

# Acetaminophen and Neurodevelopment

## The Role of Acetaminophen in the Development of Autism Spectrum Disorder (ASD)

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CEO

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disease in high-income regions

*Suggested Visual:*

*Image of vintage acetaminophen bottles from the 1950s.*

**Slide 1:** Acetaminophen, a widely used medication since the 1950s, gained popularity for treating pain and fever.

*Suggested Visual:*

*Timeline of the evolution of acetaminophen packaging over the decades, indicating that the use of aspirin decreased with the increase in the use of acetaminophen.*

**Slide 2:** Initially considered safe for pediatric use, acetaminophen became a primary choice following concerns about aspirin and the Reye Syndrome.

## Suggested Visuals:

a) Cover page of the research paper by Stephen Schultz et al.

b) Table highlighting the odds ratio of 20.9.

### Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder

The results of a parent survey

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**ABSTRACT** The present study was performed to determine whether acetaminophen (paracetamol) use after the measles-mumps-rubella vaccination could be associated with autistic disorder. This case-control study used the results of an online parental survey conducted from 16 July 2005 to 30 January 2006, consisting of 83 children with autistic disorder and 80 control children. Acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic

**KEYWORDS**  
acetaminophen;  
autism;  
paracetamol;  
vaccination



**Table 3 Adjusted<sup>a</sup> associations of analgesic use age 12–18 months with autistic disorder, 2005–6**

Variable (n = cases, controls)	Odds ratio	95% CI	p-value <sup>b</sup>
<i>Children 1–18 years</i>			
Acetaminophen (70, 67)	8.37	2.08–33.7	<b>0.003</b>
Ibuprofen (49, 53)	2.17	0.82–5.72	0.119
<i>Children 1–5 years</i>			
Acetaminophen (23, 23)	5.29	0.99–28.3	0.052
Ibuprofen (16, 19)	1.23	0.22–6.85	0.810
<i>Children 1–18 years, cases limited to children with regression</i>			
Acetaminophen (26, 67)	<b>20.9</b>	1.33–32.9	<b>0.031</b>
Ibuprofen (20, 53)	2.14	0.63–9.54	0.199

<sup>a</sup> Adjusted for age, gender, and mother's ethnicity.

<sup>b</sup> Bold type denotes significance.

300

**Slide 3:** However, in 2008, a study by Stephen Schultz et al. revealed a 20-times greater risk of regressive Autism Spectrum Disorder (autism) in children using acetaminophen between 12 and 18 months.

*Suggested Visual:*

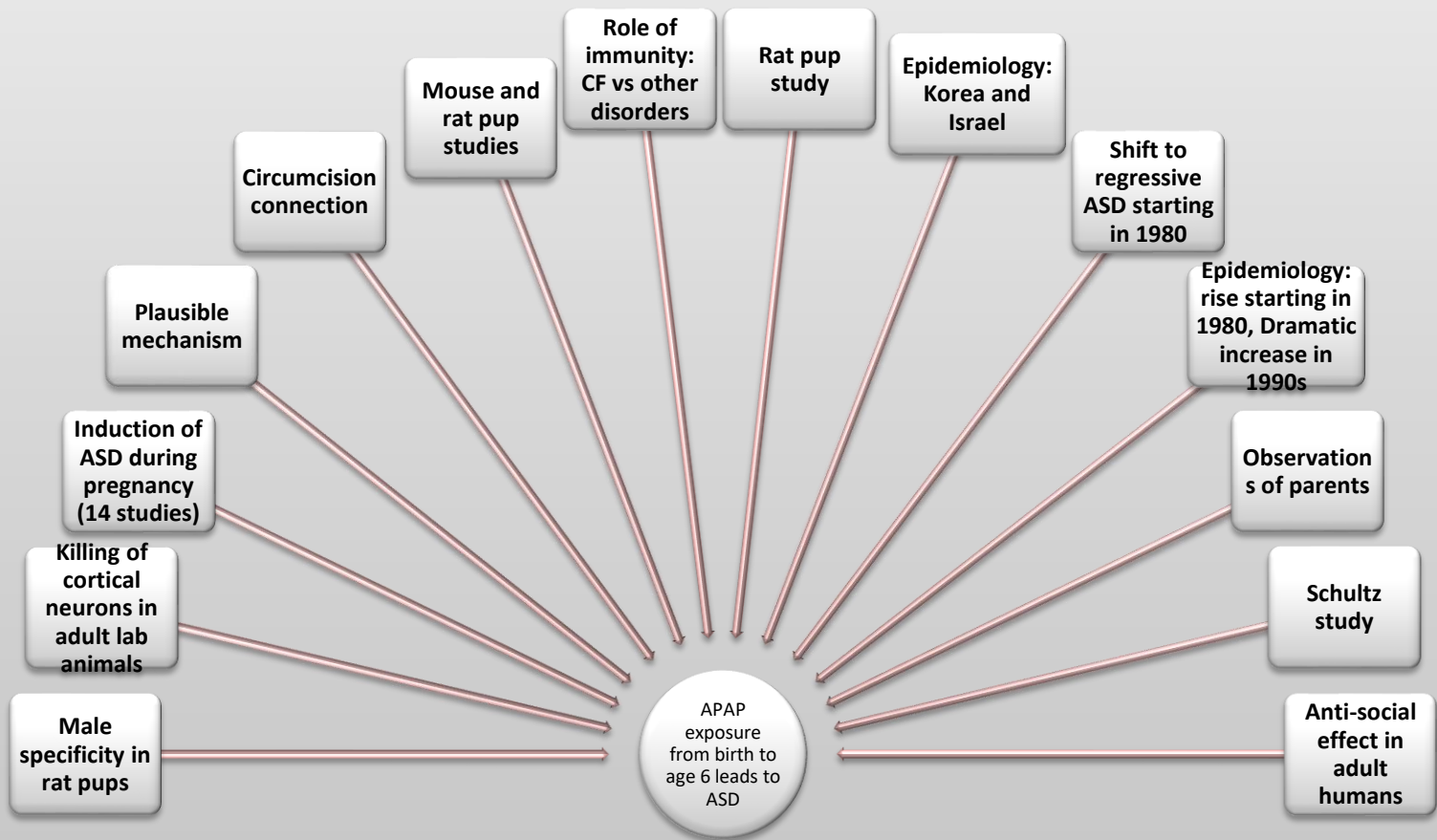
*List of 22 lines of evidence pointing out acetaminophen use as a cause of autism.*

*[Table 1 from the article published in the journal Children: *The Dangers of Acetaminophen for Neurodevelopment Outweigh Scant Evidence for Long-Term Benefits* - PubMed ([nih.gov](https://pubmed.ncbi.nlm.nih.gov/))]*

**Slide 4:** By 2022, growing evidence pointed conclusively to acetaminophen as a cause of many, if not most, cases of autism. As of 2023, 22 total lines of evidence supported this conclusion.

*Suggested Visual:*

*Evidence diagram showing the links between acetaminophen use and autism.*

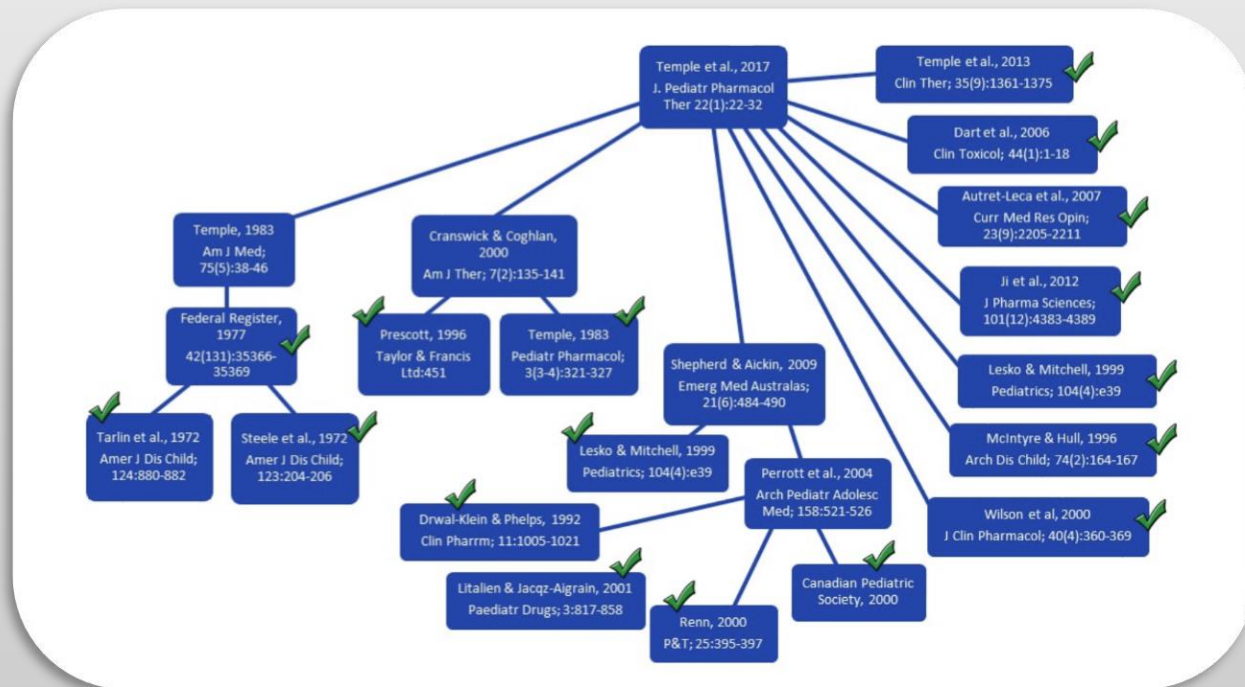


**Slide 5:** Evidence highlighted numerous associations linking acetaminophen use during early neurodevelopment to autism

## Suggested Visual:

Bubble graph of all the papers that claimed acetaminophen to be safe.

Systematic tracking of studies which claimed acetaminophen to be safe brought to light the fact that none of the experiments conducted in those studies conclusively demonstrated safety.

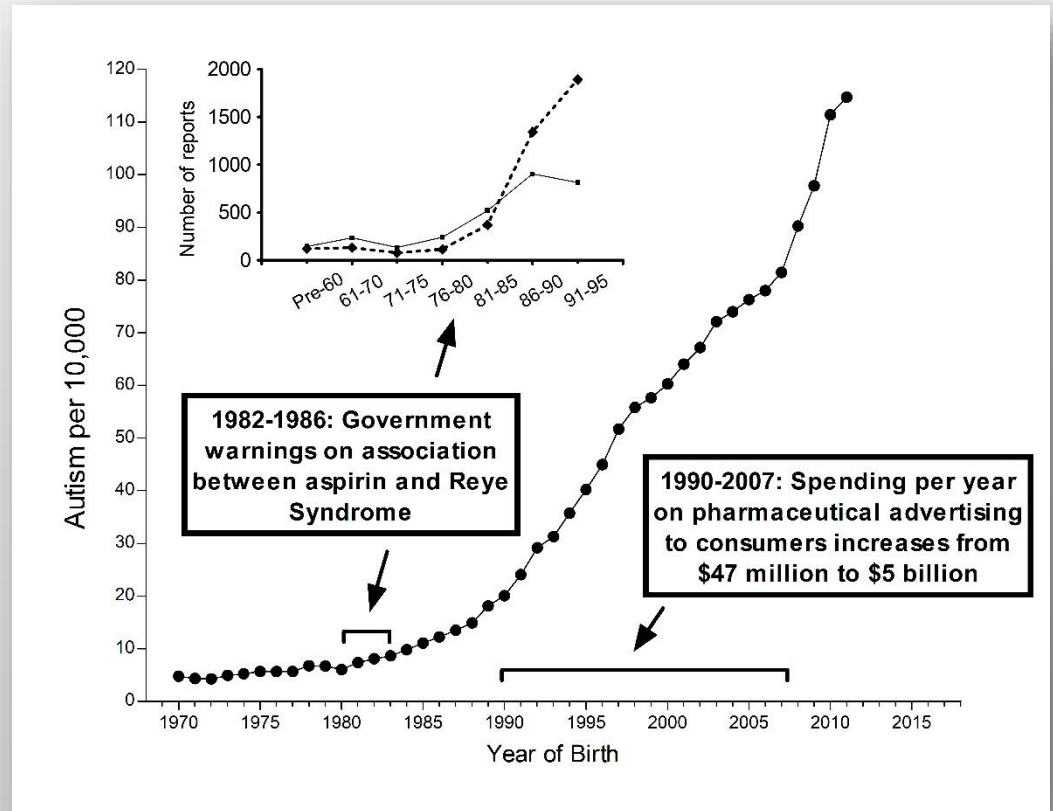


Slide 6: Acetaminophen was never proven to be safe for babies and children.

Figure reference: Figure 1 from <https://pubmed.ncbi.nlm.nih.gov/35175416/>

*Suggested Visual:*

*Diagram linking early neurodevelopment to autism with the increased use of acetaminophen.*



**Slide 7:** A dozen independent associations that connect acetaminophen and autism include findings involving circumcision, South Korean children's product discrepancies, and changes in autism prevalence, coinciding with the increased use of acetaminophen.

Figure reference: adapted from Figure 2 of <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5536672/>



# Suggested Visual: Images of previous/ongoing laboratory studies.

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**Prostaglandin E2 is an endogenous modulator of cerebellar development and complex behavior during a sensitive postnatal period**  
Shuman L. Dzen <sup>1,2</sup>, Jessica F. Knutzen <sup>1,2</sup>, Debra L. Koshi-Kohr <sup>1,2</sup> and Margaret M. McCarthy <sup>1,2</sup>  
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<sup>2</sup>Department of Physiology and Pharmacology, University of Maryland School of Medicine, Baltimore, MD 21201, USA

**Abstract**  
Prostaglandins are lipid-derived molecules that modulate the generation of ions to control ionemys systems. In addition to their proinflammatory role, prostaglandins also impact neuronal development and synaptic plasticity within the brain. In a specific system, the cerebellum has a high expression of prostaglandin receptors during development. We here explore the role of prostaglandin signaling in cerebellar development during a sensitive postnatal period. We report that mice lacking prostaglandin synthase 2 (cyclooxygenase-2) exhibit developmental delays in cerebellar maturation, including a delay in the onset of myelination, reduced synaptic plasticity, and impaired learning. These mice exhibit motor deficits, including a delay in the onset of walking and impaired balance. These mice also exhibit a significant increase in the number of neurons in the granule cell layer of the cerebellar cortex, suggesting a role for prostaglandin signaling in cerebellar development and function. Our findings demonstrate that prostaglandin signaling is essential for normal cerebellar development and function, and that disruption of prostaglandin signaling leads to developmental delays and motor deficits. Our findings also suggest that prostaglandin signaling may play a role in the regulation of neurogenesis and synaptic plasticity in other regions of the brain.

**Keywords:**  
cyclic adenosine monophosphate; development; gene expression

**Introduction**

Prostaglandin synthase (cyclooxygenase) is a membrane-bound enzyme that functions as a prostaglandin synthase, and it is essential for the production of prostaglandins (PGs) from arachidonic acid. PGs are signaling molecules that are involved in a wide variety of biological processes, including inflammation, pain, and fever. PGs also play a role in the regulation of blood pressure, platelet aggregation, and other physiological processes.

**Discussion**

Our findings demonstrate that prostaglandin signaling is essential for normal cerebellar development and function. We report that mice lacking prostaglandin synthase 2 (cyclooxygenase-2) exhibit developmental delays in cerebellar maturation, including a delay in the onset of myelination, reduced synaptic plasticity, and impaired learning. These mice exhibit motor deficits, including a delay in the onset of walking and impaired balance. These mice also exhibit a significant increase in the number of neurons in the granule cell layer of the cerebellar cortex, suggesting a role for prostaglandin signaling in cerebellar development and function. Our findings also suggest that prostaglandin signaling may play a role in the regulation of neurogenesis and synaptic plasticity in other regions of the brain.

**taminihom Induces Apoptosis in Rat Cortical Irons**  
<sup>1,2</sup>Alida Pineda, <sup>1,2</sup>Pablo Santos, <sup>1,2</sup>Alfonso Blanco, <sup>1,2</sup>Martinego Suarez-Fernandez, <sup>1,2</sup>in Gadeo <sup>1,2</sup>

**Abstract**  
Iron is an essential element for life, but its excess is toxic. Iron overload leads to liver disease, cirrhosis, and other complications. The aim of this study was to determine the effect of taminihom on iron metabolism and its effect on the expression of iron-regulatory genes in rat cortical cells. We report that taminihom treatment increases the expression of hepcidin, a key regulator of iron metabolism, and decreases the expression of iron-regulatory genes, including transferrin receptor 1 and 2. These findings suggest that taminihom may play a role in the regulation of iron metabolism and its effect on the expression of iron-regulatory genes in rat cortical cells.

**Keywords:**  
iron metabolism; hepcidin; transferrin receptor

**Introduction**

Iron is an essential element for life, but its excess is toxic. Iron overload leads to liver disease, cirrhosis, and other complications. The aim of this study was to determine the effect of taminihom on iron metabolism and its effect on the expression of iron-regulatory genes in rat cortical cells.

**Discussion**

Our findings suggest that taminihom may play a role in the regulation of iron metabolism and its effect on the expression of iron-regulatory genes in rat cortical cells. We report that taminihom treatment increases the expression of hepcidin, a key regulator of iron metabolism, and decreases the expression of iron-regulatory genes, including transferrin receptor 1 and 2. These findings suggest that taminihom may play a role in the regulation of iron metabolism and its effect on the expression of iron-regulatory genes in rat cortical cells.

## Sulbutamol Deficit in "Low-Functioning" Autistic A Pilot Study

in, Patricia Pironne, Maurizio Elia, Rosemary H. Waring, <sup>1,2</sup>inno

**Abstract**  
Sulbutamol is a beta-2 adrenergic agonist that is used to treat asthma. It has been suggested that a deficit in the expression of beta-2 adrenergic receptors may be associated with autism spectrum disorder (ASD). We report that a pilot study of the effects of sulbutamol on the behavior of children with ASD. We report that sulbutamol treatment significantly improved the behavior of children with ASD, suggesting a role for beta-2 adrenergic receptors in the regulation of behavior in this population.

**Keywords:**  
autism spectrum disorder; sulbutamol; behavior

**Introduction**

Sulbutamol is a beta-2 adrenergic agonist that is used to treat asthma. It has been suggested that a deficit in the expression of beta-2 adrenergic receptors may be associated with autism spectrum disorder (ASD). We report that a pilot study of the effects of sulbutamol on the behavior of children with ASD.

**Discussion**

Our findings suggest that a deficit in the expression of beta-2 adrenergic receptors may be associated with autism spectrum disorder (ASD). We report that a pilot study of the effects of sulbutamol on the behavior of children with ASD, suggesting a role for beta-2 adrenergic receptors in the regulation of behavior in this population.

**acetamol (Acetaminophen) Administration During Neonatal Brain Ischemia Affects Cognitive Function and Alters Its Analgesic and Anxiolytic Response in Adult Mice**  
<sup>1,2</sup>Henrik Vilgus, <sup>1,2</sup>Per Skjold, <sup>1,2</sup>Baron Glaser, <sup>1,2</sup>Andreas Fahlke, <sup>1,2</sup>Christoph G. Doherty, <sup>1,2</sup>Martin Hecht, <sup>1,2</sup>and Andreas Fahlke

**Abstract**  
Acetaminophen is a widely used analgesic and antipyretic. It has been suggested that acetaminophen may have neuroprotective effects. We report that neonatal administration of acetaminophen during brain ischemia in mice affects cognitive function and alters its analgesic and anxiolytic response in adult mice. We report that neonatal acetaminophen treatment significantly improved cognitive function and reduced analgesic and anxiolytic responses in adult mice, suggesting a role for acetaminophen in the regulation of cognitive function and behavior in this population.

**Keywords:**  
acetaminophen; brain ischemia; cognitive function; analgesia; anxiety

**Introduction**

Acetaminophen is a widely used analgesic and antipyretic. It has been suggested that acetaminophen may have neuroprotective effects. We report that neonatal administration of acetaminophen during brain ischemia in mice affects cognitive function and alters its analgesic and anxiolytic response in adult mice.

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Our findings suggest that neonatal administration of acetaminophen during brain ischemia in mice affects cognitive function and alters its analgesic and anxiolytic response in adult mice, suggesting a role for acetaminophen in the regulation of cognitive function and behavior in this population.

## PLOS ONE

frontiers in Toxicology  
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ACCEPTED MANUSCRIPT

### Therapeutic doses of acetaminophen with co-administration of cysteine and mannitol during early development result in long term behavioral changes in laboratory rats

Naveed Sultan <sup>1,2</sup>, Janina Carrasco Hernandez <sup>1,2</sup>, John Pybus <sup>1,2</sup>, John P. Jones <sup>1,2</sup>, Zachariah Karamela <sup>1,2</sup>, Caroline Smith <sup>1,2</sup>, William Paulsen <sup>1,2</sup>

**Abstract**  
Based on several lines of evidence, numerous investigators have suggested that acetaminophen exposure during early development can cause neurotoxicity. We here provide a preliminary demonstration that acetaminophen exposure during early development in rats results in long term behavioral changes in laboratory rats. We report that neonatal acetaminophen treatment significantly altered behavior in adult rats, suggesting a role for acetaminophen in the regulation of behavior in this population.

**Keywords:**  
acetaminophen; early development; behavior; neurotoxicity

**Introduction**

Based on several lines of evidence, numerous investigators have suggested that acetaminophen exposure during early development can cause neurotoxicity. We here provide a preliminary demonstration that acetaminophen exposure during early development in rats results in long term behavioral changes in laboratory rats.

**Discussion**

Our findings suggest that acetaminophen exposure during early development in rats results in long term behavioral changes in laboratory rats, suggesting a role for acetaminophen in the regulation of behavior in this population.

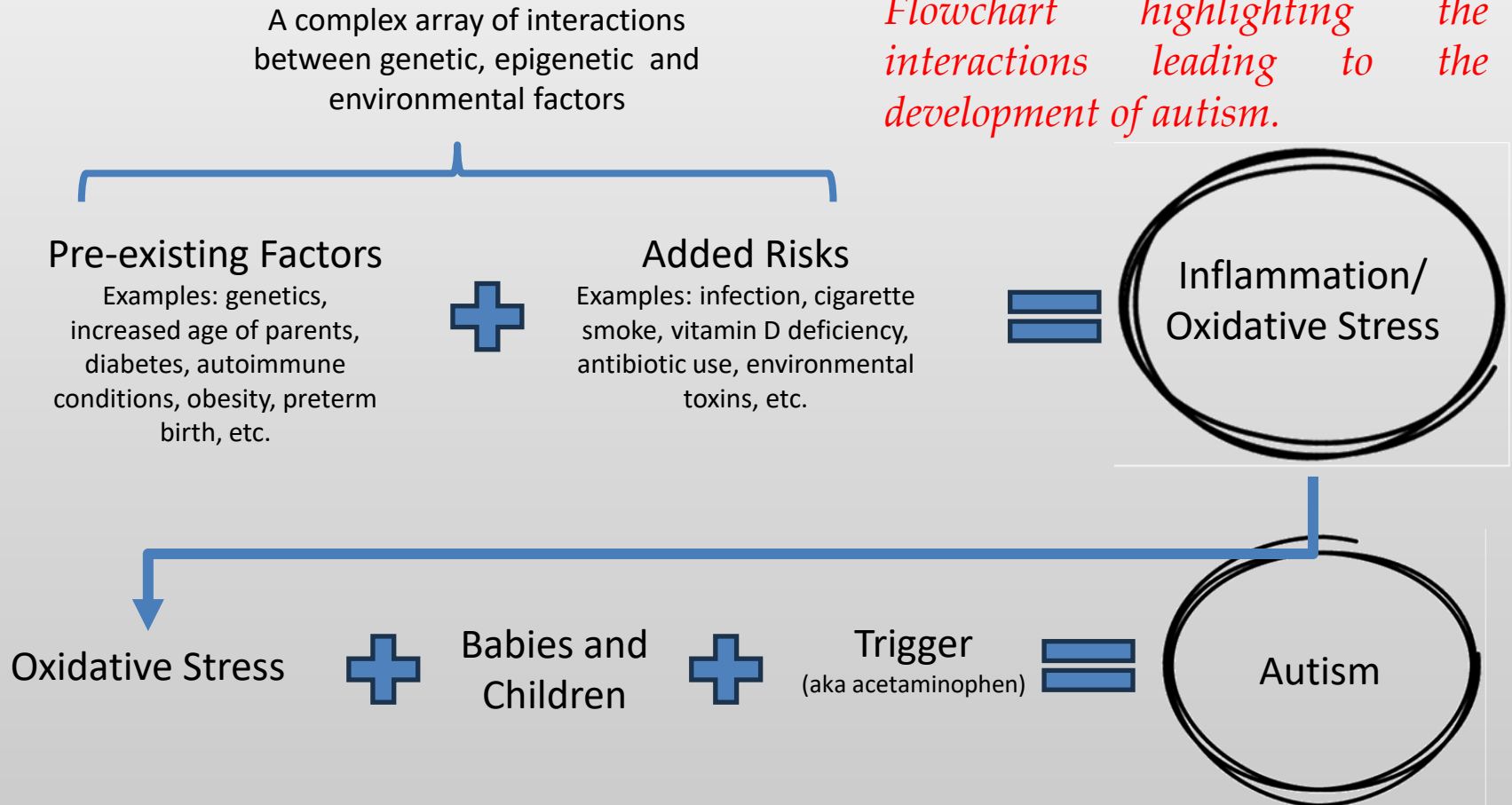
**Introduction**

Based on several lines of evidence, numerous investigators have suggested that acetaminophen exposure during early development can cause neurotoxicity. We here provide a preliminary demonstration that acetaminophen exposure during early development in rats results in long term behavioral changes in laboratory rats.

Slide 8: Numerous laboratory studies investigating the interaction between acetaminophen and the body supported this conclusion.

*Suggested Visual:*

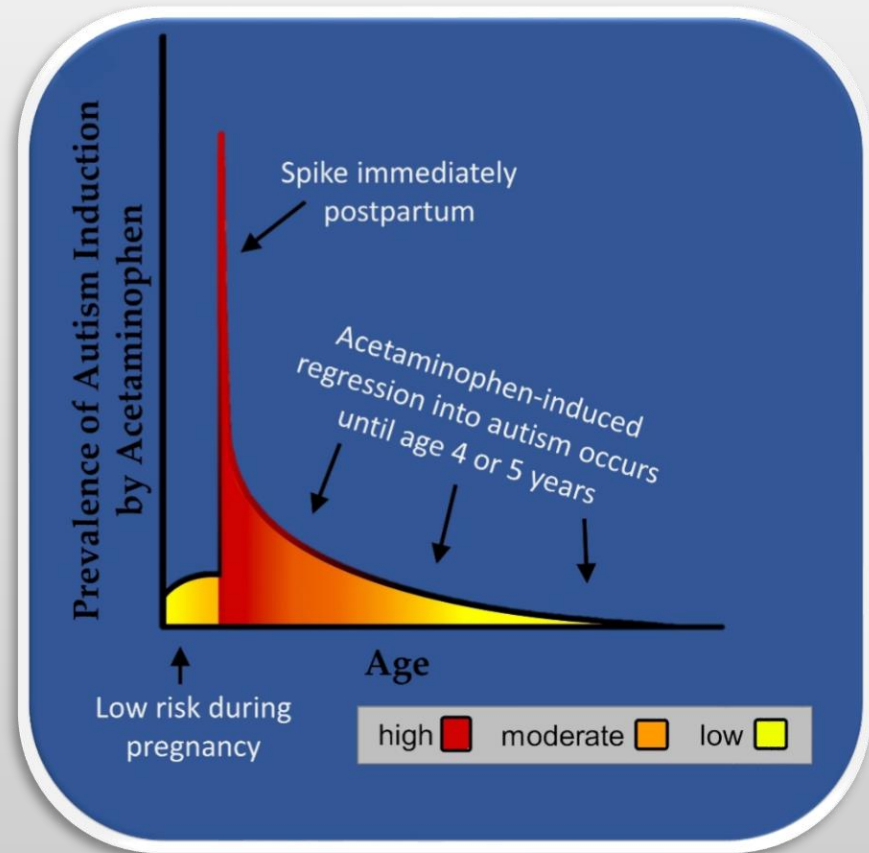
*Flowchart highlighting the interactions leading to the development of autism.*



**Slide 9:** While most babies and children exposed to acetaminophen do not develop autism, oxidative stress creates susceptibility to drug-induced injury. Oxidative stress can be caused by a variety of factors, including genetics, antibiotic use, infections, environmental toxins, and more.

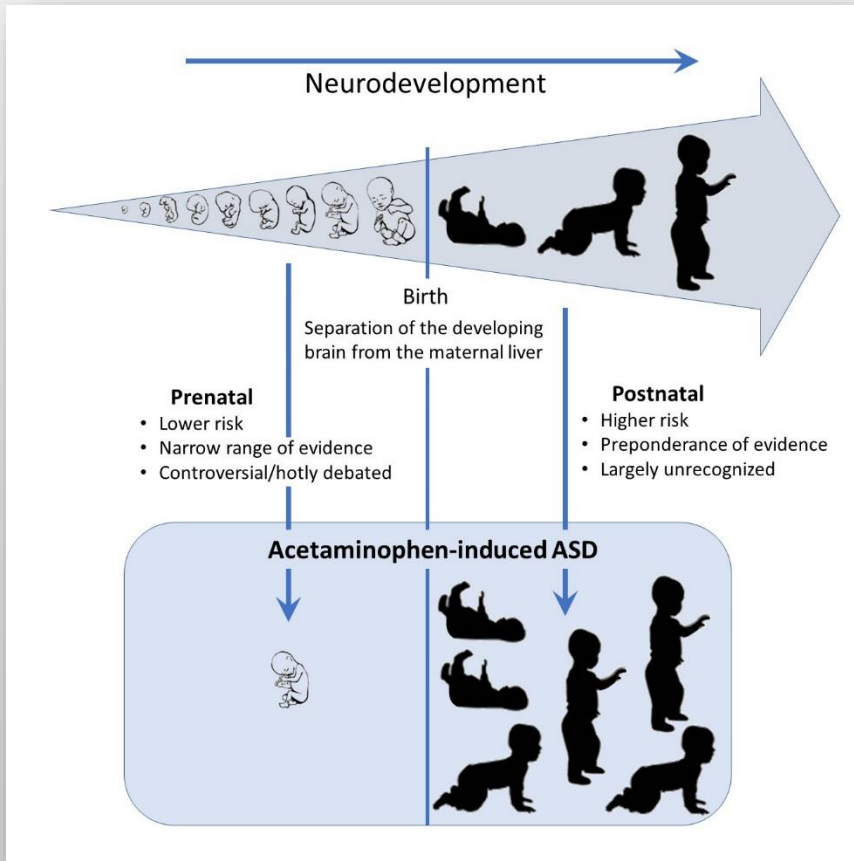
*Suggested Visual:*

*Graph highlighting the early neurodevelopmental spike.*



**Slide 10:** The time period when a baby's brain is sensitive to acetaminophen may start early in pregnancy, but the birth period is more critical. Newborns, particularly within the first 10 days, are highly sensitive due to their limited ability to process drugs.

Figure reference: Figure 2 from <https://pubmed.ncbi.nlm.nih.gov/38255358/>



*Suggested Visual:*

*Stages of neurodevelopment in babies:  
from crawling to walking.*

**Slide 11:** This sensitivity to acetaminophen extends beyond infancy, into early childhood, as seen by regressive autism, which is when the onset of autism occurs as children lose mental development.

Figure reference: graphical abstract for <https://pubmed.ncbi.nlm.nih.gov/37321575/>

*Suggested Visual:*

*Graphical image of follow-up safety studies.*

*All studies supposedly demonstrating safety were short-term studies, which focused on liver functions and not neurological functions.*

**Slide 12:** Despite proof that acetaminophen was never shown to be safe for brain development, the consensus that acetaminophen is safe for babies and children persists.

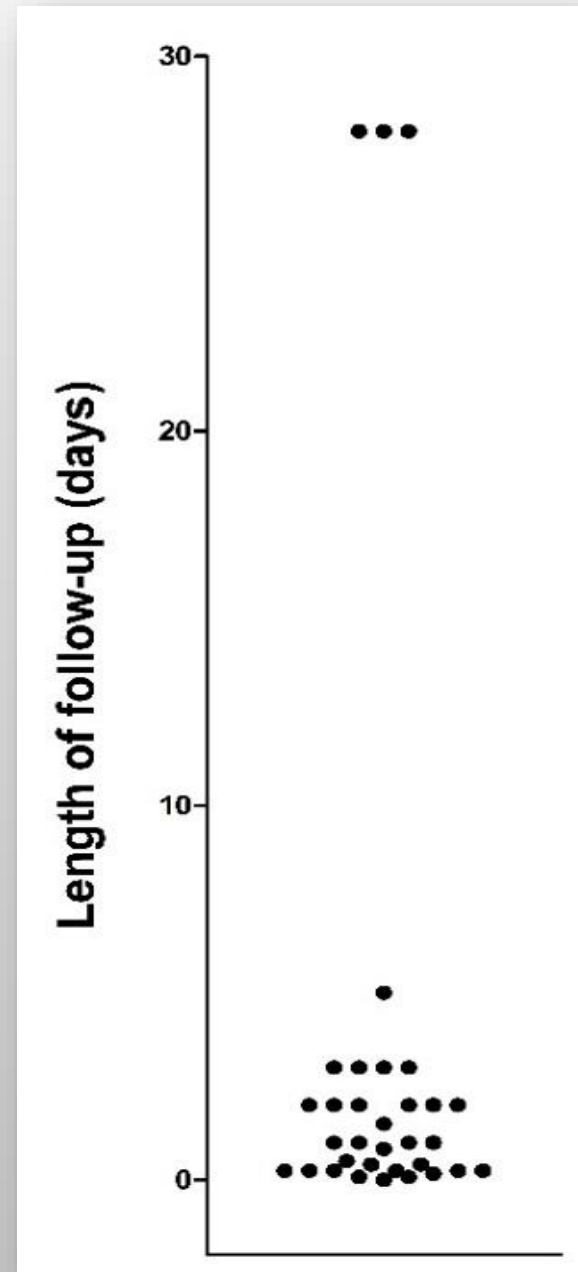


Figure reference: Figure 2 from <https://pubmed.ncbi.nlm.nih.gov/35175416/>

*Suggested Visual:*

*The study by Schultz et al.*

## Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder

The results of a parent survey

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**ABSTRACT** The present study was performed to determine whether acetaminophen (paracetamol) use after the measles-mumps-rubella vaccination could be associated with autistic disorder. This case-control study used the results of an online parental survey conducted from 16 July 2005 to 30 January 2006, consisting of 83 children with autistic disorder and 80 control children. Acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic



**KEYWORDS**  
acetamino-  
phen;  
autism;  
paracetamol;  
vaccination

**Slide 13:** The initial 2008 report by Schultz faced skepticism.

## *Suggested Visual:*

*Other studies stating the use of acetaminophen to be not safe.*

*[Animate a long list of supporting studies. Here are great examples:]*

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530408/pdf/10.1177\\_0141076814565942.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530408/pdf/10.1177_0141076814565942.pdf)  
<https://pubmed.ncbi.nlm.nih.gov/18445737/>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6822099/>  
<https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0015360&type=printable>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3534986/pdf/nihms428627.pdf>  
<https://pubmed.ncbi.nlm.nih.gov/10435209/>  
<https://pubmed.ncbi.nlm.nih.gov/28415925/>  
<https://pubmed.ncbi.nlm.nih.gov/34170958/>  
<https://pubmed.ncbi.nlm.nih.gov/24361869/>  
<https://pubmed.ncbi.nlm.nih.gov/10435209/>  
[https://www.wplaboratory.org/\\_files/ugd/119c83\\_52a241354b274586bf8c2a82d79ecb70.pdf](https://www.wplaboratory.org/_files/ugd/119c83_52a241354b274586bf8c2a82d79ecb70.pdf)  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9056471/>  
<https://pubmed.ncbi.nlm.nih.gov/29910617/>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC340185/pdf/20030600s00030p509.pdf>  
<https://pubmed.ncbi.nlm.nih.gov/31001155/>  
<https://pubmed.ncbi.nlm.nih.gov/25189402/>  
[https://www.wplaboratory.org/\\_files/ugd/119c83\\_52a241354b274586bf8c2a82d79ecb70.pdf](https://www.wplaboratory.org/_files/ugd/119c83_52a241354b274586bf8c2a82d79ecb70.pdf)  
<https://pubmed.ncbi.nlm.nih.gov/28415925/>  
<https://pubmed.ncbi.nlm.nih.gov/34046850/>  
<https://pubmed.ncbi.nlm.nih.gov/18445737/>  
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[https://www.wplaboratory.org/\\_files/ugd/119c83\\_52a241354b274586bf8c2a82d79ecb70.pdf](https://www.wplaboratory.org/_files/ugd/119c83_52a241354b274586bf8c2a82d79ecb70.pdf)  
[https://www.wplaboratory.org/\\_files/ugd/119c83\\_52a241354b274586bf8c2a82d79ecb70.pdf](https://www.wplaboratory.org/_files/ugd/119c83_52a241354b274586bf8c2a82d79ecb70.pdf)

**Slide 14:** Along with that, numerous other studies that stated acetaminophen to be not safe were also largely ignored.

## *Suggested Visual:*

### *The categories of recommended change.*

*Category 1: Administration of acetaminophen in a manner that was never intended should be discontinued.*

*Category 2: Administration of acetaminophen under conditions in which evidence demonstrates a lack of effectiveness should be discontinued.*

*Category 3: Administration of acetaminophen under conditions in which no evidence demonstrates long-term benefits of treatment or in which evidence demonstrates a lack of long-term benefits should be discontinued.*

*Category 4: Administration of acetaminophen that is no longer recommended by governing medical bodies should be discontinued.*

*Category 5: Administration of acetaminophen under conditions where evidence indicates that it is or may be beneficial should not be continued without disclosure of the drug's long-term risks for neurodevelopment. All caregivers, including parents, should be made aware of evidence related to both benefits and risks so that they can make informed decisions.*

**Slide 15:** Several advocates, such as Parker et al., call for regulatory restrictions on pediatric acetaminophen use and emphasize the need for education to all parents and caregivers.

Text reference: <https://pubmed.ncbi.nlm.nih.gov/38255358/>