757–66. doi:10.1038/s41574-021-00553-7. PMID: 34556849; PMCID: PMC8580820.
3. Baker BH, Lugo-Candelas C, Wu H, et al. Association of prenatal acetaminophen exposure measured in meconium with risk of attention-deficit/hyperactivity disorder mediated by frontoparietal network brain connectivity. *JAMA Pediatr.* 2020;174(11):1073–81. doi:10.1001/jamapediatrics.2020.3080.
4. Ahlqvist VH, Sjöqvist H, Dalman C, et al. Acetaminophen use during pregnancy and children's risk of autism, ADHD, and intellectual disability. *JAMA.* 2024;331(14):1205–14. doi:10.1001/jama.2024.3172.
5. Kamińska A. Wpływ cukrzycy na parametry farmakokinetyczne paracetamolu po podaniu dożylnym.
6. Paracetamol Polpharma. Charakterystyka Produktu Leczniczego (ChPL). Zakłady Farmaceutyczne Polpharma S.A.; 2023 [dostęp 13 października 2025]. Dostępne w: https://rejestrymedyczne.ezdrowie.gov.pl.
7. Zhu S, Ren J, Zhang Y, Sun X, Pei H, Yin B, et al. Sesamin protects against acetaminophen-induced nephrotoxicity by suppressing HMOX1-mediated apoptosis and ferroptosis. *Redox Rep.* 2025;30(1). doi:10.1080/13510002.2025.2529695.
8. Rigobello C, Klein RM, Debiasi JD, Ursini LG, Michelin AP, Matsumoto AK, et al. Perinatal exposure to paracetamol: dose- and sex-dependent effects on behaviour and brain oxidative stress markers in progeny. *Behav Brain Res.* 2021 Jun 25;408:113294. doi:10.1016/j.bbr.2021.113294. PMID: 33836167.
9. Jesus CHA, Wirt JL, Ferreira LA, Hainline J, Huizenga M, Rems L, et al. Acetaminophen attenuates pathological pain through a mechanism requiring CB1 cannabinoid receptors and diacylglycerol lipase in mice. *bioRxiv* [Preprint]. 2025 May 13:2025.05.08.652937. doi:10.1101/2025.05.08.652937. PMID: 40463236; PMCID: PMC12132488.
10. Stasiulewicz A, Lesniak A, Setny P, Bujalska-Zadrożny M, Sulkowska JI. Identification of CB1 ligands among drugs, phytochemicals and natural-like compounds: virtual screening and in vitro verification. *ACS Chem Neurosci.* 2022 Oct 19;13(20):2991–3007. doi:10.1021/acschemneuro.2c00502. PMID: 36197801; PMCID: PMC9585589.
11. Mallet C, Desmeules J, Pegahi R, Eschalier A. An updated review on the metabolite (AM404)-mediated central mechanism of action of paracetamol: experimental evidence and potential clinical impact. *J Pain Res.* 2023 Mar 29;16:1081–94. doi:10.2147/JPR.S393809. PMID: 37016715; PMCID: PMC10066900.
12. Tsuzawa K, Onimaru H, Inagaki K, Izumizaki M. Involvement of cannabinoid receptors in depression of the putative nociceptive response in spinal cord preparations isolated from neonatal rats. *J Physiol Sci.* 2023 Oct 6;73(1):23. doi:10.1186/s12576-023-00881-5. PMID: 37803279; PMCID: PMC10717773.
13. Sandrini M, Vitale G, Ruggieri V, Pini LA. Effect of acute and repeated administration of paracetamol on opioidergic and serotonergic systems in rats. *Inflamm Res.* 2007 Apr;56(4):139–42. doi:10.1007/s00011-006-6113-z. PMID: 17522810.
14. Słaby M, Szczukocka M, Pulkowski M, Słaby D, Beberok A, Wrześniok D. „Tylko dawka czyni truciznę" – czyli bezpieczeństwo stosowania paracetamolu. *Farm Pol.* 2019;75:389–95.
15. Chu S, Woodfin S, Bayliss E, Smith M, Fulp A, Mirabelli E, et al. Acetaminophen's role in autism and ADHD: a mitochondrial perspective. *Int J Mol Sci.* 2025 Sep 3;26(17):8585. doi:10.3390/ijms26178585. PMID: 40943505; PMCID: PMC12429359.
16. Adelusi OB, Venkatraman A, Akakpo JY, Ramachandran A, Jaeschke H. Iron supplementation switches mode of cell death to ferroptosis during acetaminophen-induced liver injury in mice rendering it resistant to N-acetylcysteine. *Toxicology.* 2025 Nov;517:154221. doi:10.1016/j.tox.2025.154221. PMID: 40518003.
17. Xiao Z, Liu Y, Tao Z, et al. Tungsten disulfide atomic crystals with RONS scavenging and liver targeting capabilities for acetaminophen-induced acute liver injury therapy. *J Nanobiotechnol.* 2025;23:665. doi:10.1186/s12951-025-03771-7.
18. Klein RM, Rigobello C, Vidigal CB, Moura KF, Barbosa DS, Gerardin DCC, et al. Gestational exposure to paracetamol in rats induces neurofunctional alterations in the progeny. *Neurotoxicol Teratol.* 2020 Jan–Feb;77:106838. doi:10.1016/j.ntt.2019.106838. PMID: 31644948.
19. Baker BH, Rafikian EE, Hamblin PB, Strait MD, Yang M, Pearson BL. Sex-specific neurobehavioral and prefrontal cortex gene expression alterations following developmental acetaminophen exposure in mice. *Neurobiol Dis.* 2023 Feb;177:105970. doi:10.1016/j.nbd.2022.105970. PMID: 36549432; PMCID: PMC9940030.
20. Ji Y, Azuine RE, Zhang Y, et al. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *Arch Gen Psychiatry.* 2020;77:180–9.
21. Gustavson K, Ystrom E, Ask H, et al. Paracetamol use during pregnancy and attention-deficit/hyperactivity disorder in offspring: a longitudinal sibling-control study. *JCPP Adv.* 2021;1:e12020. doi:10.1002/jcv2.12020.

22. Alemany S, Avella-García C, Liew Z, et al. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: meta-analysis in six European population-based cohorts. *Eur J Epidemiol.* 2021;36:993–1004. doi:10.1007/s10654-021-00754-4.
23. Woodbury ML, Cintora P, Ng S, Hadley PA, Schantz SL. Examining the relationship of acetaminophen use during pregnancy with early language development in children. *Pediatr Res.* 2024 Jun;95(7):1883–96. doi:10.1038/s41390-023-02924-4. PMID: 38081897; PMCID: PMC11164826.
24. 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;18:368. doi:10.1186/s12888-018-1942-1.
25. Golding J, et al. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: a longitudinal cohort study. *Paediatr Perinat Epidemiol.* 2019;33(4):1–10. doi:10.1111/ppe.12582.
26. Bérard A, Cottin J, Leal LF, et al. Systematic review and meta-analysis: acetaminophen use during pregnancy and the risk of neurodevelopmental disorders in childhood. *J Am Acad Child Adolesc Psychiatry.* 2025 Sep 30:S0890-8567(25)02106-9. doi:10.1016/j.jaac.2025.09.031. PMID: 41062061.
27. Jones JP 3rd, Williamson L, Konsoula Z, Anderson R, Reissner KJ, Parker W. Evaluating the role of susceptibility-inducing cofactors and of acetaminophen in the etiology of autism spectrum disorder. *Life (Basel).* 2024 Jul 23;14(8):918. doi:10.3390/life14080918. PMID: 39202661; PMCID: PMC11355895.
28. Szubert M, Stojko R, Sieroszewski P. Statement of the Polish Society of Gynecologists and Obstetricians on paracetamol use during pregnancy and autism risk. *Ginekol Pol.* 2025 Oct 3. doi:10.5603/gpl.108872. PMID: 41041851.
29. Prada D, Ritz B, Bauer AZ, Baccarelli AA. Evaluation of the evidence on acetaminophen use and neurodevelopmental disorders using the Navigation Guide methodology. *Environ Health.* 2025 Aug 14;24(1):56. doi:10.1186/s12940-025-01208-0. PMID: 40804730; PMCID: PMC12351903.
30. Yang Z, Luo Y, Yang Z, et al. Mitochondrial dynamics dysfunction and neurodevelopmental disorders: from pathological mechanisms to clinical translation. *Neural Regen Res.* 2026 May 1;21(5):1926–46. doi:10.4103/NRR.NRR-D-24-01422. PMID: 40537021.
31. Morand-Beaulieu S, Zhong J, Ibrahim K, et al. Electroencephalographic functional connectivity patterns in children with Tourette syndrome and attention-deficit/hyperactivity disorder. *Pediatr Neurol.* 2025 Nov;172:53–62. doi:10.1016/j.pediatrneurol.2025.08.001. PMID: 40884873.
32. Li L, Song LJ, Liu XL, Wang ZF. Roles of genetic and environmental factors in psychiatric comorbidities among children with neurodevelopmental delays. *World J Psychiatry.* 2025 Oct 19;15(10):107123. doi:10.5498/wjp.v15.i10.107123. PMID: 41112610; PMCID: PMC12531954.
33. Administracja ds. Nadużywania Substancji i Usług Zdrowia Psychicznego. *Zmiany w DSM-5: Implikacje dla poważnych zaburzeń emocjonalnych u dzieci.* 2016 [dostęp 31 sierpnia 2025]. Dostępne w: https://www.ncbi.nlm.nih.gov/books/NBK519708/.
34. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington (VA): American Psychiatric Publishing; 2013.
35. D'Souza MN, Gowda NKC, Hariharan N, Qadri SW, Palakodeti D, Muddashetty RS. Altering rRNA 2'-O-methylation pattern during neuronal differentiation is regulated by FMRP. *RNA Biol.* 2025 Dec;22(1):1–22. doi:10.1080/15476286.2025.2563986. PMID: 41042002; PMCID: PMC12498540.
36. Simoncic V, Wenger R, Monnier M, et al. Perinatal air pollution exposure and autism spectrum disorder severity: the intertwined roles of green space, grey space and healthcare accessibility. *Environ Res.* 2025 Nov 15;285(Pt 5):122577. doi:10.1016/j.envres.2025.122577. PMID: 40850432.
37. Grabrucker AM. Environmental factors in autism. *Front Psychiatry.* 2013;3:118. doi:10.3389/fpsyt.2012.00118.
38. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics.* 2017;140:e20163840.
39. Szałek E, Grześkowiak E. *Bezpieczeństwo farmakoterapii w okresie ciąży.* Katedra i Zakład Farmacji Klinicznej i Biofarmacji, Uniwersytet Medyczny w Poznaniu.
40. Kończewska-Murdzek Z, Murdzek-Wierzbicka M. *Rozwój dziecka w łonie matki.* Towarzystwo Uniwersyteckie Fides et Ratio; 2022.
41. Machoy-Mokrzyńska AM, Oronowicz K, Białecka M. *Stosowanie leków przeciwbólowych u kobiet w ciąży.* Pomorski Uniwersytet Medyczny w Szczecinie;