Journal of INDEPENDENT MEDICINE

Determinants of Autism Spectrum Disorder

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Abstract

***Background*:** Autism spectrum disorder (ASD) now affects more than one in 31 children in the United States, with prevalence rising sharply over recent decades. ASD is recognized as a complex neurodevelopmental disorder shaped by genetic, environmental, and iatrogenic influences. Clarifying the contribution of these determinants is critical to addressing the escalating public health burden.

***Methods*:** We comprehensively examined epidemiologic, clinical, and mechanistic studies evaluating potential ASD risk factors, assessing outcomes, exposure quantification, strength and independence of associations, temporal relationships, internal and external validity, overall cohesiveness, and biological plausibility.

***Results*:** Key determinants of new-onset ASD before age nine include advanced parental age, premature delivery, genetic variants, sibling recurrence, maternal immune activation, in utero drug exposure, environmental toxicants, gut–brain axis disruption, and cumulative routine childhood vaccination. These factors may converge through pathways such as immune dysregulation, mitochondrial dysfunction, and neuroinflammation, which may contribute to neurodevelopmental injury in susceptible children. Of 136 studies examining childhood vaccines or their excipients, 29 found neutral risks or no association, while 107 inferred a possible link between immunization or vaccine components and ASD or other neurodevelopmental disorders (NDDs), based on findings spanning epidemiologic, clinical, mechanistic, neuropathologic, and case-report evidence of developmental regression. 12 studies comparing fully vaccinated and completely unvaccinated populations consistently showed superior overall health outcomes among the unvaccinated, including significantly lower risks of chronic disease and neuropsychiatric disorders such as ASD. The neutral association papers were undermined by absence of a genuinely unvaccinated control group, registry misclassification, ecological confounding, and averaged estimates that obscure effects within vulnerable subgroups. We observed strong, consistent increases in cumulative vaccine exposure during early childhood and the reported prevalence of autism across successive birth cohorts. To date, no study has evaluated the safety of the entire cumulative pediatric vaccine schedule for neurodevelopmental outcomes through age 9 or 18 years.

***Conclusion*:** The totality of evidence supports a multifactorial model of ASD in which genetic predisposition, neuroimmune biology, environmental toxicants, perinatal stressors, and iatrogenic exposures converge to produce the phenotype of a post-encephalitic state. Combination and early-timed routine childhood vaccination represents a significant modifiable risk factor for ASD within a broader multifactorial framework, supported by convergent mechanistic, clinical, and epidemiologic findings, and characterized by intensified use, the clustering of multiple doses during critical neurodevelopmental windows, and the lack of research on the cumulative safety of the full pediatric schedule. As ASD prevalence continues to rise at an unprecedented pace, clarifying the risks associated with cumulative vaccine dosing and timing remains an urgent public health priority.

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Keywords: Autism, autism spectrum disorder, neurodevelopmental disorder, vaccine, vaccination, determinants, risk factors

Introduction

The term autism was coined by the Swiss psychiatrist Eugen Bleuler in 1908. He derived it from the Greek word "autos," meaning self, and he used it to describe an apparently schizophrenic patient who seemed withdrawn into himself and unable to form any interest or connection with others. In 1943, the Austrian American child psychiatrist, Leo Kanner published a paper titled "Autistic Disturbances of Affective Contact" in which he described eleven children who experienced difficulties with social interactions, adapting to changes in routines, and engaging in spontaneous activities. (1) They were unusually sensitive to stimuli (especially sound) and had food allergies and marked pickiness. They had good memories and intellectual potential, but also a propensity to repeat the words of their interlocutors (a condition called echolalia).

In 1944, the Austrian pediatrician Hans Asperger published a paper titled "The Autistic Psychopaths in Childhood" in which he described four children who seemed largely incapable of normal social interactions. Though incompetent at many ordinary tasks, they tended to focus obsessively on certain narrow interests in which they developed unusual ability or understanding. (2) Kanner believed that almost all the subjects had been born with the autistic syndrome he described. Only one case—that of Richard M.—seemed to have a normal childhood and then regress into the syndrome. Richard M. was referred to Johns Hopkins at three years and three months of age. His mother stated, "It seems he has gone backward mentally gradually for the last two years." She thought it sufficiently remarkable to mention that, following smallpox vaccination at 12 months, he had an attack of diarrhea and fever, from which he recovered in somewhat less than a week." (1)

Asperger claimed that three of his four subjects had displayed their odd personality traits since infancy with no apparent organic cause. However, he claimed that his fourth subject, "Hellmut L." suffered "severe asphyxia at birth and was resuscitated at length. Soon after his birth, he suffered infantile spasms [a form of epilepsy] and then two additional episodes in the following days, but never again." (2) Asperger expressed confidence that this boy had sustained brain damage that was a major contributing factor to his autism. In a separate paper, published in 1961, Asperger recorded a link between coeliac disease and behavioral psychoses. (3) Both Kanner and Asperger regarded the syndrome they described as very rare.

During the 1980s and 1990s, neurologists in Sweden and the UK made observational studies and expanded Kanner's original concept of autism. (4) During the late 1990s and early 2000s, an increasing number of parents reported the experience of having a child who seemed normal at birth and during the first twelve to fourteen months of life, but then suffered a sudden regression, becoming withdrawn, absent, and nonverbal—i.e., symptoms that resembled *some* of those described by Kanner and Asperger. During this period, the psychiatric profession started applying Kanner's concept of autism—which he believed to be a rare and apparently inborn disorder—to a rapidly proliferating number of children who suddenly present autistic symptoms after their first twelve to twenty months of normal development. (5)

In 1996, the American clinical immunologist, H.H. Fudenberg, published a paper in which he claimed that fifteen autism patients developed symptoms within a week after immunization with the MMR vaccine. (6) During this same period, while treating and researching inflammatory bowel disease in the UK, Dr. Andrew Wakefield was contacted by parents who told stories of their children who'd developed irritable bowels and neurological symptoms that were later diagnosed as autism. Eight children had, according to their parents, developed these symptoms shortly after receiving the MMR vaccine. Because the parents struck Dr. Wakefield as perfectly credible witnesses, and because there did indeed appear to be a close temporal association between administration of the vaccine and the onset of symptoms, he and his twelve colleagues conducted a study on these children and presented their findings in a seminal paper that was published by *The Lancet* in 1998. (7) The authors characterized their case series as raising the concern that there may be an association between MMR vaccination and autism. However, they clearly stated that they "did not prove an association," and they called for "further investigation of this syndrome and its possible relation to this vaccine."

Wakefield's paper did not immediately result in a major medical controversy. Public controversy erupted in 2004, shortly after the U.S. Court of Federal Claims had established a consolidated proceeding to evaluate thousands of parental petitions alleging that multiple vaccines administered in early childhood had caused regression into autism—known as the Omnibus Autism Proceeding (formally created in 2002). (8) In February 2004, *Sunday Times* journalist Brian Deer, writing for a major British newspaper owned by Rupert Murdoch's

News Corporation, published a report alleging that Dr. Andrew Wakefield had undisclosed financial conflicts of interest, calling into question his impartiality in investigating a potential link between the MMR vaccine and autism. (9) The timing indicates that this initial report regarding Wakefield was part of the broader campaign to discredit the claims of petitioners in the Omnibus Autism Proceeding. In 2009 the U.S. Court of Federal Claims ruled that no link between vaccines (and vaccine preservatives and adjuvants) had been proven, and therefore dismissed the claims of the over 5,000 petitioners. (10) However, in the case of one petitioner, Dr. John S. Poling, a neurologist at Johns Hopkins Hospital, the court conceded that his 19-month-old daughter Hannah's regression into autism had been caused by multiple childhood vaccines she received all at once. (11) Moreover, the DOJ's lead expert witness, Dr. Andrew Zimmerman—a pediatric neurologist at Kennedy Krieger Institute in Baltimore who was abruptly dismissed during the Proceeding under suspicious circumstances—subsequently stated his belief that there was a link between vaccination and autism in the case of Yates Hazelhurst. (12)

The court's ruling for the rest of the petitioners did not dispel their persistent perception that their children regressed into autism shortly after receiving multiple childhood vaccines in one well-child visit. Some observers have noted apparent inconsistencies between the Court's ruling and adverse event profiles described in vaccine package inserts. For example, the package insert for the MMR vaccine states that side effects may include seizures, encephalomyelitis (inflammation of the brain), transverse myelitis (inflammation of the brain and spinal cord), syncope (loss of consciousness), polyneuropathy, ataxia (lack of voluntary muscle coordination, speech changes, abnormal eye movements), Guillain-Barré Syndrome, and progressive neurological disorder. (13)

Likewise, many parents observed that their normal child quickly developed a high fever and/or seizures after receiving vaccines, and then regressed into autism immediately following this initial illness. Though the child's pediatrician and the CDC acknowledged that high fever, seizures (with and without an accompanying fever) are side effects of vaccination, these same public health authorities insisted that the fever and seizures were not linked to the child's regression into autism. And yet, as many parents saw with their own eyes, the regression *immediately followed* the initial vaccine side effects. The basis for this conclusion has been a subject of ongoing discussion, particularly in light of temporal proximity between observed events.

According to CDC estimates, the incidence of autism consistently rose every year of the Omnibus Autism Proceeding (2004-2009) and has continued to rise every year since. The trend seemed to have begun in the late eighties and continued unabated ever since. In 1970, autism is estimated to have afflicted 1 in 10,000 children in the United States. (14) In 2000, the prevalence is estimated to have been 1 in 150 children aged eight years. According to an April 2025 CDC report, autism prevalence in 2022 is estimated to have been 1 in 31 children aged eight years. (15) The cohort of eight-year-olds in 2000 were born in 1992. In that year, 15,556 children (ages 6 to 22 years) in the U.S. received special education services for ASD. By 2011 this figure had risen by more than 25-fold, to 406,957. (16)

The most salient feature of this steeply rising trend of autism incidence and prevalence is that it began shortly after the passage of the National Childhood Vaccine Injury Act (NCVIA) in 1986, which granted blanket liability protection to vaccine manufacturers if their products caused injury or death. (17) Since then, the number of new vaccines on the childhood schedule has greatly proliferated from 12 shots in 1986 to 54 shots in 2019. (18)

In 2011, the editors of *The Lancet* subsequently retracted Wakefield's paper, even though none of the witness testimony, clinical findings, or reasoning presented therein were shown to be erroneous. The paper included the following statement: "If there is a causal link between measles, mumps, and rubella vaccine and this syndrome, a rising incidence might be anticipated after the introduction of this vaccine in the UK in 1988." (7)

Public health authorities, universities, and medical societies have consistently and vehemently denied a link between vaccination and autism without offering any alternative hypothesis for what *is* causing it. CNN's chief medical correspondent, Sanjay Gupta, articulated this orthodoxy when he asserted on national television, "We don't know what causes autism, but we do know it's not caused by vaccines." (19) For many families, this conclusion has remained a subject of concern and ongoing debate.

Autism spectrum disorder is defined in DSM-5/DSM-5-TR as a single neurodevelopmental disorder (NDD) characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior. (20) Impartial investigators who try to ascertain the causes of ASD must contend with problems arising from the metaphorical use of the term "spectrum" to describe a broad range

and severity of symptoms, from profoundly disabled on one end to mildly dysfunctional on the other. Though all these symptoms may be manifestations of related neurological pathologies, identifying and delineating their causes remains highly complex and challenging due to the sheer number of genetic and environmental factors and confounding variables that are likely at play. The most rational investigative approach is therefore to identify cases of severe autism in which marked autistic regression quickly followed from an identifiable insult.

Over the years, the authors of Diagnostic and Statistical Manual of Mental Illnesses (DSM) have changed the definition of ASD. In 2013, the DSM-5 advised clinicians that attention deficit hyperactivity disorder (ADHD) and ASD could be diagnosed together. This marked a change from DSM-IV/DSM-IV-TR, in which an ASD diagnosis excluded ADHD. DSM-5 replaced the prior umbrella term "pervasive developmental disorders (PDD)," consolidating autistic disorder, Asperger disorder, and PDD-NOS (Pervasive Developmental Disorder - Not Otherwise Specified) under ASD. Rett syndrome is no longer classified within ASD and is considered separately. (20) ASD has a strong overlap with several PDD that have features of sequelae of encephalitis during childhood including hyperkinesis, ADHD, semantic-pragmatic disorder, dyspraxia/developmental coordination disorder, Tourette syndrome, tic disorder, dyslexia, and Irlen syndrome. Classifying autistic disorder, Asperger disorder, and PDD-NOS as manifestations of ASD adds to the difficulty of identifying a specific disorder and ascertaining its cause or causes.

What follows is a synthesis of the results and conclusions of epidemiologic, clinical, mechanistic, and multi-omics studies addressing ASD risk factors. Following our review, we present an argument for why the existing studies on ASD have made little to no practical progress in illuminating, preventing, or curing it. While the body of literature on ASD continues to grow, it has yielded no actionable insights for how to slow the rising incidence and prevalence of autism. We conclude by presenting an investigative method for determining the most likely cause of profound autism in children who experienced a normal birth and normal development during their first 12 to 20 months of life, but then regressed into a nonverbal, withdrawn, and disabled state.

Background: Prevalence and Risk Factors

The World Health Organization (WHO) estimates that ASD affects approximately 1 in 127 children globally. (21) In the United States, early epidemiologic studies in the 1970s reported prevalence as low as 1 in 10,000 whereas the Centers for Disease Control and Prevention (CDC) now reports a prevalence of 1 in 31 children in 2022 (see **Table 1** for underlying per-1,000 rates), a notable increase from 1 in 150 in 2000. (14,15) Among children aged 8 years in 2022, ASD prevalence was 32.2 per 1,000 children (one in 31) across the 16 sites, ranging from 9.7 in Texas (Laredo) to 53.1 in California. (22) Alongside the data from the WHO and CDC, Grosvenor et al., found that among U.S. children, autism diagnosis rates increased substantially from 2011 to 2022, with the highest prevalence observed in 5- to 8-year-olds, rising from approximately 10 per 1000 to 30 per 1000 in 2022. (23)

This striking increase is illustrated in **Figure 1**, which compiles early epidemiologic estimates together with CDC ADDM Network surveillance data to show the exponential rise in autism diagnoses from the 1970s to 2025. (14,15) Rising prevalence has fueled public concern and intensified scrutiny of possible risk factors.

Vaccines, particularly the measles-mumps-rubella (MMR) vaccine, have been the subject of widespread debate. As seen by the previous statistic, states such as California have higher vaccine compliance and concordantly higher rates of ASD. (22) The U.S. childhood vaccine schedule has come under scrutiny, as it recommends that children receive **31–34 doses by age two and 41–44 doses by age six** (see **Table 2**), administered without risk stratification for the target infectious diseases." (24–26) This relationship is further illustrated in **Figure 2**, which compares autism prevalence trends with the increasing number of recommended vaccine doses administered to U.S. children, demonstrating strong parallel trajectories. At the same time, increasing attention is focused on non–vaccine-related risk factors, including genetic susceptibility, prenatal and perinatal exposures (e.g., maternal infection, medication, air pollution), and advanced parental age. Identifying these multifactorial contributors is crucial to developing informed prevention and early-intervention strategies. (27,28)

Complexity in Prevalence, Etiology, Diagnosis, and Treatment

Phenotype Heterogeneity

Autism is not a singular condition but rather a spectrum, with wide variability in symptom presentation, severity, comorbidity, and prognosis. This het-

erogeneity complicates the estimation of prevalence, as definitions and diagnostic criteria have evolved over time and across geographic regions. Before DSM-5, DSM-IV contained an exclusionary clause that prevented a person from being diagnosed with both ASD and ADHD. A clinician had to choose the diagnosis that best fits the patient's symptoms. The recognition of the frequent co-occurrence of these conditions in clinical practice led to the removal of the exclusionary rule in the DSM-5. This change allows for a more accurate and comprehensive diagnosis, which better informs us of treatment and support strategies for affected individuals. The change allowed for a co-occurring diagnosis of ADHD and autism was made in 2013 with the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Based on scientific literature and meta-analyses, studies show that between 50% and 70% of individuals diagnosed with ASD also present with comorbid ADHD. (30) The transition from DSM-IV to DSM-5 criteria, for instance, has significantly altered classification thresholds. (20) Moreover, ASD is diagnosed more frequently in males, with male-to-female ratios of approximately 4:1. Gender biases in symptom recognition and diagnostic practices may contribute to underdiagnosis in females. (27)

Established Non-Vaccine Risk Factors

The etiology of ASD is multifactorial. Twin and family studies estimate heritability to be high, yet no single gene has accounted for significant variation in phenotypic expression. Instead, ASD is linked to hundreds of common and rare genetic variants. Environmental factors, including prenatal stress, maternal metabolic conditions, infections, toxic exposures, and premature delivery may increase risk by interacting with genetic factors and subsequent exposures such as combination vaccination. Epigenetic mechanisms may further mediate these gene-environmental interactions. While many children later diagnosed with ASD may exhibit typical or near-typical development during early infancy, diagnosis generally occurs in early childhood through behavioral observation and developmental screening, although access to timely and accurate evaluation varies globally. Delayed diagnosis is common in children from under-resourced communities or with co-occurring conditions. In many low- and middle-income countries, diagnostic infrastructure is lacking, and cultural stigma may further delay identification.

Developmental Regression

Regression from a previously higher stage of development is common after the onset of ASD, suggesting that early childhood exposures may play a role in the pathogenic process of neuropsychiatric disease and neurodivergence. In studies of autistic children, the prevalence of developmental regression is estimated to be between 25% and 40%, affecting about one-third of children on the spectrum. (31) Regression involves the loss of previously acquired skills, typically during the toddler years. The timing of regression typically falls around 21 months, with most cases presenting before the child reaches three years of age. Temporal clustering after vaccination has been reported, though temporal association alone is insufficient to establish causation. These observations should be interpreted with consideration of potential recall bias, ascertainment timing, and variability in phenotype classification. This early onset is crucial, as it often coincides with critical language and social development milestones. Notably, only 6% of children with regression experience a complete loss of all acquired skills; most retain a portion of their abilities, despite facing setbacks. “Regression” in autism usually means a clear loss of previously acquired skills—most often single words or early phrases, joint attention, and social engagement—after an initial period of typical-looking development. A meta-analysis by Barger and colleagues synthesized dozens of studies and estimated that roughly a third of autistic children experience some form of developmental regression, with most onsets clustering in the second year of life (around 18–24 months). (31) The review also underscored why estimates vary: studies define regression differently (language-only vs. broader social-communication loss), rely on different sources (parent report vs. prospective measures), and examine different time windows, all of which shift prevalence and timing figures.

Longitudinal work adds texture. In the SNAP study, Baird and co-authors followed children with and without reported regression and found that, while the “regression” group shows a distinct early developmental pattern—initial gains followed by loss—the core autism phenotype tends to converge over time; where differences persist, they are most apparent in language and adaptive communication profiles. (32) Similarly, Bernabei and colleagues reported that children with regression display different developmental trajectories than those without, again highlighting language as a key domain of vulnerability and emphasizing heterogeneity in both

onset and outcome. (33)

Epidemiology

While increased screening and detection may account for some of the rise in cases of ASD among children, similar new cases are not developing in adults. These observations suggest that ASD is triggered during the critical stages of immunological and neurological development before adulthood. It is also unlikely that screening and detection account for the dramatic rise in profound autism. "Profound autism" is used to describe autistic individuals with high support needs. The criteria are based on studies and consensus efforts, notably a 2021 Lancet Commission report. A consensus definition from the International Society for Autism Research defines a person with profound autism as someone who: meets the diagnostic criteria for ASD, is at least eight years old (recognizing characteristics may appear earlier), requires lifelong, round-the-clock adult supervision for physical and mental health, safety, and well-being, shows adaptive functioning skills significantly below their age level, requiring constant assistance with most daily living activities like bathing and dressing, has either an IQ below 50 or limited verbal communication beyond single words or fixed phrases, primarily to express basic needs. These severe characteristics are persistent, not temporary, and have the greatest public health impact of all common childhood illnesses. Currently, more than half a million American children live with profound autism, representing 26.7% of all autism cases — a proportion that continues to rise at an alarming rate. (34,35)

Treatment and Clinical Management

There are no FDA-approved drugs to treat primary ASD. Therapy is complex and requires individualized, multidisciplinary approaches. Evidence-based interventions include applied behavior analysis, speech and language therapy, occupational therapy, and educational support. Pharmacologic treatment may be used to manage associated conditions such as irritability, anxiety, or inattention but is not a primary intervention for core ASD symptoms. Access to these services is uneven, with systemic barriers such as cost, location, and provider availability influencing outcomes. Autism spectrum disorder represents a multifaceted and increasingly prevalent NDD with diverse presentations, complex etiology, and variable diagnostic and treatment pathways.

Mechanistic Considerations

Prevalence of ASD continues to dramatically rise beyond attribution to improved ascertainment, diagnostic criteria, and service availability, complicating comparisons across regions and time. Systematic reviews and large overviews underscore substantial heterogeneity across sex, co-occurring conditions, and developmental trajectories, with male predominance and probable under-recognition in females. Longstanding evidence indicates that most genetic risk resides in common variation with contributions from rare and de novo variants in synaptic, chromatin-remodeling, and neurodevelopmental pathways; gene–environment interplay and epigenetic mechanisms likely modulate expression and penetrance environmental domains repeatedly examined include maternal immune activation (MIA) and autoimmunity, perinatal adversity, air pollution, metals/trace elements, nutrition, infections, and the gut–brain axis. Mitochondrial and redox abnormalities are reported in a subset, providing biologic plausibility for vulnerability to inflammatory or toxicant exposures in sensitive windows. Because children with ASD are known to be largely born as normal infants, there has been considerable focus on exposures and triggers from iatrogenic and environment sources early in childhood.

Vaccine-Related Evidence

Public discourse has focused heavily on vaccines—especially live-attenuated MMR—since the seminal publication by Dr Andrew Wakefield et al. in the *Lancet* 1998. (7) This led to a series of investigations by the Institute of Medicine. At the request of the sponsoring agencies, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), the Institute of Medicine (IOM) established the Immunization Safety Review Committee to evaluate the evidence on possible causal associations between thimerosal-containing vaccines 2001 and MMR (2004) and ASD. There were eight reports in total. In the final 2004 report the authors stated: “There are, however, little data to shed light on how many families believe that vaccination caused their child's autism, so that the magnitude of concern in the general population is uncertain. However, the committee concludes that because autism can be such a devastating disease, any speculation that links vaccines and autism means that this is a significant issue.” Because no large prospective, randomized, double-blind trial had been conducted with the MMR vaccine given in its

usual combinations with other vaccines, the IOM could not conclude that combination vaccination was noninferior to deferral of childhood vaccination with respect to ASD as an outcome. (36) Bjelogrlic however concludes, in light of the relevant scientific literature, the Bradford Hill criteria are met, indicating that vaccines do play a significant causal role in producing autism and intellectual disabilities. This is based on the 7 criteria that are stated in the paper's conclusion. (37)

Methods

This narrative review aimed to synthesize findings across epidemiologic, clinical, and mechanistic domains using a structured but non-systematic approach, with consistent terminology applied across study domains. Unless studies employed causal designs, associations were interpreted descriptively, and both positive and null findings were reported where available. Potential sources of confounding, selection bias, and measurement bias were explicitly considered in evaluating study validity and weight of evidence.

Literature Search Strategy

A broad literature search was conducted across major biomedical and multidisciplinary databases, including PubMed, Scopus, Web of Science, Google Scholar, and relevant gray literature sources. Boolean operators and controlled vocabulary (e.g., Medical Subject Headings [MeSH]) were used to construct search strings combining terms such as *"autism," "ASD," "neurodevelopmental disorder," "vaccination," "immunization," "adjuvant,"* and *"thimerosal."* The search encompassed all available publication years without a lower date limit and included records indexed through 2025.

Inclusion/Exclusion Criteria

Eligible studies encompassed epidemiologic cohort and case–control designs, prospective and retrospective observational studies, mechanistic and molecular investigations, animal models, and peer-reviewed systematic reviews and meta-analyses. Studies were included if they examined ASD incidence, risk factors, or biological correlates in relation to vaccination, immune activation, environmental toxicants, genetic polymorphisms, or gut–brain axis disruption. The review also incorporated selected gray literature, including government reports, legal documents, conference abstracts, and preprints, where these provided unique data or contextual information not otherwise available in the peer-reviewed literature, while prioritizing peer-reviewed sources for primary scientific conclusions. Narrative reviews, commentaries, and editorials without primary data were cited qualitatively for mechanistic context. Studies were excluded if they did not report autism, neurodevelopmental outcomes or relevant mechanistic data, lacked sufficient methodological detail, or examined unrelated psychiatric or behavioral endpoints.

Data Extraction, Synthesis and Analysis

From each eligible study, data were extracted on study design, sample size, and timeframe. Exposure variables (e.g., vaccination, toxicant, or infectious agent), outcome measures (e.g., ASD diagnosis, neurobehavioral assessments, cytokine or biomarker profiles), and implicated biological mechanisms (e.g., inflammation, epigenetic modification, mitochondrial dysfunction) were systematically recorded. Findings were synthesized thematically across biological, environmental, and epidemiologic domains, with a focus on vaccination-related evidence and its mechanistic intersections with other determinants of ASD. The integration encompassed genetic, immunologic, metabolic, microbial, and toxicant pathways to identify converging mechanisms and remaining gaps in understanding. For vaccine-related studies, each paper was independently evaluated by six co-authors, who assessed study design, exposure validity, and outcome reporting. Findings were classified as suggesting either a positive or null association between vaccination and ASD or other NDDs, with consensus achieved through group discussion. Visual and conceptual models were developed to illustrate interactive frameworks linking prenatal, perinatal, and postnatal exposures to ASD pathogenesis.

Results

Overview

Across the evidence base, multiple domains show signals relevant to ASD: immune dysregulation (autoimmunity, cytokine/chemokine differences, neuroinflammation imaging and tissue studies), maternal immune activation, environmental toxicants (including selected trace elements/metals), gut–brain axis alterations, mitochondrial/oxidative stress biology, neuroanatomic/neuronal signaling differences, genetic liability, pharmacological exposures and perinatal factors such as prematurity. Findings varied in strength and reproducibility across domains and are often sensitive to exposure timing, biospec-

imen matrix, and phenotype definition. We comprehensively investigated the literature for exposures before routine childhood vaccination across various domains in the text below (**Supplementary Table S1**). (38–144)

Parental Age

Advanced paternal age is a more consistent risk factor for autism than maternal age, though both play a role. Multiple population-based studies indicate that autism risk begins to rise measurably among mothers older than 35 years and fathers older than 40 years, with the risk increasing progressively with advancing parental age. (66,71,127) As men age, the number of spontaneous (de novo) genetic mutations in their sperm increases. These new mutations, not inherited from either parent, are believed to be a major contributor to the increased autism risk associated with older fathers. Sandin et al. associated advanced parental age and greater parental age difference with increased autism risk. Compared to fathers under 30, fathers over 40 face a 5.75 times greater risk of having a child with autism, and the risk for fathers over 50 is even higher. The number of mutations transferred from father to child accumulates with age. For instance, a 36-year-old father transmits about twice as many mutations as a 20-year-old, and a 70-year-old transmits roughly eight times as many. (71) Dehesh et al. saw that conversely, greater paternal and maternal ages were associated with an increased risk of autism in their children. The adjusted odds ratios for older mothers and fathers were 1.47 (95% CI 1.33–1.62) and 1.51 (95% CI 1.40–1.62), respectively, indicating that both maternal and paternal age independently contribute to ASD susceptibility. (127)

Research has uncovered a more complex relationship between maternal age and autism risk, often described as a "U-shaped curve". Mothers over 40 face a significantly increased risk of having a child with autism compared to those in their 20s. The risk is estimated to be 40–80% higher for mothers over 40 compared to those aged 25–29. This may be due to factors including genetic abnormalities, health issues like diabetes and obesity, or longer exposure to environmental toxins. A smaller, but significant, risk has been observed for children born to very young mothers, such as teenagers. This might be linked to factors other than genetics, including socioeconomic or health issues. The age effects of both parents appear to have a combined influence on autism risk. The risk can be higher when both parents are older. An increased risk of autism has also been observed in children whose parents have a large age gap. (66)

Genetics and Gene–Environment Interplay

Gaugler et al. reported that most genetic links to ASD reside in common mutations. (38) Considering familial heritability of approximately 50%, the authors concluded most was due to common variation, and only rare de novo mutations contribute substantially to phenotypic expression in 2.6%. Accordingly, population studies highlight familial liability (e.g., parental psychiatric history) and parental age effects, aligning with polygenic risk and inherited/epigenetic mechanisms that can interact with environmental inputs. (41,71) Apte and Kumar summarized common polymorphisms across domains of social-behavioral, vocalization, synaptic assembly, memory, synaptic transmission, learning, and vocal learning. Variants that span multiple domains included SHANK 1, 2, 3, CNTINAP2, NRXN1, 2, AND NLGN4X, 4Y. Along with the specific genes, Apte et al., described proteins involved in ASD and found that roughly 19 proteins (11 synapse related and 8 related to transcription regulation and chromatic remodeling) are involved in ASD. (125) Beyond these synaptic and neurodevelopmental loci, one of the most consistently replicated findings involves MTHFR gene polymorphisms, which influence folate metabolism and DNA methylation—pathways essential to neurodevelopment. A systematic review and meta-analysis of 17 studies (Razi et al., 2020) demonstrated a significant association between the C677T variant and ASD risk under multiple models: dominant (OR = 1.47, 95% CI 1.13–2.93), allelic (OR = 1.37, 95% CI 1.08–1.74), and CT vs CC (OR = 1.45, 95% CI 1.13–1.85). Conversely, the A1298C variant showed no overall association but appeared protective among Caucasians, decreasing ASD risk in subgroup analyses. (126) Together, these results highlight methylation-dependent gene–environment interactions that may amplify or buffer neurodevelopmental risk depending on background folate status and ancestry. Natural experiments and stressors (e.g., severe storms) emphasize timing-dependent environmental impacts superimposed on background genetic susceptibility. (41) Yin et al. replicated associations between parental psychiatric disorders and increased autism risk, consistent with inherited and environmental contributions. (40)

Siblings of children with autism spectrum disorder (ASD) represent one of the most well-established high-risk groups, reflecting the strong familial aggregation of autism traits across generations. Early cohort and registry studies consistently show that

having an affected sibling increases the likelihood of ASD diagnosis by 5- to 10-fold compared to the general population, highlighting both shared genetic liability and potential common environmental or epigenetic influences within families. (145) Ozonoff et al. (2024) reported updated results from the multinational *Baby Siblings Research Consortium*, which prospectively followed 1,605 infants with an older autistic sibling. By age 3, 20.2 % of siblings met criteria for ASD, a recurrence rate roughly ten times higher than the population baseline and consistent with prior estimates. (146) Recurrence risk was significantly greater in families with multiple affected siblings, in male infants, and when the proband was female, supporting a dose-dependent and sex-modulated model of inherited susceptibility. Socioeconomic and racial disparities also modified recurrence, suggesting that gene–environment interactions and early-life exposures influence phenotypic expression beyond purely genetic liability.

Maternal Immune Activation

Converging population and biomarker data link maternal inflammatory states during gestation with increased ASD risk in offspring. Nutritional–endocrine milieus such as gestational vitamin D status show links to autism-related traits, suggesting environmentally modulated genetic programs in corticogenesis and immune development. (73) Gene–nutrient interactions illustrate this interplay: prenatal vitamin use modified by one-carbon metabolism gene variants has been associated with ASD risk differences, consistent with methylation-sensitive developmental pathways. (69) Schmidt et al. found that low periconceptional prenatal-vitamin use combined with specific one-carbon-metabolism gene variants was linked to higher autism risk, indicating gene–nutrient interaction. (69) Surén et al. reported that periconceptional folic-acid supplementation was associated with reduced autism risk. (97) Causes of systemic maternal inflammation include chronic and acute infections, periodontal disease, and vaccination during pregnancy. Thus in-utero encephalitis may be a common final pathway to the post-partum risk of developing ASD in the infant.

Elevated mid-pregnancy C-reactive protein, clinical chorioamnionitis, and documented in-utero infections each associate with greater odds of ASD or broader neuropsychiatric outcomes, consistent with maternal immune activation acting during sensitive windows. (43,92,101) Evidence also implicates pregnancy complications with inflammatory components hypertensive disorders of pregnancy and maternal anemia in later NDD, including ASD. (76) Febrile illness in pregnancy shows positive associations with ASD risk and suggests antipyretic-modulated pathways, reinforcing the role of systemic cytokine signaling. (75) Brand et al. reported that hypertensive disorders of pregnancy were linked with higher rates of NDD, including ASD, after covariate adjustment. (39) Yin et al. found that parental psychiatric disorders were associated with elevated odds of autism in offspring across Swedish and Finnish nationwide cohorts. (40) Kinney et al. observed higher autism prevalence among birth cohorts with prenatal exposure to hurricanes/tropical storms in Louisiana compared with unexposed cohorts. (41) Avalos et al. noted in cohort analyses that maternal prenatal cannabis use correlated with increased autism risk in offspring. (42) Brown et al. identified a positive association between elevated maternal C-reactive protein during pregnancy and autism risk in a national birth cohort. (49) Tsamantioti et al. reported associations between chorioamnionitis and long-term NDD, including ASD, in offspring. (98) Kujabi et al. and Jenabi et al., in separate meta-analyses, each found that neonatal jaundice was associated with higher odds of autism. (99,100) In a large Israeli population cohort (n = 153,321; 25.7% exposed), maternal influenza vaccination during pregnancy was associated with a 22% higher crude risk of ASD in offspring (HR = 1.22, 95% CI 1.14–1.31), which attenuated to aHR = 0.97 (0.91–1.05) after extensive adjustment for sociodemographic and gestational covariates (Neeman et al., 2025). Although reported as null, this attenuation could reflect overadjustment or residual confounding, suggesting that a modest association cannot be definitively ruled out pending peer review and replication. (138)

Acute and Chronic Infections

Infections during pregnancy have been associated with increased risk for ASD and schizophrenia in offspring. Viral and bacterial infections during gestation are well-associated with later NDD diagnosis. (90) Zhou et al. reported that currently available pharmacological agents have at best only a modest benefit for the treatment of repetitive restrictive behaviors in ASD, with the most evidence supporting antipsychotic medications. The authors call for further studies. (142) Various viral infections during pregnancy are linked with ASD diagnosis (e.g., rubella, congenital cytomegalovirus, influenza) in offspring. Bacterial infections during gestation can also be associated with ASD (e.g., urinary tract infection, genital infections) in offspring. (140) Cheslack-Postava et al., found that epidemiologic studies have provided evidence that prenatal expo-

sure to maternal infection is associated with an increased risk of developing schizophrenia in offspring. (141) Maternal inflammation and notably elevations in cytokines, which are known to cross the placenta and the blood brain barrier of the embryo, potentially play a role in the pathogenesis of incipient ASD. Maternal febrile illness has been associated with increased ASD risk, and population cohorts show higher long-term neuropsychiatric risk after in-utero infection, consistent with cytokine-mediated effects during neurodevelopment. (75,107) Beyond prenatal infections, tissue-level data also point to postnatal persistent viral antigen: in ileal biopsies from children with developmental disorder and ileocolonic lymphonodular hyperplasia, measles virus RNA was detected in 75/91 cases vs 5/70 controls and localized to follicular dendritic cells and some lymphocytes, consistent with chronic mucosal immune activation. (144)

Periodontal Disease

Periodontal disease isn't just a mouth problem, it's a chronic inflammatory state that can spill into the bloodstream during pregnancy. That matters because sustained maternal immune signaling is one plausible route by which the fetal brain is affected, as summarized in a recent causality review of maternal immune activation and autism. (135) Consistent with that biology, a trial-based follow-up study found that treating periodontitis during pregnancy was linked to fewer toddlers screening positive for autism on the M-CHAT, with higher maternal and cord IL-6 among those who screened positive. (136) Broader evidence ties maternal periodontitis to adverse obstetric outcomes and potential epigenetic effects in offspring mechanisms that make the neurodevelopmental link biologically plausible.

Premature Delivery

Crump et al. showed that preterm birth (before 37 weeks of gestation) and early-term birth carried increased autism risk in a large nationwide cohort. (85) Common risk factors for systemic inflammation such as acute and chronic infections, periodontal disease, and maternal vaccination are well-recognized risk factors for pre-term delivery. Laverty et al., pooled prevalence estimates for autism in preterm samples and found that it was 20% when using screening tools and 6% when using diagnostic assessments. The odds of an autistic diagnosis were 3.3 times higher in individuals born preterm than in the general population. (128) Independent evidence synthesis aligns with the RSV label's caution. A 2024 meta-analysis of randomized trials of RSVpreF vaccination in pregnancy found a 24% relative increase in preterm delivery among vaccine recipients (RR, 1.24; 95% CI, 1.08–1.44), while noting that Pfizer's RSVpreF (Abrysvo) was FDA-approved for use in pregnancy after the pivotal trials and that a similar GSK program was halted for a preterm-birth safety signal. The authors suggest mitigating risk by restricting use closer to delivery. (139)

Autoimmunity and Autoantibodies

Meta-analytic and register-based studies indicate that maternal autoimmune diseases and family immune conditions track with higher ASD risk, supporting autoimmune/autoinflammatory mechanisms in susceptible dyads. (43,61) Asthma in parents has been associated with ASD in offspring in by Gong et al., consistent with shared immune-genetic liability or immune milieu effects during pregnancy. (44) Endocrine-immune interfaces may also matter: maternal hypothyroxinemia and polycystic ovary syndrome, both linked to immune and metabolic dysregulation, have been associated with increased ASD risk. (72,76) Chen et al., in a systematic review and meta-analysis, concluded that maternal autoimmune disease is associated with increased autism risk in offspring. (61) Zerbo et al. documented greater prevalence of immune-mediated conditions among individuals with autism within an integrated health-care system. (43) Robinson-Agramonte et al. synthesized clinical and laboratory evidence indicating immune dysregulation in autism, including elevated autoantibodies in subgroups were strongly associated with autism. (116)

Cytokines, Chemokines and Neuroinflammation

Postmortem and molecular-imaging studies demonstrate microglial activation/density differences and altered neuroimmune signaling in ASD cortex, alongside case-control evidence of reduced TSPO binding in young adults, suggesting atypical glial states rather than uniform neuroinflammation. (56,60,63) Circulating and tissue biomarkers frequently show oxidative-stress/methylation abnormalities and altered neurotrophic signaling (e.g., BDNF), patterns that can be downstream of sustained cytokine activity and immune-metabolic stress. (56) Brown et al. found that higher maternal CRP was linked to increased autism risk, supporting a prenatal inflammatory signal. (49) Morgan et al. demonstrated microglial activation and increased microglial density in dorsolateral prefrontal cortex in autism versus controls. (56) Vargas et al. reported neuroglial activation and neuroinflammation across

multiple brain regions in postmortem autism tissue. (63) Zürcher et al. detected lower regional TSPO binding in young adults with autism than in controls, suggesting altered microglial/immune-related signaling. (60) James et al. observed elevated oxidative-stress markers and reduced methylation capacity in children with autism relative to controls. (64)

Mitochondrial and Redox Biology

Case–control and clinical studies consistently report oxidative stress, impaired methylation capacity, and mitochondrial abnormalities in ASD, pointing to bioenergetic vulnerability during brain development. (58,64) Experimental toxicology and reviews describe how specific exposures (e.g., organic/inorganic mercury species; adjuvant-triggered immune activation) can perturb mitochondrial function and redox balance in infant or cellular models, offering mechanistic plausibility for exposure-by-susceptibility effects. (42,56–58) These pathways dovetail with immune activation and neuroinflammation, potentially amplifying risk in subgroups with preexisting metabolic fragility. Nickel et al. documented altered peripheral markers of mitochondrial function in adults with autism compared with controls. (58) James et al. observed increased oxidative stress and impaired methylation capacity in children with autism, consistent with redox vulnerability. (64) Marcos Sales et al. showed that acute thimerosal exposure impaired mitochondrial function in an infant experimental model. (212) Angrand et al. reported convergence of inflammatory and autophagy pathways with aluminum-adjuvant exposure in susceptible genotypes relevant to autism biology. (197)

Neurodevelopmental and Neuroanatomic Findings

Neuroimaging and postmortem data indicate atypical trajectories such as early brain enlargement in children with regressive presentations—and glial/immune alterations, underscoring neurodevelopmental timing effects of post-encephalitic changes. (56,60,63) Perinatal factors that shift developmental timing and brain maturation—prematurity/early-term birth and birth mode differences have been associated with ASD risk at the population level, although sibling-compare and causal-inference designs attenuate some associations, suggesting partial confounding. (54,85) Maternal hypothyroidism has been linked to ASD. (72) Nordahl et al. found that brain enlargement was associated with developmental regression in preschool-age boys with autism. (67) Morgan et al. provided evidence of increased microglial density and activation in prefrontal cortex in autism. (56) Zürcher et al. reported lower TSPO binding in young adults with autism, indicating altered glial signaling relative to controls. (60)

Metabolic and Fertility Domains

Metabolic conditions in pregnancy (obesity, diabetes) are linked to elevated ASD risk in multiple cohorts, reinforcing immunometabolic pathways. (77,79,94,99) Xiang et al. found that maternal diabetes during pregnancy was linked to higher autism risk in offspring. (91) Li et al. and Krakowiak et al. each reported associations between maternal obesity/metabolic conditions and increased risks of autism and related developmental outcomes. (93,94) Maher et al. and Brand et al. each linked hypertensive disorders of pregnancy with elevated risks of NDD including ASD. (39,82) Djuwantono et al. and Andreadou et al. each reported that assisted reproductive technology was associated with increased autism risk in pooled analyses, while Fountain et al. identified associations for specific Assisted Reproductive Technology (ART) modalities in California births. (53,89,112) Velez et al. observed that infertility histories were associated with higher odds of autism in offspring. (111) Guo et al. noted that, among individuals with obesity, gestational weight loss carried risks to perinatal outcomes tied to neurodevelopmental vulnerability. (87) Wiegersma et al. associated prenatal maternal anemia with later NDD, including ASD. (84)

Environmental Toxicants and Trace Elements

Multiple cohorts link prenatal or early-life air pollution particularly traffic-related pollutants, NO_2, and source-specific PM with higher ASD odds or autistic traits, with some spatial and component-specific heterogeneity. (47,68,114,115) Large studies also implicate pesticides and organophosphate exposures during gestation, as well as PBDE flame retardants, in relation to ASD risk or traits. (74,108,109) Metals/trace elements remain an active area: baby-tooth and biomonitoring studies show dysregulated metal uptake timing in ASD and group differences in blood/urine elements, while ecological proximity to metal-emitting facilities associates with ASD prevalence. (57,59,62) Ding et al. examined cadmium, lead, arsenic, and mercury exposure across 53 studies and found significantly higher concentrations of these heavy metals in the hair, blood, and urine of children with ASD compared to controls. The authors concluded that toxic metal–induced oxidative stress and epigenetic dysregulation likely contribute to ASD pathogene-

sis and emphasized limiting maternal and early-life exposure to these elements. (65) Windham et al. reported that autism prevalence varied with spatial patterns of hazardous air pollutants in the San Francisco Bay Area, with higher odds in areas of elevated exposures. (68) Volk et al. found that higher traffic-related air pollution and particulate matter were associated with increased odds of autism. (47) Pagalan et al. linked prenatal ambient air-pollution exposure with autism in population-based analyses. (45) Murphy et al. associated prenatal nitrogen-dioxide exposure with higher autism risk. (114) Flanagan et al. showed that pregnancy exposure to local, source-specific particulate matter related to autism in a Swedish cohort. (115) Dickerson et al. observed higher autism prevalence near industrial facilities releasing arsenic, lead, or mercury. (62) Khaled et al. reported mercury-related biomarker patterns and altered urinary porphyrins correlating with autism severity in Egyptian children. (55) Arora et al. identified dysregulated fetal and postnatal metal-uptake timing in autism using deciduous-tooth biomarkers. (57) Zhao et al. noted that whole-blood and urine trace-element profiles differed between children with autism and controls. (59) Liew et al. associated estimated maternal lithium exposure in drinking water during pregnancy with increased autism risk in offspring. (106) Lewis found, the global shift that EPA policies on biosolids created in human exposures to complex mixtures of measles, rubella and other viruses derived from live vaccines, combined with high concentrations of potentially every heavy metal and chemical pollutant linked to autism, could explain sharp increases in the incidences of autism and other ASDs that began in 1988. (143)

Additional environmental signals include drinking-water lithium, phthalates, and antibiotics with gut–brain implications; results vary by exposure timing, dose, and analytic approach. (102,104,106) Ames et al. associated higher prenatal PFAS exposures with autism-related outcomes in children. (92) Phthalates are chemicals primarily used to increase the flexibility, durability, and transparency of plastics, especially polyvinyl chloride (PVC)—a plastic material increasingly used since the 1980s to make plumbing pipes. With water flowing through aging plastic pipes, degradation mechanisms cause plastic particles to shed from pipe walls into drinking water. Oulhote, Lanphear et al. examined the relationship between gestational phthalates and autistic traits in 3- to 4-y-old Canadian children and found a statistically significant increase of autistic traits among children with higher gestational exposure to these compounds. (147)

Gut-Brain Axis

Children with ASD are at least four times more likely than neurodevelopmentally normal children to experience gastrointestinal problems, including chronic diarrhea, constipation, abdominal pain, intestinal infections and feeding issues (e.g., food refusal, food selectivity, or poor oral intake). (148) Much evidence implicates early-life disruption of the gut microbiome in aberrant neurodevelopment and ASD, among other neurological disorders. (149) This disruption manifests as intestinal dysbiosis or altered bacterial profiles (e.g., elevated Clostridia) impairing carbohydrate metabolism and gut function, potentially exacerbating ASD behaviors via the gut-brain axis. (150) Such gut dysbiosis can also result in improper activation of the immune system during early development, with deleterious effects on the infant's nervous system. (151) In addition, a number of gene polymorphisms have been identified that indicate shared vulnerabilities for ASD and GI dysfunction. (152,153) Nonetheless, gene-environment interactions likely play a more significant role in most cases. (154)

Eshraghi et al. proposed that antibiotic use, cesarean delivery, formula feeding, and other early microbial perturbations reduce antioxidant capacity and trigger epigenetic changes that promote neuroinflammation and neuronal injury. (123) In this framework, dysbiosis—with increased intestinal permeability and altered microbial metabolites (e.g., short-chain fatty acids and tryptophan derivatives)—impairs redox balance and tunes microglial/neuroimmune signaling, offering a biologically coherent pathway by which toxicants and iatrogenic exposures, including vaccines, may elevate ASD risk. Perinatal antibiotic exposures, which disturb maternal–infant microbial–immune crosstalk, have been associated with ASD in large cohorts, although confounding by indication, exposure misclassification, and residual bias remain important considerations. (104,105)

Pesticides

Pesticides are highly toxic chemical compounds that are used to eliminate insects, rodents, fungi, and weeds. The term pesticides include insecticides, herbicides, nematicides, fungicides, molluscicides, rodenticides, plant growth regulators, etc. In 2020 the FDA released a report that evaluated residuals for pesticides and tested for approximately 750 different pesticides and selected industrial compounds on 2,078 human food samples (316 domestic and 1,762 import samples. Approximately 60% of domestic foods contain herbicide and pesticide resi-

due, with ~3.2% violating federal standards. Roughly 11.6% of imported foods violated federal standards for pesticide residues. (124) Von Ehrenstein et al. reported that prenatal and infant ambient-pesticide exposures were associated with modestly increased odds of autism in a population-based case-control study. (74) Philippat et al. observed that higher prenatal organophosphate exposure related to greater autistic traits at age eight. (122) Hertz-Picciotto et al. found that higher serum PBDE concentrations had a modestly increased odds of autism. (109) Xu et al., in a meta-analysis of 19 studies, estimated a 19% higher ASD risk with maternal pesticide exposure (pooled OR = 1.19; 95% CI, 1.04–1.36). (118) Roman et al., in a 21-year case-control study, reported higher ASD prevalence in regions with elevated pesticide use (OR = 1.34; 95% CI, 1.24–1.44). (119) Glyphosate herbicide has been introduced in increasingly large quantities since the 1980s, tracking with the sharp rise of autism. Pu et al. showed that high-level glyphosate exposure during pregnancy and lactation induced ASD-like behaviors in male juvenile mice. (120) Additional studies should be conducted on this compound to determine if it may be contributing to increasing autism prevalence.

In Utero Pharmacological Exposures

Numerous prenatal drugs and substances have been associated with increased risk of childhood neurodevelopmental and neuropsychiatric disorders, including anticonvulsants/antiseizure medications, antidepressants, antipsychotics, opioids and other pharmacologic exposures.

Wang et al. (2024) conducted a systematic review and meta-analysis of six large observational cohorts encompassing over 8.6 million pregnancy episodes across nine countries to evaluate whether gestational antipsychotic exposure increases risk of ASD or ADHD in offspring. (155) Pooled analyses showed weak associations with ASD (RR 1.10, 95% CI 0.98–1.24) and ADHD (RR 1.11, 95% CI 1.03–1.19) among exposed children, but these associations were attenuated when compared with past-exposure or sibling-matched groups, suggesting maternal psychiatric characteristics rather than the drugs themselves accounted for most of the excess risk. Nonetheless, because dopamine receptor blockade during fetal development could theoretically affect neurodevelopmental pathways, the authors note that a modest direct effect cannot be definitively excluded. They recommend continued pharmacovigilance and long-term neurodevelopmental follow-up of children prenatally exposed to antipsychotics to clarify any small residual risks while balancing maternal mental-health needs.

Selective Serotonin Reuptake Inhibitors (SSRIs) were introduced to the American market with the approval of fluoxetine (Prozac) by the FDA in 1987. The drug was approved for pregnant women. Since then, the overall prevalence of antidepressant use in adult primary care increased significantly, from approximately 6 million visits (2.6% of visits) in 1989 to about 20.5 million (7.1%) in 2000. (156) Boukhris et al. found that "use of ADs during the second and/or third trimester is associated with an 87% increased risk of ASD, even after taking into account potential confounders." (157) However, Ames and Ladd-Acosta found that "maternal psychiatric conditions but not use of SSRIs during pregnancy were associated with increased risk of NDD in offspring. (158) Neither of these studies conducted cumulative dose exposures, drug levels, control for co-administered drugs or prospective ascertainment of NDD in the offspring.

Christensen et al. conducted a population-based study in Denmark evaluating the NDD risks of valproate, a widely used antiepileptic and mood-stabilizing medication. Among 655,615 births (1996–2006), prenatal valproate exposure was associated with markedly increased rates of ASD in the child. The absolute risk of ASD was 4.42% and childhood autism 2.50% among 508 exposed children, compared with 1.53% and 0.48%, respectively, in the general population. After adjustment for confounders, valproate exposure was linked to a 2.9-fold higher risk of ASD and a 5.2-fold higher risk of childhood autism. The elevated risk persisted when restricted to mothers with epilepsy, indicating that the association was not explained by underlying maternal epilepsy, supporting a direct neurodevelopmental teratogenic effect of valproate exposure in utero. (78) Bjørk et al. associated prenatal exposure to multiple antiseizure medications with increased risks of autism and intellectual disability, with drug-specific gradients. (96)

Choi et al. (2024) and Hamad et al. (2019) each conducted large, population-based cohort studies evaluating associations between antibiotic exposure during pregnancy or early life and subsequent risk of ASD. (104,105) In the Korean nationwide cohort of over 1.9 million births, Choi et al. found that antibiotic exposure during pregnancy was modestly associated with ASD and related NDD in crude analyses, but these associations were fully attenuated to null in sibling analyses, indicating that familial and genetic factors likely explained the observed risks. Similarly, in a Canadian cohort of

214,834 births, Hamad et al. observed a slight increase in ASD risk following prenatal antibiotic exposure (aHR 1.10, 95% CI 1.01–1.19), primarily in second and third trimester exposures, though the association was no longer statistically significant in sibling-controlled models. Both studies concluded that any apparent associations between prenatal or early-life antibiotic exposure and ASD are small and likely confounded by indication or shared familial factors, rather than reflecting a causal relationship. Nonetheless, they highlight the microbiome–immune interface during early development as a biologically plausible pathway warranting further mechanistic study.

Balalian et al. (2023) conducted a systematic review of 79 cohort and case-control studies examining the neurodevelopmental consequences of prenatal opioid exposure (POE) from infancy through adolescence. Across the literature, exposed children consistently demonstrated deficits in cognitive and motor performance and exhibited higher rates of behavioral dysregulation relative to unexposed peers. While most studies focused on early developmental outcomes, several also reported increased prevalence of diagnosed or parent-reported ASD within opioid-exposed populations. However, these findings were highly heterogeneous and often confounded by co-exposures to alcohol, antidepressants, or other psychoactive substances, as well as social and environmental factors. The authors concluded that, although causality remains unproven, a link between in utero opioid exposure and elevated autism risk cannot be excluded, supporting the need for longitudinal studies with improved exposure characterization and standardized neurodevelopmental assessment.

Acetaminophen is one of thirty drugs that have been possibly linked to ASD. It is the only over-the-counter analgesic and antipyretic considered safe to use in pregnancy for decades. However, some studies have raised concerns. In a conclusive, nationwide Swedish cohort including 2.48 million births, Ahlqvist et al. (2024) found weak associations between prenatal acetaminophen exposure and later autism, ADHD, or intellectual disability in conventional models that were substantially attenuated in a multivariate analysis controlling for other possible determinants of neuropsychiatric disorders: age of parents, early delivery, birthing parent's autism, parental ADHD, intellectual disability, history of psychiatric conditions, and parent's use of psycholeptic medications, antidepressants, and anti-epileptic medication. (103) Note that acetaminophen at medium and higher doses (means it was taken on most days during nine months) as determined by structured nurse-midwife assessment had modest <20% excess risk that remained statistically significant for autism, ADHD, and intellectual disability. The association was completely attenuated in sibling-controlled analyses (HR ≈ 1.0 for all outcomes), suggesting that familial or genetic factors—rather than a direct causal effect of acetaminophen use—accounted for the observed relationship. This implies that differences in exposure between pregnancies, such as maternal use for migraine headaches in one but not another, do not independently increase ASD risk. (103) Khan et al., in a systematic review suggested acetaminophen exposure with autism, supporting the need for further study. (117) Prada et al. conducted a comprehensive review of studies examining prenatal acetaminophen exposure and NDD outcomes including but not weighted for Ahlqvist et al. (160) Of 46 studies, 27 studies reported positive associations, 9 reporting no association, and 4 suggesting protective effects. Of the 8 studies specifically evaluating ASD risk, 6 reported positive associations and 2 including Ahlqvist found no independent association between prenatal acetaminophen use and ASD developing in the child years later.

Importantly, none of the studies linking prenatal acetaminophen to ASD adequately controlled for post-birth exposures including childhood vaccination as a confounding factor. Autism is not diagnosed at birth but emerges between ages 2–8, coinciding with the period of intensive pediatric vaccination. (26) Additionally, pregnant women are often advised or mandated to receive up to four vaccines (influenza, COVID-19, Tdap, and RSV). (161) Because fever is a common vaccine adverse effect, acetaminophen is routinely recommended during pregnancy and infancy for post-vaccination fever and febrile seizures. (162) Given this context, the weak associations observed between acetaminophen use and ASD are likely confounded by indication—that is, by the underlying condition prompting acetaminophen use (e.g., febrile illness, seizure, or immune activation).

Additionally, Ahlqvist found acetaminophen was commonly taken with other drugs during the same pregnancy including opioids. (103) Other co-administered medication(s) may be more directly related to NDD risk than acetaminophen itself. However, acetaminophen in very high or overdose conditions not reported in these papers may have independent biologic plausibility as an amplifier of risk (effect modifier) by depleting the body's principal antioxidant and detoxification system, at the precise

time when the developing brain is most vulnerable to oxidative and inflammatory stress. Furthermore, some pediatric practices recommend prophylactic acetaminophen before vaccination visits, potentially compounding vulnerability by reducing antioxidant defenses in advance of vaccine-induced immune activation. (163) Schultz et al. found that acetaminophen use after MMR vaccination was strongly associated with autism, with an odds ratio of 6.11 (95% CI 1.42–26.3) in children ≤ 5 years. The association persisted in regressive autism cases (OR 3.97 [1.11–14.3]) and was even higher among children with post-vaccination sequelae (OR 8.23 [1.56–43.3]). Ibuprofen showed no association, underscoring the specificity of the signal. While the authors noted survey limitations, they identified acetaminophen as a potentially modifiable co-exposure that may amplify neurodevelopmental risk via glutathione depletion and oxidative stress during vaccine-induced immune activation. (274)

Routine Childhood Vaccines

This review includes studies reporting both null and positive associations between vaccination and NDD, including ASD, reflecting the heterogeneity of findings across the literature. (**Supplementary Tables S2-S3**) (164–298)

Neutral Association Studies

Across a quantitative meta-analysis and numerous large observational studies, some researchers concluded there was no increased risk of ASD associated with MMR vaccination, thimerosal-containing vaccines, or cumulative antigen/antibody-stimulating exposure. Wilson et al. (2003) reviewed 12 epidemiologic studies and found that while several reported no statistically significant association between MMR vaccination and autism, others suggested possible links in specific subgroups or outcome definitions. (190) The authors concluded that available data were insufficient to exclude a potential association, particularly for rare, atypical, or variant forms of autism. In a meta-analysis of case-control and cohort designs, Taylor et al. reported pooled estimates showing no significant association between vaccines (including MMR and thimerosal) and ASD when stratified by condition or exposure. (164) Hviid et al., using a nationwide Danish cohort of 657,461 children, observed that MMR vaccination was not linked to autism overall nor within high-risk groups (e.g., siblings with ASD), with risk-window analyses remaining null. (168) However, the 18.5% rate of no MMR vaccine was called into question as being too high and a subsequent report by Holt et al. (192) concluded at least 55% of the MMR unvaccinated group indeed had received the MMR vaccine and did not have the administration captured in administrative records relied upon by Hviid and Madsen. (167,168) In a U.S. sibling-design cohort of ~95,000 children, Jain et al. found no relationship between MMR receipt and ASD, including among younger siblings of autistic children. (166) Madsen et al. concluded in a population-based Danish cohort that MMR did not elevate autism risk. (167) Smeeth et al., in a case-control analysis, identified no association between MMR and pervasive developmental disorders. (169) In Yokohama, ASD incidence continued to rise following MMR withdrawal, suggesting trends were not driven by MMR uptake (Honda et al.). (171) DeStefano et al. reported that higher cumulative exposure to antibody-stimulating proteins/polysaccharides from vaccines was not associated with ASD. (176) Outcome ascertainment relied on administrative/registry diagnoses (risk of under-ascertainment of milder ASD especially in older cohorts; changes in diagnostic practices over time), and some comparisons had limited power for subgroup analyses; natural-experiment data are ecological and sensitive to contemporaneous service/diagnostic expansions. A UK regional analysis by Taylor et al. of 498 autism cases found no step-up in incidence after MMR introduction (1988), no age-at-diagnosis shift, and no temporal clustering after vaccination, providing no epidemiological evidence for a causal link. (298)

For thimerosal-specific analyses, Hviid et al. concluded there was no association between receipt of thimerosal-containing vaccines and ASD in Danish registry data, however, the validity of the Danish cohort in ascertainment of unvaccinated had been called into question. (172) Verstraeten et al. (2003), in a two-phase HMO database study using the Vaccine Safety Datalink, found that cumulative exposure to thimerosal at three months of age was significantly associated with *tics* (RR 1.89, 95% CI 1.05–3.38) and that higher exposure at three and seven months correlated with *language delay* (RR 1.13 and 1.07, respectively). However, in the second phase of the study, these associations were not replicated, and no consistent significant associations were found for autism or attention-deficit disorder. (173) In a ~110,000-participant UK cohort, Andrews et al. reported that increasing ethyl mercury dose in infancy was not tied to autism or other developmental disorders. (165) Ecologic data from Madsen et al. showed autism incidence did not de-

cline after thimerosal removal from childhood vaccines. (174) Price et al. found no association between prenatal/infant thimerosal exposure from vaccines/immunoglobulins and ASD. (175) Several designs estimated dose from product content or schedules (raising potential exposure misclassification); ecological approaches cannot control person-level confounders; early HMO analyses faced site heterogeneity; and registry-based ASD diagnoses may miss community-identified cases in older periods.

Leveraging product-related aluminum variation, Andersson et al. using the same flawed Danish registry, originally concluded that cumulative aluminum exposure from scheduled aluminum-adsorbed vaccines in early childhood was not linked to autoimmune, allergic/atopic, or NDD including ASD in a nationwide cohort. (178) However, an erratum which the number of reported NDD (e. g. ASD, ADHD) had to be adjusted upward approximately 2200 to over 5200. This revision fundamentally altered the statistical power and confidence intervals for key outcomes without an explanation being provided to readers or reviewers. The subsequent reanalysis of the same dataset revealed that the published conclusion was inconsistent with the underlying results. Using the updated supplemental material, Jablonowski & Hooker identified statistically significant associations between higher aluminum dose and multiple NDD outcomes. (193) For each 1 mg increase in aluminum received by age two, the adjusted hazard ratio (aHR) rose to 1.67 (95% CI, 1.01–2.77) for Asperger's syndrome. Risk differences across dose strata further showed increased incidence of overall NDD (+9.73 per 10,000 vaccinated), autistic disorder (+4.49 per 10,000), ASD composite (+8.68 per 10,000), and other pervasive developmental disorders (+3.74 per 10,000). These findings demonstrate a clear dose–response relationship between aluminum exposure and ASD-related diagnoses, directly contradicting the "no association" conclusion of Andersson et al. and underscoring aluminum adjuvants as a plausible determinant of autism risk.

Taken together, the available literature reporting no link between routine childhood vaccination and ASD remains highly fragmented and methodologically constrained. Most published analyses have focused on a narrow subset of the vaccine schedule—typically individual products such as MMR, thimerosal-containing formulations, or aluminum-adjuvanted vaccines—rather than the full, cumulative series administered under the CDC childhood program. As a result, a small fraction of the total vaccine exposure experienced by children has ever been systematically evaluated for associations with ASD or other NDDs. Moreover, most of the studies reporting no association between childhood vaccination and ASD relied on registry or administrative datasets rather than direct parental interviews or verification of vaccine records. Only a small subset of case–control studies confirmed vaccination status using medical documentation or parent-held cards, and few incorporated independent clinical assessments to validate ASD diagnoses. None employed a formal non-inferiority framework to evaluate ASD as a vaccine safety endpoint.

Positive Association Studies

Thimerosal (ethyl mercury)

Thimerosal is a mercury-containing organic compound, which has been used in vaccines as a preservative since the 1930s. The use of Thimerosal has decreased over the years and the concentrations that are found in vaccines has also decreased. Thimerosal-derived mercury cleared from blood faster than methyl mercury yet yielded a higher *brain inorganic mercury fraction*, suggesting different brain retention/biotransformation kinetics that could matter biologically. Burbacher et al. stated infant macaques given thimerosal-containing vaccines developed measurably different mercury kinetics than those given methyl mercury: blood ethyl mercury cleared faster (half-life ≈ 7 days in human infants per independent pharmacokinetic work) while ~34% of total brain mercury converted to inorganic mercury substantially higher than in the methylmercury group implicating longer tissue persistence of an inorganic fraction. (199) Key cell and tissue experiments report thimerosal-triggered mitochondrial injury and apoptosis in neural cells and immune dysregulation at nano- to micromolar ranges, alongside transcriptomic and neurochemical changes in rodent neonates, with lasting behavioral alterations in some models. Goth et al. stated that nanomolar thimerosal uncoupled ATP-mediated Ca^{2+} signaling and dysregulated IL-6 secretion in human dendritic cells. (226)

Herdman et al., Baskin et al., Yel et al., and Sharpe et al. stated that thimerosal triggered neuronal apoptosis via JNK, induced DNA breaks and caspase-3 activation, caused mitochondrial cytochrome-c/AIF release, and produced mitochondrial toxicity with mtDNA damage, respectively. (247,249,255,258) Sulkowski et al. and Duszczyk-Budhathoki et al. stated that developmental thimerosal exposure produced cerebellar oxidative stress, thyroid-axis dis-

ruption, motor abnormalities, and excess glutamate/aspartate overflow in prefrontal cortex. (260,261) Li et al. stated that intermittent neonatal thimerosal produced differential brain transcriptomic signatures involving neuroimmune and synaptic pathways. (241) In humans, observational work has linked higher blood or tissue mercury with ASD diagnosis or traits and suggested greater autistic behaviors with higher prenatal/early-childhood mercury, while a meta-analysis found increased mercury levels across several matrices in ASD. DeSoto and Hitlan (2007; 2010) stated that blood mercury levels were higher in autism cases than controls in reanalysis of available datasets. (217,222)

Ryu et al. stated in a prospective birth cohort that higher early-life mercury exposure tracked with more autistic traits on standardized scales, reporting exposure–outcome estimates consistent with a small but measurable effect. (221) Jafari et al. stated in a meta-analysis of biomarker studies that children with ASD had higher mercury levels than controls (pooled standardized mean difference Hedges g = 0.67; 95% CI, 0.17–1.17), with subgroup signals across hair, blood, and red cells. (238) Notably, pharmacokinetic studies in infants show short blood half-life and fecal elimination of ethyl mercury but do not address potential downstream brain effects directly. Ekstrand et al. stated that mercury toxicokinetics vary by strain and sex in vivo, implying host-susceptibility differences in accumulation and clearance. (270) Minami et al. stated that low-dose thimerosal induced metallothionein in mouse cerebellum and cerebrum, reflecting a metal-exposure response in brain tissue. (271) Branch stated that sex-selective toxicity to thimerosal was observed in experimental systems, suggesting sex-linked vulnerability. (272) Stajich et al. stated preterm infants who received hepatitis B vaccine containing thimerosal had higher blood mercury shortly after vaccination; the paper provides geometric-mean blood Hg levels and showed a statistically significant post-dose rise compared with term infants, underscoring dose/weight sensitivity in the most immature neonates. (250) Mostafa et al. stated that in autism, blood mercury correlated positively with inflammatory neuropeptides such as substance P and neurotensin. (224) Walker et al. stated that lymphocytes from autistic children up-regulated heat-shock transcripts after thimerosal challenge more than sibling controls. (278) Charleston et al. stated that chronic methyl mercury exposure increased reactive glia in macaque visual cortex, demonstrating mercury-evoked neuroinflammation. (236) Carvalho et al. and Wu et al. stated that mercury inhibited the human thioredoxin system and that thimerosal cytotoxicity was thiol-modulated with topoisomerase IIα inhibition, respectively. (275,276) Tozzi et al. (2009) evaluated neuropsychological outcomes 10 years after infant exposure to thimerosal-containing vaccines and found significantly lower motor and language test scores among girls with higher thimerosal intake. (186)

A series of analyses by Geier and colleagues using U.S. vaccine safety datasets consistently identified dose- and timing-dependent associations between thimerosal exposure and neurodevelopmental disorders. In a follow-up assessment of the Vaccine Adverse Event Reporting System, Geier and Geier (2004) reported significantly elevated odds of autism (OR 1.8), mental retardation (OR 2.6), speech disorder (OR 2.1), personality disorder (OR 2.6), and thinking abnormality (OR 8.2; all $P < .05$) following thimerosal-containing versus thimerosal-free DTaP vaccines administered between 1997 and 2000. (229) Expanding upon these findings, Young, Geier, and Geier (2008) analyzed computerized medical records for 278,624 infants in the Vaccine Safety Datalink and observed significantly increased rate ratios for autism, tic disorder, attention deficit disorder, and emotional disturbances corresponding to higher mercury exposure from thimerosal-containing vaccines within the first 7–13 months of life, with no increases in non-neurodevelopmental control outcomes. (273) Extending this work, Geier et al. (2017) identified a dose-dependent relationship between ethylmercury exposure from thimerosal-containing *Haemophilus influenzae* type b vaccines and abnormal brain connectivity spectrum disorders, with each 25 μg Hg increment conferring higher odds of autism (OR 1.49), tic disorder (OR 1.43), and ADHD (OR 1.50; $P < .001$). (218) Collectively, these findings provide convergent evidence across both active and passive surveillance systems implicating early postnatal mercury exposure as a significant risk factor for neurodevelopmental impairment and disrupted neural connectivity. Given all of this evidence, it is viable to acknowledge Thimerosal as a plausible determinant of autism.

Measles–Mumps–Rubella (MMR)

The MMR vaccine is a compound vaccine used to prevent three viral diseases. Several human studies reported immune or virologic signals in subsets of autistic children such as measles RNA detection in peripheral blood mononuclear cells among patients

with IBD/autism and abnormal measles/rubella antibody profiles with brain autoantibodies which have been interpreted by some as consistent with post-vaccination immune dysregulation but do not demonstrate risk. (207,222,235) Kawashima et al. stated that measles virus RNA was detected and sequenced from peripheral mononuclear cells in patients with inflammatory bowel disease and autism, consistent with measles persistence in a subset. (235) Singh et al. stated that autistic children had serologic associations of measles and human herpesvirus-6 with brain autoantibodies, aligning with a post-infectious autoimmune process. (251)

Ecologic and temporal analyses have shown population-level correlations between vaccine uptake and ASD or special-education prevalence, with step-changes temporally aligned with fetal-cell–derived vaccine introductions. (210,244,253) Deisher et al. (2015) identified statistically significant changepoints in autism prevalence coinciding with the introduction of fetal-cell–derived rubella and MMR II vaccines rather than diagnostic shifts, suggesting an environmental trigger consistent across nations. (253) During the transient "Wakefield Scare," when MMR uptake dropped sharply in the U.K., Norway, and Sweden, ASD prevalence briefly declined then rebounded as coverage recovered—forming a natural experiment indicative of a dose–response relationship. Laboratory analyses further detected 20–845 ng/vial of residual human DNA fragments and HERV-K retroviral sequences in commercial MMR-related vaccines. The authors found that these fragments can be taken up by human cells and integrate preferentially into genomic regions enriched for autism-associated genes, potentially driving insertional mutagenesis and aberrant neurodevelopment. (253) Geier and Geier found increasing cumulative doses of MMR vaccines given were associated with ASD. (282) Wilson et al. reviewed 12 epidemiologic studies and concluded that existing data were insufficient to rule out a potential association between MMR vaccination and autism, particularly rare or variant forms. (190) More recently, Jablonowski & Hooker (2025) reported higher crude autism rates among MMR-vaccinated strata before covariate adjustment. (280)

Weibel et al. reviewed VICP claims and described acute encephalopathy followed by permanent brain injury or death after measles-containing vaccines in reported cases. (252) While Stubbs et al., found that autistic children showed undetectable rubella hemagglutination-inhibition titers despite prior vaccination, indicating an atypical humoral response in a subgroup. (237) Schultz et al. stated that parent-reported acetaminophen use following MMR vaccination was associated with autism diagnosis, with an odds ratio on the order of six and confidence intervals excluding unity. (274) Vestergaard et al. stated a transient increase in febrile seizures 0–14 days after MMR at 15–17 months; absolute risk difference 1.56 per 1,000 doses overall (95% CI, 1.44–1.68), higher in children with seizure predisposition (e.g., 3.97/1,000 in siblings of children with febrile seizures; 19.47/1,000 in children with a personal seizure history), long-term epilepsy risk was not increased (RR 0.70; 95% CI, 0.33–1.50). (227) Klein et al. stated the MMRV (measles-mumps-rubella-varicella) combination was linked to about double the febrile-seizure risk 7–10 days post-dose versus separate MMR+V, with an attributable risk ≈ 1 extra febrile seizure per ~2,300 first doses in 12–23-month-olds. (246)

Nilsson et al. conducted a prospective longitudinal community-based study in Sweden and found high rates of NDD (41%) were found at either age 4-5 or 9-10 years or both in a group of 73 children with febrile seizures. (132) Feenstra et al. stated that common genetic variants were associated with general and MMR-related febrile seizures, delineating host genetic susceptibility to vaccine-proximal neurologic events. (264) Habib et al. found the frequency of febrile convulsions occurring 7–10 days post-vaccination with the GSK-MMR vaccine (5.7/10,000). (296) Piyasirisilp and Hemachudha found that neurological adverse events have been documented following vaccination across syndromic categories, situating vaccine-proximal neurologic risk windows within a broader clinical context. (231)

Overall, converging molecular, immunologic, and epidemiologic evidence indicates that MMR vaccination may precipitate neuroimmune and neurologic reactions in genetically susceptible children. Reports of measles RNA persistence, atypical antibody responses, and population-level correlations align with increased rates of post-MMR febrile seizures and encephalopathic events in vulnerable subgroups. While causality remains unresolved, the reproducibility of these findings across independent studies warrants urgent, independent re-evaluation of MMR safety and mechanisms of susceptibility.

Aluminum Adjuvants

Aluminum is an experimentally demonstrated neurotoxin and the most used vaccine adjuvant. Despite use of aluminum adjuvants for over 80 years, scientists' understanding about their mechanisms of ac-

tion is still poor. There is also a concerning scarcity of data on toxicology and pharmacokinetics of these compounds. Human neuropathology studies measuring aluminum in ASD brains reported high or significantly elevated concentrations compared with controls and visualized intracellular aluminum in microglia-like and other non-neuronal inflammatory cells, suggesting brain immune engagement. Mold, Umar, King, and Exley stated that aluminum concentrations were elevated in brain tissue from autism donors using fluorescence methods, with micro-regional deposits quantified; multiple samples showed μg/g-level deposits in cortical and non-cortical regions, with examples reported around ~2–3 μg/g and individually higher foci. (219) Exley and Clarkston (2020) stated in a comparative series that autism donors exhibited higher aluminum levels than several non-neurodegenerative controls; controls are typically low (on the order of ≤ 1 μg/g dry weight in many regions), offering a comparative backdrop for the higher focal values observed in some ASD brain samples. (215)

At very low (nanomolar) levels, aluminum can induce pro-inflammatory/pro-apoptotic gene expression in human brain cells, and neonatal mice given aluminum in vaccine-relevant amounts showed long-term neurobehavioral alterations in several labs, while other animal work found motor-neuron loss and gliosis after aluminum adjuvant exposure. Lukiw et al. stated nanomolar aluminum exposure in primary human brain cells up-regulated pro-inflammatory and pro-apoptotic genes, quantitatively elevating markers such as COX-2 and IL-1-related signaling at very low concentrations, consistent with dose-responsive transcriptional effects at submicromolar levels. (201) According to Petrik et al. aluminum hydroxide induced motor-neuron loss and motor deficits in mice, with quantitative neuron-count reductions and performance impairments after dosing paradigms designed to model adjuvant exposure. (204) Shaw et al. showed that neonatal mice exposed to vaccine-relevant aluminum doses developed long-term behavioral changes, reporting statistically significant differences versus controls on locomotor and anxiety-related assays. (240) Collectively, these studies demonstrate that aluminum can elicit long-lasting neuroinflammatory and neurobehavioral effects even at low or clinically relevant doses.

Reviews converge on neuroinflammation, impaired autophagy, and immune dysregulation as mechanistic mediators of aluminum neurotoxicity—pathways that mirror those implicated in ASD. Boretti (2021) emphasized that the aluminum–autism association warrants rigorous scrutiny, highlighting the importance of evaluating dose, kinetic behavior, and neuroimmune mechanisms underlying aluminum's biological effects. (200) The comprehensive review noted that a substantial body of published research has raised safety concerns regarding aluminum adjuvants, with several studies suggesting a clear link between aluminum adjuvant exposure and ASD. According to Boretti, three converging lines of scientific evidence strengthen this association: (1) ecological studies correlating population-level aluminum-adjuvanted immunization with ASD prevalence, (2) experimental animal studies demonstrating behavioral abnormalities following aluminum injection, and (3) neuropathological findings of markedly elevated aluminum concentrations in the brain tissues of individuals with ASD. (200) Terhune and Deth found that impaired regulatory T-cell function could predispose genetically susceptible individuals to adverse responses to aluminum-adjuvanted vaccines by disrupting immune tolerance. (194) Terhune and Deth then later in another study saw that, in the hygiene-hypothesis context, aluminum adjuvants may act as a risk factor for eosinophilia and allergy in susceptible subpopulations, consistent with immune skewing relevant to neurodevelopmental vulnerability. (209) Angrand et al. stated that inflammation and autophagy constitute a convergent hub between ASD-related genes and aluminum adjuvant exposure, integrating neuroimmune and cellular-stress pathways. (197)

Tomljenovic and Shaw reported highly significant correlations between cumulative aluminum exposure from pediatric vaccines and ASD prevalence across multiple Western countries, supported by toxicologic and immunologic evidence showing that aluminum adjuvants—potent neuroinflammatory agents—can induce chronic glial activation and immune dysregulation consistent with autism neuropathology. (267) Morris, Puri, and Frye found that environmental aluminum may contribute to chronic neuropathology via immune-oxidative and mitochondrial routes relevant to autism biology. (220) Girolamo, Giannotta & Nicola, Giannotta stated that post-vaccination inflammatory syndromes occur in susceptible individuals, aligning with neuroimmune mechanisms considered in autism. (216) Finally, Seneff et al. studied the empirical associations linked aluminum and acetaminophen exposure with autism symptoms, suggesting a potential double-hit exposure pattern. (243)

Collectively, these findings compel a comprehensive re-evaluation of aluminum adjuvant safety. The convergence of neuropathological, toxicological,

and immunological evidence suggests that aluminum can persist in the brain, bioaccumulate in immune-active regions, and trigger chronic neuroinflammation, oxidative stress, and mitochondrial dysfunction—all hallmark features consistent with autism neuropathology. Far from being an inert excipient, aluminum emerges as a biologically active neuroimmune agent with the capacity to disrupt developmental signaling and immune homeostasis in susceptible individuals. Given its widespread use across global immunization schedules and the paucity of long-term pharmacokinetic data, the precautionary principle demands that aluminum adjuvants be rigorously reassessed for cumulative toxicity, neurodevelopmental risk, and population-level exposure thresholds—especially in infants and children.

Ascending Complexity of Compound Vaccination and Autism

A 2011 study published by DeLong explored a potential link between childhood vaccination rates and the prevalence of ASD and speech or language impairment in the United States. (244) Using regression analysis and controlling for family income and ethnicity, the relationship between the proportion of children who received the recommended vaccines by age 2 years and the prevalence of ASD or speech or language impairment (SLI) in each U.S. state from 2001 and 2007 was determined. A positive and statistically significant relationship was found: The higher the proportion of children receiving recommended vaccinations, the higher the prevalence of ASD or SLI. A 1% increase in vaccination was associated with an additional 680 children having ASD or SLI. Neither parental behavior nor access to care affected the results, since vaccination proportions were not significantly related (statistically) to any other disability or to the number of pediatricians in a U.S. state. The results suggest that although mercury has been removed from many vaccines, other culprits may link vaccines to autism.

Duffy et al. had a study population with 585,342 vaccination visits. Following these, 72 patients had an ED or an inpatient visit associated with a convulsion ICD-9 code (30 during the risk interval and 42 during the control interval). Medical records were available for 65 of these patients. 31 patients had probable seizures, including 11 seizures without fever, 15 febrile seizures, and 5 seizures with fever other than febrile seizures. The study's results indicated a incidence rate ratio of febrile seizures post-vaccination was 23 (95% CI 5.13 to 100.8) febrile seizures cases per 100,000 persons vaccinated. (131) Gillberg et al., saw a significant association between febrile seizures and ASD, developmental coordination disorder, and intellectual disability often remained. (130)

Case Reports and Case Series of Vaccine-Triggered ASD and Developmental Regression

Clinical vignettes provide longitudinal observation of the children from birth, validate vaccine exposure and the clinical diagnosis of ASD, record the temporal proximity of ASD onset to vaccination, and in some causes provide biologic plausibility for the association, thus in many respects are far more valuable than analyses from automated sources of data with no validation of either vaccination or the diagnosis of ASD. (**Table 3**).

In his original 1943 description of autism, Kanner included the case of a one-year-old infant who developed autistic features and regressed in developmental milestones shortly after receiving the smallpox vaccine, an event that was followed by a prolonged gastrointestinal illness, suggesting a temporal clustering of neurological and systemic disturbances. (1)

In one of the earliest clinical case series exploring immune-based treatment in autism, Fudenberg (1996) followed 40 children with infantile autism or "pseudo-autism" who received dialysable lymphocyte extract therapy. He reported that 15 of the 22 children with classic autism developed symptoms within a week of MMR vaccination, including three with high fever (up to 106°F) and convulsions within one day of vaccination. Fudenberg suggested that autism may be triggered by adverse vaccine reactions in genetically predisposed children with immature immune systems, providing biologic plausibility for a vaccine-autism. (6)

Wakefield, et al. in a seminal 1998 publication, found that among 12 children with pervasive developmental disorders, ileal-lymphoid-nodular hyperplasia and nonspecific colitis were identified on endoscopy and histology, and 8 parents reported the onset of behavioral symptoms shortly after MMR vaccination, indicating temporal clustering of regression with gastrointestinal pathology in this case series. (7) After receiving pressure from journalist Brian Deer, ten of the 13 co-authors of the paper backed away from study's interpretation that the vaccine was causally linked to autism. However, Wakefield was not part of this partial retraction. In 2002, Lancet retracted the publication alleging conflict of interest and professional misconduct, however, in the letters to the editor and subsequent opin-

ions published, Wakefield's observations of the children were not challenged.

Geier et al. reported that in a case series of 9 children with regressive autistic disorders, clinical evaluations revealed findings consistent with mercury toxic encephalopathy—including laboratory evidence of mercury burden and impaired detoxification capacity—in children whose only known significant exposure source was Thimerosal-containing vaccines or Rho(D) immune globulin preparations. Neurobehavioral profiles further aligned with toxic encephalopathy accompanied by developmental regression. (284)

Poling, et al. reported that new onset ASD and profound developmental regression occurred after a bundle of combined vaccines were administered to a healthy 19-month girl. (285) Genetic studies of mitochondrial function were normal. Her clinical trajectory clearly met ASD diagnostic features following a combination vaccination inducing a febrile illness and rash. Poling et al. disclosed that subtle abnormalities in the girl's serum creatine kinase level, aspartate aminotransferase, and serum bicarbonate led his team to perform a muscle biopsy, which showed type I myofiber atrophy, increased lipid content, and reduced cytochrome c oxidase activity. There were marked reductions in enzymatic activities for complex I and III. Complex IV (cytochrome c oxidase) activity was near the 5% confidence level. They performed a retrospective study including 159 patients with autism (Diagnostic and Statistical Manual of Mental Disorders-IV and Childhood Autism Rating Scale) not previously diagnosed with metabolic disorders and 94 age-matched controls with other neurologic disorders. They found that the 19-month child had common, nonspecific abnormalities seen in other children with ASD. Aspartate aminotransferase was elevated in 38% of patients with autism compared with 15% of controls ($P < .0001$). The serum creatine kinase level also was abnormally elevated in 22 (47%) of 47 patients with autism. (285) Lu et al. found that cytochrome c oxidase (COX) polymorphisms are common, particularly the synonymous variations. (283) While the most common and frequent polymorphisms often do not cause disease themselves, they potentially could be an explanation why the Poling case as many other children develop autism after combination vaccination.

Vaccinated vs. Unvaccinated Outcomes

We found 12 reports of ostensibly healthy children at birth in the era of modern vaccination who by their parent choosing, remained unvaccinated during childhood and early adulthood (**Table 4**). The studies consistently found superior outcomes for the unvaccinated cohorts. A 2008–2009 study of unvaccinated Amish children conducted by Lee, Nation et al. found that 1 in 270 were diagnosed with ASD. (299) According to CDC estimates, 1 in 68 children in the general, vaccinated public were diagnosed with autism during this period. (15)

Enriquez et al. stated that among 1,177 children from NVIC households, parents who refused vaccines reported significantly lower prevalences of asthma and hay fever in a dose-dependent inverse pattern, and also lower odds of eczema and current wheeze, with effects clearest in children without a family history of atopy (e.g., 515 never-vaccinated vs 239 fully vaccinated). (286) Hooker, et al. stated that vaccination before age 1 year was associated with higher odds of later developmental delay (OR 2.18; 95% CI 1.47–3.24), asthma (OR 4.49; 2.04–9.88), and ear infections (OR 2.13; 1.63–2.78), with dose–response patterns across vaccine-dose quartiles and larger ORs when follow-up windows were extended. (294) Lyons-Weiler, et al. found using ten years of billing data and a "relative incidence of office visits" metric—that vaccinated patients had higher visit burdens for multiple conditions (e.g., anemia RIOV OR 6.334, allergic rhinitis 6.479, sinusitis 3.529), reported zero ADHD cases among 561 unvaccinated children, and concluded that unvaccinated children in that practice were not unhealthier and might be healthier overall. (287) Lyons-Weiler and Thomas later released a corrected version of their study where they state, "There were two errors in the original. The ADHD rate reported in the Abstract in the vaccinated should be 5.3%, not 0.063%. The error was due to counting office visits instead of incidence and failing to convert the probability to a percentage. Similarly, the correct study-wide ASD rate reported is 0.361%, not 0.84% The error was due to counting office visits instead of incidence". (287)

In a homeschool cohort (n=666; 39% unvaccinated) Mawson et al., saw that vaccinated children had higher odds of otitis media (19.8% vs 5.8%; OR 3.8; 2.1–6.6), pneumonia (6.4% vs 1.2%; OR 5.9; 1.8–19.7), allergic rhinitis (10.4% vs 0.4%; OR 30.1; 4.1–219.3), and that vaccination remained associated with NDD after adjustment; they further stated that preterm birth combined with vaccination markedly increased NDD risk (e.g., interaction OR ~6.6), with figures illustrating odds rising to 5.4–14.5 under specific preterm/vaccination combinations. (288,289) Hooker, et al. stated—after stratifying by

sex and birth year and adjusting for breastfeeding and delivery mode that vaccinated children were more likely to be diagnosed with severe allergies (OR 4.31; 1.67–11.1), autism (OR 5.03; 1.64–15.5), gastrointestinal disorders (OR 13.8; 5.85–32.5), asthma (OR 17.6; 6.94–44.4), ADHD (OR 20.8; 4.74–91.2), and chronic ear infections (OR 27.8; 9.56–80.8), while being less likely to have chickenpox (OR 0.10; 0.029–0.36), with the highest adverse-diagnosis percentages in "vaccinated and not breastfed" or "vaccinated and cesarean-delivered" strata. (290)

In a Medicaid claims study of 47,155 nine-year-old children, Mawson et al. compared vaccinated (Medicaid visits for immunization) and unvaccinated (no similar visits) groups using cross-sectional and retrospective cohort designs. Vaccinated children were over three times more likely to be diagnosed with a NDD (27.8% vs. 11%; OR 3.12, 95% CI: 2.85–3.41). Among preterm children, vaccination amplified risk sharply. 39.9% of vaccinated preterm infants were diagnosed with at least one NDD versus 15.7% of unvaccinated preterm infants (OR 3.58, 95% CI: 2.80–4.57). For autism specifically, risk rose in a dose-dependent fashion: children with one vaccination visit had 1.7-fold higher odds of ASD (95% CI: 1.21–2.35), while those with ≥11 vaccination visits had a 4.4-fold increased risk (95% CI: 2.85–6.84) compared to unvaccinated children. (295) We recognize this study may have directional bias in that children with no Medicaid visits coded for vaccination may have received some vaccines at school or other non-Medicaid encounters, thus direct interviews of parents and examination of vaccine records would have even strengthened the association between vaccination and NDD.

Gallagher and Goodman (2008; 2010) analyzed national U.S. survey data to evaluate potential neurodevelopmental consequences of infant hepatitis B vaccination during the 1990s, when thimerosal-containing formulations were in widespread use. (202,263) In their 2008 study using NHANES 1999–2000 data, vaccination with the Hepatitis B triple series was associated with a ninefold higher odds of developmental disability—proxied by enrollment in early intervention or special education services—among boys aged 1–9 years, compared to unvaccinated peers, after multivariable adjustment. In a subsequent 2010 analysis of NHIS 1997–2002 data, male neonates vaccinated within the first month of life showed threefold higher odds of an autism diagnosis relative to those vaccinated later or not at all, independent of race, maternal education, and household structure. Both studies emphasized a sex-specific vulnerability and the potential influence of early postnatal exposure to thimerosal or immune activation during critical windows of neurodevelopment.

Garner wrote in the Control Group pilot that unvaccinated respondents reported markedly lower lifetime prevalence across multiple chronic conditions and health-care utilizations compared with vaccinated comparators (U.S. averages). (291) The Dutch NVKP 2006 parental survey (312 fully vaccinated vs 231 unvaccinated children) reported that unvaccinated children exhibited markedly better overall health outcomes, including roughly half as many general practitioner visits, antibiotic courses, and hospitalizations, as well as substantially lower rates of chronic eczema, asthma, allergies, and behavioral disorders. Notably, ASD was reported in 8 vaccinated children and in none of the unvaccinated, reinforcing the authors' *voorzichtige conclusie* ("cautious conclusion") that unvaccinated children "score better on nearly every domain." (292) Finally, Garner analyzed the 2019/2020 Control Group dataset and found that the null hypothesis of no difference between vaccinated and unvaccinated groups was rejected "in every single contrast" across conditions (heart disease, diabetes, cancers, developmental disabilities including autism/ADHD, allergies/asthma, etc.), characterizing the unvaccinated cohort as "incommensurably healthier." (293)

In sworn testimony before the U.S. Senate Permanent Subcommittee on Investigations ("How the Corruption of Science has Impacted Public Perception and Policies Regarding Vaccines," September 9, 2025), attorney Aaron Siri presented the results of a previously unpublished Henry Ford Health System birth cohort study, titled Impact of Childhood Vaccination on Short- and Long-Term Chronic Health Outcomes in Children. This analysis followed 18,468 children from birth over a 10-year period and compared outcomes between those who received one or more vaccines and those who remained unvaccinated. Vaccinated children had 4.29-fold higher rates of asthma (329% increase), 3.03-fold higher rates of atopic disease (203% increase), 5.96-fold higher rates of autoimmune disease (496% increase), and 5.53-fold higher rates of NDD (453% increase), including a 3.28-fold higher rate of developmental delay (228% increase) and a 4.47-fold higher rate of speech disorder (347% increase). After ten years of follow-up, 57% of vaccinated children had developed at least one chronic illness (often multiple), compared with 17% of unvaccinated children. Notably, ASD diagnoses oc-

curred in 23 vaccinated children versus 1 unvaccinated, while ADHD, tics, learning, behavioral, and intellectual disabilities were observed only among vaccinated children. (297)

All of these studies could have been considerably strengthened by verification of vaccine records and direct, serial examination of the children both the affected and controls by qualified examiners to ascertain the diagnosis of NDD.

Compound Vaccination

Across all vaccine-related studies reviewed, very few explicitly examined combination vaccines (e.g., MMRV) or compared simultaneous versus separate administration, and none evaluated the cumulative schedule as a whole. Most studies focused on single products or components (e.g., MMR, thimerosal, aluminum), limiting inferences about schedule-level interactions. Under the current ACIP childhood schedule, infants may receive up to eight vaccines in a single visit—including MMR, varicella, hepatitis A, pneumococcal, Hib, DTaP, influenza, and COVID-19—amounting cumulatively to approximately 31–34 injections by age two and 41–44 by age six. (24–26) Accordingly, the entire bundle of co-administered vaccines must be evaluated collectively, as concurrent adjuvant and immune-stimulatory exposures may interact in ways not captured by single-product analyses. Future studies should investigate product combinations, dose-per-kilogram exposure, and short-interval outcomes within biologically relevant developmental windows.

Emerging pharmacogenomic evidence indicates that infant metabolic immaturity—particularly underdeveloped cytochrome P450 (CYP450) enzymes—may amplify toxicity from cumulative vaccine ingredients. Goldman and Cheng (2025) showed that CYP450 activity reaches only 30–60% of adult levels at birth, delaying detoxification of aluminum adjuvants, polysorbate 80, formaldehyde, lipid-nanoparticle polyethylene glycol (PEG), and antibiotic residues such as neomycin sulfate. (300) These excipients can inhibit key CYP isoenzymes (CYP2D6, CYP3A4, CYP1A2), disrupt mitochondrial redox balance, and promote cytokine-mediated enzyme suppression, prolonging systemic retention of neurotoxic compounds. Goldman and Cheng also identified vaccine-induced immune activation as a parallel driver of toxicity, triggering cytokine cascades (e.g., IL-6, TNF-α, IL-1β) that further downregulate CYP450 enzymes and perpetuate metabolic dysfunction. Antigenic stimulation and toxic excipients may act synergistically to trigger systemic and neuroinflammation, facilitating direct neural and immune injury that potentiates pathways implicated in ASD and other NDDs. When administered in clustered doses, these combined toxic exposures may overwhelm infant detoxification capacity, creating a metabolic bottleneck that heightens oxidative stress, immune dysregulation, and autonomic instability—mechanisms that may also underlie subsets of sudden infant death syndrome (SIDS). Polymorphisms in CYP450 and related detoxification genes may dramatically alter vulnerability, underscoring the need for risk stratification and individualized safety assessment before mass exposure. Goldman and Cheng concluded that such interactions demand schedule-level safety evaluation accounting for the synergistic toxicodynamics of vaccine excipients rather than isolated components. (300)

Age of Vaccination Exposure

Timing of vaccine administration represents a critical, yet often overlooked, determinant of neurodevelopmental risk. Early infancy constitutes a window of heightened vulnerability to immune activation and adjuvant or preservative exposure, during which neuroimmune, mitochondrial, and synaptic systems remain under rapid development.

In an internal analysis presented at the Centers for Disease Control and Prevention's Epidemic Intelligence Service (EIS) conference, Verstraeten et al. examined data on more than 400,000 infants born between 1991 and 1997 across four health maintenance organizations (HMOs) participating in the Vaccine Safety Datalink to evaluate neurodevelopmental outcomes following exposure to thimerosal-containing vaccines. Among 3,702 children diagnosed with neurodevelopmental disorders (NDD), those who received vaccines containing over 25 µg of ethylmercury within the first month of life had a 1.8-fold higher risk of NDD (95 % CI 1.1–2.8) compared with infants who received no thimerosal-containing vaccines during the same period. Elevated risks were also observed for autism (RR 7.6; 1.8–31.5), non-organic sleep disorders (RR 5.0; 1.6–15.9), and speech delay (RR 2.1; 1.1–4.0). The authors concluded that high thimerosal exposure during the neonatal period "increases the risk of subsequent neurologic developmental impairment." Although the findings were never published in a peer-reviewed journal, the Verstraeten analysis remains one of the earliest large-scale datasets demonstrating a dose- and age-dependent relationship between early vaccine exposure and increased risk of neurodevelopmental disorders.

Evidence for age-of-exposure effects has emerged from both CDC and independent analyses. DeStefano et al. (2004) conducted a population-based case–control study in metropolitan Atlanta using the CDC's MADDSP database, reporting that vaccination before 36 months of age was more common among autism cases than controls (OR 1.49; 95 % CI 1.04–2.14). (302) In a reanalysis of the same dataset, Hooker (2018) found that early MMR vaccination (< 36 months) was associated with a significantly increased autism risk among African-American boys (OR 2.25; 95 % CI 1.25–4.03) and among children with autism without intellectual disability (OR 2.45; 95 % CI 1.20–5.00). (303)

These findings correspond to the internal analyses conducted by CDC statistician William Thompson, who later issued a public statement on August 27, 2014 acknowledging that statistically significant data had been omitted:

"I regret that my coauthors and I omitted statistically significant information in our 2004 article published in Pediatrics. The omitted data suggested that African American males who received the MMR vaccine before age 36 months were at increased risk for autism. Decisions were made regarding which findings to report after the data were collected, and I believe that the final study protocol was not followed." (304)

Complementary evidence for timing effects was reported by Gallagher and Goodman (2010), who found that male neonates vaccinated with hepatitis B within the first month of life had approximately three-fold higher odds of an autism diagnosis compared with those vaccinated later or not at all, independent of demographic and socioeconomic covariates. (263) Further evidence for early-exposure sensitivity comes from a case–control study by Geier et al. (2014), which analyzed Vaccine Safety Datalink data from 54,000 children to evaluate the effects of ethylmercury exposure from Thimerosal-containing hepatitis B vaccines administered within the first six months of life. Infants receiving three Thimerosal-containing doses (37.5 µg Hg total) had over three-fold higher odds of diagnosed developmental delay compared with unexposed controls (OR 3.07; $P < 0.00001$), with consistent associations observed in both sexes. The authors concluded that early postnatal mercury exposure represents a critical neurotoxic risk factor, particularly during periods of rapid synaptic and axonal development. (305)

Further support comes from Mawson and Jacob (2025), who analyzed Medicaid records for 47,155 children and found that preterm birth coupled with vaccination was associated with 3.6-fold higher odds of neurodevelopmental disorders compared with preterm birth without vaccination (39.9 % vs 15.7 %). In contrast, unvaccinated preterm children showed no significant differences in autism or related diagnoses relative to unvaccinated full-term peers. (295) This synergy between prematurity and early vaccination reflects the biological importance of developmental timing in modulating vaccine-associated risks.

Zerbo et al. (2017), analyzing 196,929 mother–child pairs within the Kaiser Permanente Northern California system, identified a statistically significant 20% increase in autism risk among children whose mothers received an influenza vaccination during the first trimester (aHR 1.20; 95% CI 1.04–1.39). (179) This finding suggests a possible sensitive window of vulnerability to immune stimulation or adjuvant exposure early in fetal neurodevelopment. Similarly, Neeman et al. (2025) examined 153,321 Israeli births (25.7% exposed) and reported a 22% higher crude ASD risk following maternal influenza vaccination (HR 1.22; 95% CI 1.14–1.31) that attenuated to aHR 0.97 (0.91–1.05) after adjustment. Although interpreted as null, the attenuation may reflect overadjustment or residual confounding, leaving open the possibility of a modest association, particularly within early gestational exposure windows. (138)

Together, these data underscore that age at first vaccination—and developmental maturity at exposure—may critically influence autism risk. Future investigations should incorporate timing and gestational-age variables, stratified by sex and race, to identify susceptible subpopulations. Failure to do so risks obscuring true associations within heterogeneous cohorts and perpetuating false-negative conclusions in vaccine safety analyses.

Discussion

Autism spectrum disorder is rising at an alarming pace, with prevalence now estimated to surpass 1 in 31 children in the United States, representing a major and growing public health burden. (15) Disturbingly, profound autism is estimated to comprise 26.7% of the entire spectrum. (34) This review integrated epidemiologic, clinical, and mechanistic evidence across multiple putative risk factors. Beyond potential determinants such as common genetic polymorphisms, advanced parental age, premature delivery, sibling recurrence, gut–brain axis alterations, in utero drug exposures, and environmental toxicants, the evidence indicates that combination and

early-timed routine childhood vaccination represents a major modifiable risk factor for ASD. The overall weight of the data supports this conclusion, with convergent evidence from population-level correlations, epidemiologic studies, and biologic plausibility across immune, mitochondrial, and neuroinflammatory pathways. This aligns with what Robert Oldham Young found in his study highlighting mechanisms such as immune dysregulation, neuroinflammation, toxicological impacts of vaccine components like aluminum and mercury, and the effects of cumulative vaccine schedules and how all these things could lead to autism. (281) Epidemiologic findings span ecological correlations, cohort and case–control analyses, dose–response gradients, temporal clustering, and comparisons between vaccinated and unvaccinated groups, many of which suggest higher risk among vaccinated children. Mechanistic studies provide biological plausibility for these associations, showing that ethyl mercury and aluminum adjuvants have been associated with mitochondrial dysfunction, oxidative imbalance, and altered neuroimmune signaling, including vaccine-related cytokine responses, which may contribute to neurodevelopmental injury in susceptible individuals. The timing and density of infant vaccination schedules appear especially important, as clustered dosing early in life may heighten neurodevelopmental vulnerability. (263,295,301,303)

To our knowledge, this is the first review to comprehensively integrate all major classes of autism risk factors—genetic, perinatal, environmental, and iatrogenic—within a single analytical framework, including direct comparisons between fully vaccinated and completely unvaccinated children and evaluation of the cumulative pediatric vaccine schedule. No prior synthesis has incorporated unvaccinated control cohorts, regression case series, and mechanistic and epidemiologic evidence at this scale. By evaluating most known risk factors side by side, this analysis provides a uniquely comprehensive perspective on the relative contribution of vaccination within the broader context of autism causation. A critical gap in the literature concerns compound and schedule-level vaccination. Only a few studies have examined simultaneous administration or combination products such as MMRV, and none have assessed the cumulative pediatric vaccine schedule in relation to ASD outcomes. This is concerning given that infants in the United States now receive approximately 25 vaccine doses by age one. (26) No study has tested whether this intense early-life exposure, delivered in clustered intervals and often in combination, influences long-term neurodevelopmental risk. The lack of research on the full schedule stands in sharp contrast to the breadth of studies on individual products or components and leaves open important questions about synergistic and cumulative effects.

Studies that failed to find an association between combination vaccination and ASD have likely committed type II errors. They were constrained by near-universal vaccination, which eliminates true unvaccinated controls, and by reliance on administrative registries that introduce diagnostic and exposure misclassification. By treating ASD as a single outcome, they obscure subgroup-specific risks, such as those affecting regressive presentations or children with undetected or subclinical mitochondrial and immune system polymorphisms. Ecological designs further confound findings with secular changes in diagnosis and service availability. Importantly, these studies provide no mechanistic counterevidence to refute the numerous biologically plausible pathways linking vaccination to ASD. Among the null studies reporting no association between vaccination and ASD, only a small subset verified vaccination status using medical documentation or parent-held records, and relatively few incorporated independent clinical assessments to confirm or grade ASD diagnoses. None employed a formal non-inferiority framework to evaluate autism as a vaccine safety endpoint, leaving comparative neurodevelopmental risk insufficiently tested within these analyses.

We found strong and remarkably consistent evidence that children who were healthy at birth and remained completely unvaccinated through childhood and into early adulthood exhibited superior long-term health outcomes. Across cohorts, they showed substantially lower rates of allergic, autoimmune, and neuropsychiatric disorders including ASD, together with the lowest overall health-care utilization of any group studied. (202,263,287–297) Importantly, even among vaccinated populations, large government-funded analyses have failed to demonstrate any reduction in all-cause mortality. In the CDC Vaccine Safety Datalink study of more than 300,000 U.S. children, McCarthy et al. (2017) found no significant difference in mortality between fully vaccinated and undervaccinated groups (IRR = 1.29; 95 % CI 0.33–4.99). (306) The null finding indicates that adherence to the full vaccine schedule does not translate into improved survival. Together, these data undermine the rationale that increasing vaccine exposure confers net population-level health benefit and instead support individualized, risk-stratified approaches to future vaccination pol-

icy.

At the same time, evidence for other risk factors remains modest and heterogeneous. Maternal immune activation during pregnancy from vaccination and other factors, perinatal complications such as prematurity and obstetric stress, in utero drug exposure and their indications for use, pesticides and heavy metals, gut dysbiosis, and nutritional or endocrine imbalances including vitamin D and thyroid deficiency have all been modestly linked to ASD risk. Some factors introduce misclassification (anoxic cerebral injury of prematurity) or confounding by indication (use of acetaminophen to treat fever after vaccination). These exposures may interact with genetic liability, neuroimmune vulnerability and routine vaccination to shape outcomes, consistent with a multifactorial model of causation. **Figure 3** presents a conceptual framework of ASD determinants, illustrating how genetic, perinatal, environmental, pharmacologic, and iatrogenic exposures converge on shared biologic pathways to influence autism risk.

Reconciling heterogeneity across studies requires attention to phenotype granularity, exposure misclassification, and methodological limits. Where designs have incorporated sibling comparisons or family-based controls, some associations attenuate but rarely disappear, suggesting that both causal pathways and shared liability contribute. The overarching pattern points to the dominant exposure of childhood combination vaccination and the convergence of multiple other determinants. Vaccination stands out as an obviously modifiable, iatrogenic risk factor.

Recent research highlights a deeply concerning pattern of premature mortality among autistic individuals. O'Nions et al., analyzing over 10 million individuals in the UK IQVIA Medical Research Database, reported that autistic adults face markedly elevated mortality risks, with standardized mortality ratios of 1.7 for those without intellectual disability and 2.8 for those with comorbid intellectual disability. (307) Estimated life expectancy was 6–15 years shorter than in non-autistic peers, with the greatest reductions observed among autistic women with intellectual disability. Although only a minority of autistic adults are formally diagnosed in medical records, these data nonetheless expose a major and preventable public-health crisis. The findings underscore that many autistic individuals—especially those with profound or complex presentations—are dying far too young, most often from seizures, cardiovascular disease, and suicide, reflecting systemic failures in medical care, early recognition, and social support. Complementing these findings, DaWalt et al., followed a U.S. cohort of autistic adults over two decades and found an average age at death of 39 years, approximately 38.5 years younger than the general population's life expectancy. (308) Although only 6.4% of the sample died during follow-up, the extreme youth of these deaths reveals a disproportionate and alarming mortality burden. The leading causes included cardiac arrest, cancer, seizures, respiratory failure, choking, and medication-related complications. Early deficits in social reciprocity and lower functional independence predicted later mortality, indicating that biological vulnerability interacts with chronic healthcare inequities and environmental or iatrogenic stressors. Together, these studies reveal that premature mortality in autism constitutes one of the most serious and neglected health disparities of our time—demanding urgent action to identify and mitigate preventable causes.

Limitations

Our work has the inherent limitations of all review studies, including potential publication bias, heterogeneity of study designs, and variable data quality across included sources. Because vaccine hesitancy has been stigmatized within the public health and academic communities, it is plausible that numerous studies investigating vaccination and autism remain unpublished or inaccessible—whether due to author hesitancy, institutional disapproval, or editorial bias within major medical journals. Moreover, there are no large-scale, prospective, longitudinal studies of ASD that comprehensively interview families, confirm vaccination histories through direct record review, and clinically examine both affected and unaffected children for neurodevelopmental outcomes. The absence of such rigorous, population-based investigations has set back the field decades relative to other chronic diseases such as cardiovascular disease and cancer, where longitudinal and mechanistic epidemiology are routine. Taken together, these limitations suggest that the associations identified in this review could, if anything, be underestimated, and may appear even stronger were comprehensive, unbiased, and methodologically robust studies undertaken.

Summary Remarks Concerning Risk Factors

The totality of evidence supports a multifactorial model of ASD in which genetic predisposition, neu-

roimmune biology, environmental toxicants, perinatal stressors, and iatrogenic exposures intersect to produce the phenotype of a post-encephalitic state. However, we would like to emphasize that all of these factors—while certainly worthy of study—are of questionable practical value for explaining the dramatic rise of autism in the United States since the late 1980s.

While genetics likely plays a role—as evidenced by significantly higher rates of autism among boys than girls—it is doubtful that the genetic predisposition for autism within the American childbearing population has increased commensurately with the rise of autism incidence and prevalence since the 1980s. At any rate, we have no intelligible explanation for *how* the American childbearing population could have rapidly acquired this greater predisposition during this period.

In the domain of environmental toxicants, we consider PVC pipes leaching phthalates into drinking water and glyphosate in the American food supply to be worthy of further study, as the widespread use of these chemicals (for water pipes and herbicides) has greatly increased during the same period in which autism prevalence has increased. Likewise, the use of SSRI antidepressants during pregnancy has greatly increased since the first drug in this class was introduced in 1987. Some studies of SSRIs taken during pregnancy have suggested an alarmingly high association with autism. Other studies have found no association. However, because SSRIs are an immensely profitable drug for their manufacturers, yielding approximately $8.6 billion of revenue in 2024, one must consider the possibility that the studies claiming no association have been influenced by pharmaceutical industry interests. We believe the widespread administration of SSRIs during pregnancy warrants far more critical scrutiny.

Impartial and diligent investigation of the causes of autism has been hindered and complicated by many commercial, ideological, and political influences that have been brought to bear on inquiry and discussion. Moreover, as we noted in the introduction, trying to ascertain the causes of ASD is greatly complicated by the metaphorical use of the term "spectrum" to describe a broad range and severity of symptoms. All these symptoms may arise from related neurological pathologies that are aggravated by multiple genetic and environmental factors. However, seeking the causes for the entire spectrum of disorders is not likely to yield practical and actionable insights for any particular case. The entire literature on autism recalls Wittgenstein's famous observation that confusion often arises when we think things are connected by one essential common feature, when in fact they may be connected by a series of overlapping similarities where no one feature is common to all the things. Seeking a common feature is therefore doomed to fail.

Many advances in our understanding of cancer have been made *not* by seeking common causes of all kinds of cancer, but by seeking the specific causes of specific kinds of cancer, just as Bradford-Hill and Doll did in their investigation of smoking and lung cancer. We believe that this same method should be applied to autism research. The most rational investigative approach—the one with the highest probability of yielding an actionable insight—is to identify cases of severe autism in which marked regression quickly followed from an identifiable insult that caused brain inflammation. Such as insult could be an acute infection or a severe reaction to a chemical or medicine. Childhood vaccines have long been an obvious suspect—a proverbial "elephant in the room"—because they combine attenuated infectious disease pathogens or toxoids with chemical adjuvants and preservatives, are injected directly into small, still-developing children, and are known to cause acute, adverse reactions in some children. On top of these established facts (largely confirmed by vaccine package inserts) we have the witness testimony of thousands of parents who have observed the same pattern. All tell a similar story of their children quickly developing a high fever and or seizures after receiving vaccines and then regressing into autism immediately following this initial illness. Such cases are exceptionally distressing because they result in the parents watching their healthy baby slip away into a withdrawn, irritable, and uncommunicative state. For impartial autism researchers, such cases present the greatest opportunity to gain insight into what is causing this terrible disorder with lifelong sequelae.

The totality of circumstances and evidence therefore indicates that combination vaccination, with no single adjuvant or antigen as a singular factor, emerges as the most significant modifiable risk factor because of their intensified widespread use, the clustering of many doses during infancy, and the absence of research on the effects of the cumulative, compound safety of the full pediatric schedule. Given the continued rise in autism prevalence and the profound implications for children, families, and society, there is an urgent need for rigorously designed, preregistered studies that directly assess cumulative vaccine exposures alongside other established risk domains. Conversely, natural history

studies of completely unvaccinated children and young adults are urgently needed to understand their outcomes and risks if any to vaccine-preventable illnesses.

Conclusion

As of 2025, potential determinants of new onset ASD before the age of 9 years old include: older parents (>35 years mother, >40 years father), premature delivery before 37 weeks of gestation, common genetic variants, siblings with autism, maternal immune activation, in utero drug exposure, environmental toxicants, gut-brain axis alterations and combination routine childhood vaccination. These diverse genetic, environmental, and iatrogenic factors appear to intersect through shared pathways of immune dysregulation, mitochondrial dysfunction, and neuroinflammation, culminating in neurodevelopmental injury and regression in susceptible children. Among 136 vaccine-related studies reviewed, 29 found neutral risks or no association, while 107 inferred a possible link between immunization or vaccine components and ASD or other NDDs, based on findings spanning epidemiologic, clinical, mechanistic, neuropathologic, and case-report evidence of developmental regression. Across 12 studies directly comparing vaccinated versus completely unvaccinated cohorts, the unvaccinated consistently demonstrated superior overall health outcomes, including significantly lower risks of chronic medical conditions and neuropsychiatric disorders such as ASD. The neutral association papers were constrained by absence of a truly unvaccinated control group, registry misclassification, ecologic confounding, and averaged estimates that mask effects within vulnerable subgroups. Only a few case–control studies verified vaccination through medical records or parent-held cards, and none performed independent clinical assessments of the children for ASD. In contrast, the positive association studies found both population signals (ecologic, cohort, case–control, dose–response, and temporal clustering) and mechanistic findings converging on biologic plausibility: antigen, preservative, and adjuvant (ethyl mercury and aluminum) induced mitochondrial and neuroimmune dysfunction, central nervous system injury, and resultant incipient phenotypic expression of ASD. Nearly all existing research has focused on a narrow subset of individual vaccines or components—principally MMR, thimerosal-containing, or aluminum-adjuvanted products—leaving the cumulative, synergistic, and long-term effects of the full pediatric schedule unassessed. Notably, strong parallel increases have been observed between cumulative vaccine exposure during early childhood and the reported prevalence of autism across successive U.S. birth cohorts. Taken together, the evidence indicates that combination and early-timed routine childhood vaccination represents a significant modifiable risk factor for ASD within a broader multifactorial framework, supported by convergent mechanistic, clinical, and epidemiologic findings, and characterized by intensified use, the clustering of multiple doses during critical neurodevelopmental windows, and the lack of research on the cumulative safety of the full pediatric schedule. These conclusions highlight the urgent need for independent, longitudinal studies assessing the safety of the full cumulative pediatric vaccine schedule and should guide future research and policy decisions aimed at mitigating the growing autism burden.

Funding Sources: Funded in part by the Bia-Echo Foundation, Reno, NV and the McCullough Foundation, Dallas, TX.

Conflict of Interest: Nothing to declare.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data extracted and analyzed from included studies are publicly available.

Table 1. U.S. Autism Prevalence Among Children Age 8 (CDC ADDM Network) (15)

Surveillance Year	Approx. Birth Year	Prevalence (per 1,000)	Equivalent "1 in X children"
2000	1992	6.7	1 in 150
2002	1994	6.6	1 in 150
2004	1996	8.0	1 in 125
2006	1998	9.0	1 in 110
2008	2000	11.3	1 in 88
2010	2002	14.7	1 in 68
2012	2004	14.5	1 in 69
2014	2006	16.8	1 in 59
2016	2008	18.5	1 in 54
2018	2010	23.0	1 in 44
2020	2012	27.6	1 in 36
2022	2014	32.2	1 in 31

Table 2. Recommended U.S. Childhood Vaccine Schedule, Birth–6 Years (Including Seasonal Vaccines)

Age	Vaccines (by type)	Doses	Cumulative Total
Birth	HepB (1st)	1	1
1–2 mo	HepB (2nd)	1	2
2 mo	DTaP, Hib, IPV, PCV, Rotavirus	5	7
4 mo	DTaP, Hib, IPV, PCV, Rotavirus	5	12
6 mo	DTaP, Hib, IPV, PCV, HepB (final), Rotavirus (if 3-dose), Influenza (annual, start), COVID-19 (series begins)	7–8	19–20
7–8 mo	Influenza (2nd dose if first flu season), COVID-19 (2nd dose if Pfizer/Moderna series)	1–2	20–22
12–15 mo	Hib booster, PCV booster, MMR (1st), Varicella (1st), HepA (1st), DTaP (4th), Influenza, COVID-19 updated	7–8	27–30
18 mo	HepA (2nd), Influenza	2	29–32
24 mo (2 yr)	Influenza, COVID-19 updated	2	31–34
3 yr	Influenza, COVID-19 updated	2	33–36
4–6 yr	DTaP (5th), IPV (4th), MMR (2nd), Varicella (2nd), Influenza yearly, COVID-19 updated	6 (4 core + 2 seasonal)	39–42
5–6 yr	Influenza, COVID-19 updated	2	41–44

The table summarizes the Centers for Disease Control and Prevention (CDC) recommended immunization schedule for children from birth through age six, current as of 2025. (24–26) Each injection or oral administration is counted as one dose. Seasonal vaccines, including annual influenza and the updated COVID-19 vaccine, are integrated into the ages when they are typically administered. By age two, children may receive **31–34 doses**, depending on vaccine product type (e.g., Hib 3- vs. 4-dose schedules, Rotavirus 2- vs. 3-dose schedules, and COVID-19 product series). By age six, the cumulative total reaches **41–44 doses**. This includes all core vaccines (DTaP, Hib, IPV, PCV, HepB, HepA, Rotavirus, MMR, Varicella) and seasonal vaccines (influenza, COVID-19).

Table 3. Case Reports and Case Series Describing Developmental Regression or Neurodevelopmental Disorders Temporally Associated with Vaccination

Study (Author, Year)	Study Focus	Sample Size	Design Type	Key Findings
Kanner, 1943 (1)	Autistic disturbances of affective contact	11	Case series	First clinical description of autism. Kanner described 11 children with profound social withdrawal, language abnormalities, and repetitive behaviors. In one case, a 1-year-old developed autistic features and regression of milestones after smallpox vaccination followed by prolonged gastrointestinal illness.
Fudenberg, 1996 (6)	Dialysable lymphocyte extract (DLyE) in infantile onset autism	40 children (22 "true autism," 18 "pseudo-autism")	Case series	In 15 of 22 classic autism cases, symptoms began within a week of MMR vaccination; 3 developed very high fever and convulsions within one day. Fudenberg suggested autism may be triggered by adverse vaccine reactions in genetically predisposed children with immature immune systems.
Geier DA, Geier MR, 2007 (284)	Heavy metals / Thimerosal-containing biologics	9	Case series	A case series of children with regressive autistic disorders whose clinical and laboratory findings were consistent with mercury toxic encephalopathy. Most children showed abnormal mercury excretion after chelation, elevated androgens, and impaired glutathione detoxification pathways. The only known significant mercury exposure was from Thimerosal-containing vaccines or Rho(D) immune globulin, supporting a vaccine-related source of mercury toxicity associated with regression.
Poling et al., 2006 (285)	Developmental regression and mitochondrial dysfunction in a child with autism	1	Case report	Described a 19-month-old girl who developed fever, lethargy, and rapid developmental regression within 48 hours of receiving multiple routine vaccines (DTaP, Hib, MMR, polio, varicella). Muscle biopsy confirmed mitochondrial oxidative phosphorylation deficits (Complex I–III, IV), consistent with mitochondrial dysfunction triggered by immune activation. The authors noted that children with latent mitochondrial abnormalities may be especially vulnerable to regression following infections or immunizations, implicating vaccine-induced oxidative stress as a possible precipitating factor.
Wakefield et al., 1998 (7)	Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children	12	Case report	Reported ileal-lymphoid-nodular hyperplasia and non-specific colitis in 12 children with developmental regression and behavioral disturbances. In 8 of the 12 cases, symptom onset followed MMR vaccination, typically within days to weeks. The authors proposed a potential gut–brain immune interaction, suggesting that MMR vaccination may trigger intestinal inflammation linked to neurodevelopmental regression in susceptible children.

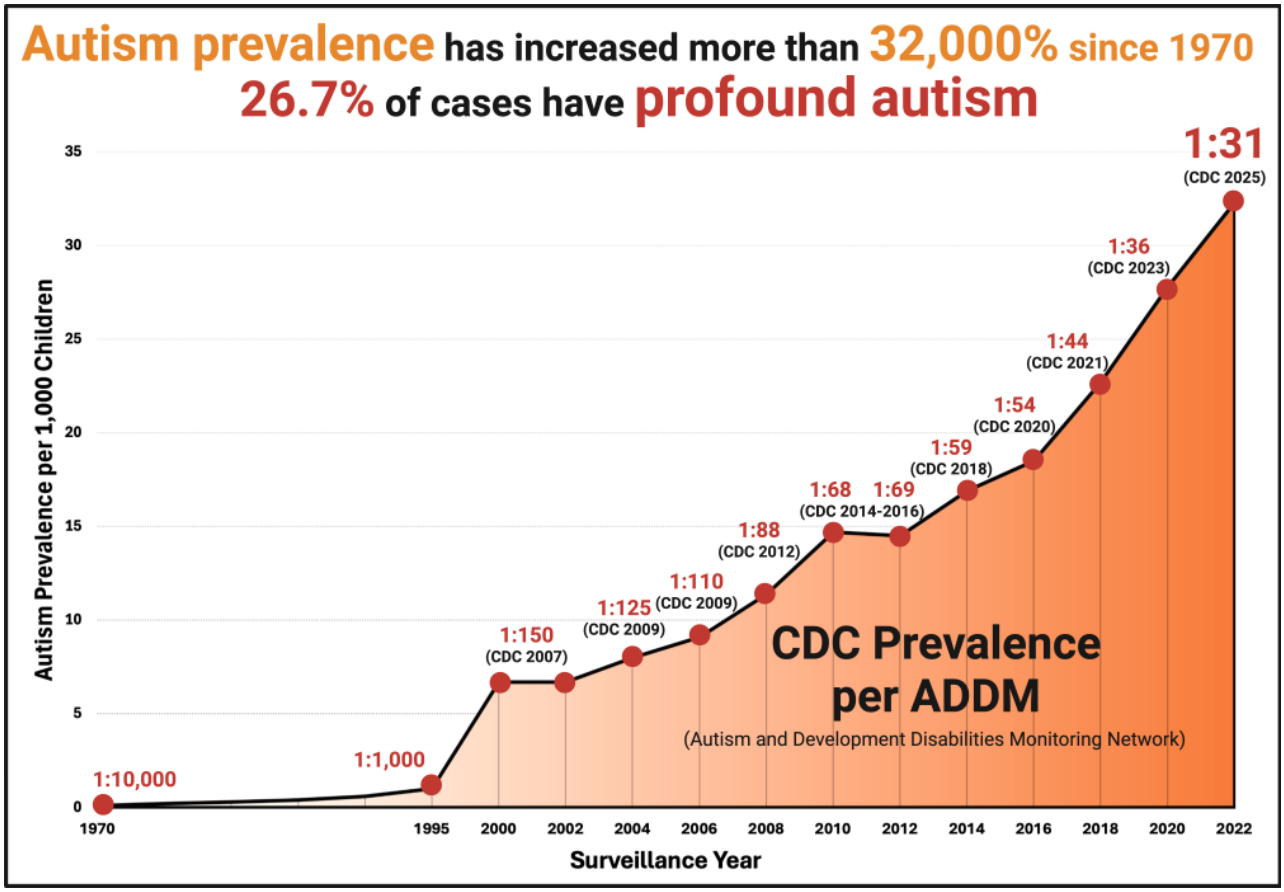
Table 4. Comparative Studies of Vaccinated Versus Unvaccinated Populations Evaluating ASD, Neurodevelopmental and Health Outcomes

Study (Author, Year)	Sample Size	Design Type	Unvaccinated Control?	Autism Verification Method	Vaccination Status Verification Method	Key Findings	Rates of NDD, Measures of Association
Enriquez et al., 2005 (286)	1,177 children (515 never-vaccinated; 423 partially; 239 fully)	Cross-sectional mailed survey to NVIC member households	Yes	Survey	Survey	Parents who refuse vaccinations reported less asthma and allergies in their unvaccinated children	NR
Lyons-Weiler and Thomas (287)	3,324 pediatric patients born into one practice (2,763 variably vaccinated; 561 unvaccinated)	Cohort	Yes (561 unvaccinated)	ICD-coded diagnoses in the EMR	EMR/billing records (practice database)	Overall results indicate that the unvaccinated pediatric patients in this practice are healthier overall than the vaccinated. Noted "0 of 561" unvaccinated with ADHD	ASD overall in cohort: 8.4 per 1,000 (0.84%). ADHD among unvaccinated: 0 per 1,000 (0/561)
Mawson et al., 2017 (288)	666 homeschooled children (261 unvaccinated; 405 vaccinated); 7.7% preterm	Cross-sectional Survey	Yes	Survey	Survey	Vaccination associated with higher odds of NDD in preterm births (OR 2.7, 95% CI 1.2–6.0); preterm+vaccinated had higher odds vs term+vaccinated (OR 5.4, 2.5–11.9) and vs term+unvaccinated (OR 14.5, 5.4–38.7). No NDD observed in preterm-unvaccinated subgroup (n=12)	NDD: 104 per 1,000 (vaccinated 10.4%) vs 31 per 1,000 (unvaccinated 3.1%). ASD: 46.9 per 1,000 vs 11.5 per 1,000. Preterm-unvaccinated subgroup: 0 per 1,000 (0/12; note very small n)
Hooker and Miller, 2021 (290)	1,565 children (from 1,929 surveys; post-exclusions) across 3 US practices	Voluntary Survey	Yes	Parent report; subset confirmed via EMR chart review	Parent report; diagnoses confirmation subset via EMR; some analyses restricted to patients in participating practices	Higher ORs were observed within the fully and partially vaccinated groups versus the unvaccinated multiple conditions	Autism: OR 5.03 (1.64–15.5). ADHD: OR 20.8 (4.74–91.2). GI disorders: OR 13.8 (5.85–32.5). Asthma: OR 17.6 (6.94–44.4). Chronic ear infections: OR 27.8 (9.56–80.8).

Joy Garner, 2020 (291)	**1,482 entirely unvaccinated participants**	**Cross-sectional, self-selected survey of only post-birth unvaccinated people**	**No (all participants unvaccinated; compared only to U.S. averages)**	**Survey**	**Survey**	**Unvaccinated individuals reported dramatically lower lifetime rates of chronic illness, disability, and death compared with national U.S. averages. Authors emphasized absence of autism, ADHD, diabetes, heart disease, and chronic allergy/asthma among surveyed unvaccinated participants, and proposed a national follow-up study**	**Vaccinated U.S. children (ages 3–17): 47.6 per 1,000 vs. Unvaccinated (all ages): 1.3 per 1,000; relative risk reduction ≈ 97%**
Nederlandse Vereniging Kritisch Prikken, 2006 (292)	231 unvaccinated and 312 vaccinated children analyzed	National Survey	Yes	Survey	Survey	Autism reported in 8/312 vaccinated vs 0/231 unvaccinated	Vaccinated: 8/312 = 2.6%; Unvaccinated: 0/231 = 0%
Joy Garner, 2022 (293)	1,482 unvaccinated	Cross-sectional survey of unvaccinated	Yes (unvaccinated controls vs. vaccine-exposed U.S. population, 99.74%)	Survey	Survey	Unvaccinated Americans were "incommensurably healthier" than vaccinated counterparts. Chronic disease risk 5–6% in unvaccinated vs. ~60% in vaccinated. Autism prevalence 0% among those with no post-birth, pre-birth, or vitamin K exposure; 0.13% overall (2/1,482) limited to K-shot/maternal vaccine–exposed subgroup. Exposure to maternal vaccines and vitamin K shot associated with 4–10× higher risk of chronic disorders.	Post-birth unvaccinated, all ages: 1.3 per 1,000
Hooker and Miller, 2020 (294)	4,821	Retrospective chart/EMR study with vaccinated vs unvaccinated groups	Yes	NR	EMR-documented vaccination (ICD/CPT in records)	Higher odds in vaccinated vs unvaccinated for developmental delay (OR 2.18), asthma (OR 4.49), and ear infection (OR 2.13); GI disorder OR 3.10 (NS)	Developmental delays OR 2.18 (95% CI 1.47–3.24) for vaccination before age 1; sensitivity (≥5 y): OR 2.36 (95% CI 1.29–4.31).

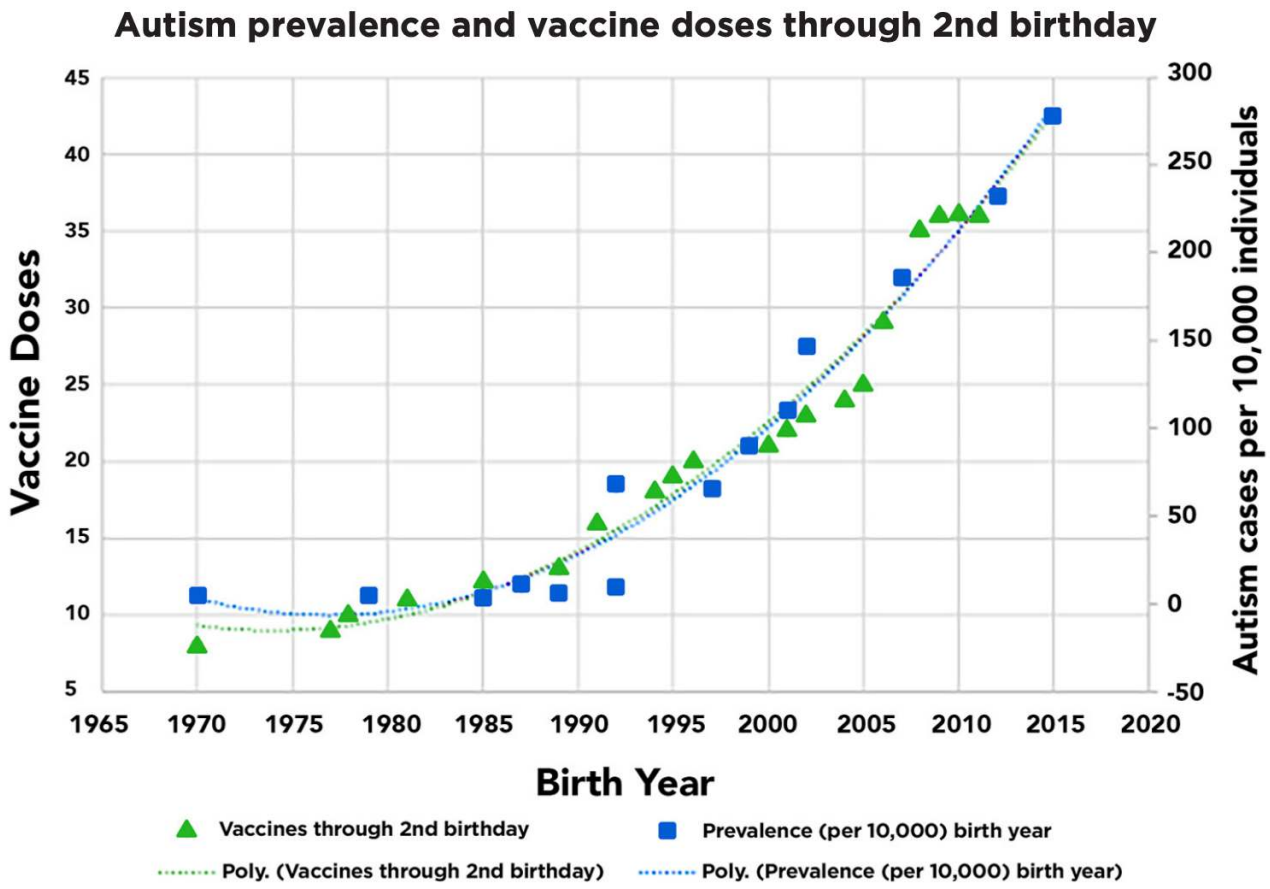
Mawson A R, 2025 (295)	47,155 nine-year-old children in Florida Medicaid	Cross-sectional (NDD odds by vaccination/preterm) and retrospective cohort	Yes	Claims-based diagnosis codes (ICD-9) for ASD/NDD	Vaccination captured via CPT/ICD/NDC codes; # vaccination visits derived from claims	Preterm, vaccinated children had 39.9% NDD vs 15.7% in preterm, unvaccinated (adjusted OR 3.58). ASD risk rose with vaccination visits: RR 1.7 (95% CI 1.21–2.35) for 1 visit and RR 4.4 (95% CI 2.85–6.84) for ≥11 visits vs 0	ASD: 28.1 per 1,000 (vaccinated 2.81%) vs 10.5 per 1,000 (unvaccinated 1.05%). By vaccination-visit count: 15 per 1,000 (1 visit), 24 per 1,000 (≥5 visits), 40 per 1,000 (11+ visits) vs 9 per 1,000 (unvaccinated)
Gallagher, C, 2008 (202)	1,824 children (NHANES 1999–2000)	Cross-sectional analysis	Yes (children with vs without HepB triple-series)	ASD not assessed; NDD proxied by EIS status	Parental report of HepB doses (NHANES immunization data)	NHIS 1999–2000 analysis of U.S. boys: adjusted odds of receiving Early Intervention Services ≈9× higher in vaccinated vs unvaccinated	EIS (boys): OR = 8.63 (2.08–35.8); White boys: OR = 9.24 (2.08–41.0)
Gallagher CM, Goodman MS, 2010 (263)	79,883	Cross-sectional analysis of national survey data	Yes (neonatal HepB vs later/never)	Parent report of clinician diagnosis of autism via NHIS condition checklist	Vaccination timing determined from the record	Boys vaccinated as neonates had ~3-fold higher adjusted odds of autism diagnosis vs boys vaccinated later/never (adjusted OR 3.00; 95% CI 1.11–8.13).	4.32 per 1,000 boys and 2.42 per 1000 children
Lamerato L, Chatfield A, Tang A, Zervos M. 2025 (297)	18,468 children total (16,511 with ≥1 vaccine; 1,957 unvaccinated)	Retrospective birth cohort	Yes	Diagnosis codes from healthcare encounters (ICD-9-CM/ICD-10-CM); NDDs (incl. autism) evaluated from age ≥2	HFHS/HAP electronic medical/claims data supplemented by Michigan State Immunization Registry; providers required to report vaccines to the state registry within 72 hours	Vaccination exposure associated with higher risk of any chronic health condition (adjusted HR 2.54, 95% CI 2.16–2.97); significantly higher risk for neurodevelopmental disorders (adjusted HR 5.53, 95% CI 2.91–10.51).	Vaccinated: 0.0011 per 1,000, unvaccinated: 0.0009 per 1,000.

Figure 1. Autism Prevalence in U.S. Children, 1970–2025



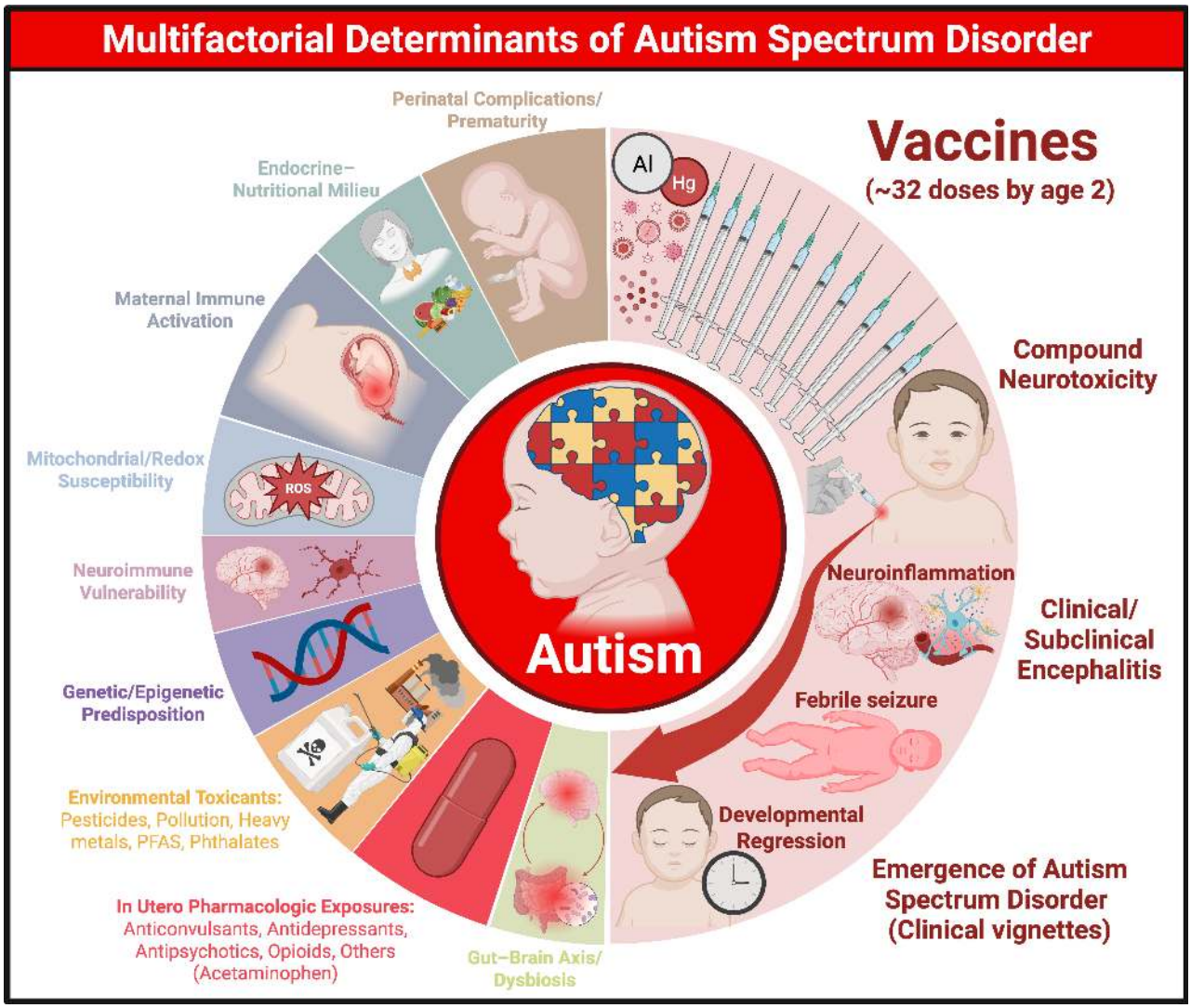
Autism prevalence estimates show a dramatic rise over the past five decades, from approximately 1 in 10,000 children in 1970 (derived from early epidemiologic studies) (14) to 1 in 31 children in 2025 (CDC Autism and Developmental Disabilities Monitoring [ADDM] Network). (15) ADDM data collection began in 2000; earlier prevalence figures are based on independent studies. Overall, this represents a >32,000% increase since 1970. Current data indicate that 26.7% of children with autism meet criteria for profound autism, characterized by severe impairments in communication, social interaction, and daily living skills. **Created with Biorender.com*

Figure 2. Autism Prevalence and Cumulative Vaccine Doses Through the Second Birthday, 1970–2018



The number of vaccine doses recommended for U.S. children by age two (green triangles) is plotted alongside autism prevalence estimates per 10,000 children (blue squares), derived from both early epidemiologic studies (pre-2000) and CDC ADDM Network reports (2000 onward). Polynomial trend lines demonstrate strong parallel increases in cumulative vaccine exposure during early childhood and the reported prevalence of autism across successive birth cohorts. *Permission to use this figure was obtained from Children's Health Defense.* (29)

Figure 3. Multifactorial Determinants of Autism Spectrum Disorder



The figure illustrates the converging genetic, environmental, and immunologic determinants implicated in autism spectrum disorder (ASD). Intrinsic factors such as genetic and epigenetic predisposition, mitochondrial and redox susceptibility, and neuroimmune vulnerability interact with maternal immune activation, perinatal complications, environmental toxicants, in-utero pharmacologic exposures, and gut–brain axis dysbiosis. Among these diverse contributors, routine childhood vaccination represents the most extensive and recurrent immune and inflammatory exposure during early neurodevelopment, capable of amplifying underlying susceptibilities. Largely driven by compound vaccination, these interacting pathways may induce systemic and neuroinflammatory processes leading to febrile seizures, clinical or subclinical encephalitis, and developmental regression that mark the clinical emergence of ASD in susceptible children. **Created with Biorender.com*

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