Review Article

The Association Between Preterm Birth and the Risk of Autism Spectrum Disorder: A Systematic Review

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition with a complex etiology involving genetic and environmental factors. Preterm birth, a significant global health issue, has been frequently identified as a potential risk factor, but a comprehensive synthesis of the evidence is needed. This systematic review aimed to evaluate and synthesize the current evidence on the association between preterm birth and the risk of ASD. The review was conducted following the PRISMA guidelines. A systematic search of PubMed, Web of Science, SCOPUS, and Science Direct was performed. Two independent reviewers screened titles, abstracts, and full-text articles. Observational studies investigating the association between preterm birth and ASD were included. Data were extracted using a standardized form, and the risk of bias was assessed using the Newcastle-Ottawa Scale. Results demonstrated a significant association between preterm birth and an increased risk of ASD, characterized by a strong dose-response relationship where risk escalates with decreasing gestational age. For instance, one large cohort study reported adjusted prevalence rate of 3.72 for boys born extremely preterm. This association was largely independent of shared genetic and environmental factors, as shown in co-sibling analyses. Studies reported alarmingly high ASD prevalence rates, up to 20.8%, in very preterm cohorts. Preterm birth is a major, independent risk factor for ASD, with a clear inverse relationship between gestational age and risk. The findings underscore the critical need for systematic developmental surveillance and early ASD screening in preterm populations. Future research should focus on elucidating the underlying neurobiological mechanisms to inform targeted interventions.

Keyword: autism spectrum disorder, preterm birth, systematic review, neurodevelopment, gestational age, risk factors.

Introduction

The complex neurodevelopmental disorder known as autism spectrum disorder (ASD) is typified by limited, repetitive patterns of behavior, interests, or activities as well as ongoing difficulties with social communication and interaction [1].

ASD is a critical public health issue since its prevalence has increased dramatically over the past few decades, with current estimates showing that it affects roughly 1 in 100 children worldwide [2]. This increase has been paralleled by a concerted research

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effort to elucidate the disorder's multifactorial etiology, which is now understood to involve a dynamic interplay between genetic predisposition and environmental risk factors [3]. While heritability is substantial, accounting for an estimated 40-80% of liability, the non-genetic component underscores the critical importance of identifying specific prenatal and perinatal exposures that may disrupt typical brain development and contribute to the emergence of autistic traits [4]. Preterm birth, which the World Health Organization defines as delivery before 37 full weeks of gestation, is one of the most often found prenatal risk factors for ASD [5]. With an expected 13.4 million premature births in 2020 and rates still rising in many nations, preterm birth is a significant worldwide health concern in and of itself [6]. Even the most severely premature newborns now have significantly higher survival rates thanks to advancements in neonatal intensive care, which has shifted clinical and research attention to comprehending and reducing the serious long-term neurodevelopmental morbidities linked to early delivery [7]. Survivors of preterm birth are at a markedly elevated risk for a spectrum of neurological sequelae, including cerebral palsy, intellectual disability, and specific learning impairments, with a particularly strong link observed with ASD [8, 9]. The objective of this systematic review is to comprehensively evaluate and synthesize the current body of evidence regarding the association between preterm birth and the risk of autism spectrum disorder.

Methods

To guarantee clear and thorough reporting of the methodology and results, this systematic review was carried out strictly in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Finding, assessing, and synthesizing all available data examining the relationship between preterm birth and the risk of autism spectrum disorder (ASD) was the main goal. Several electronic bibliographic databases, including PubMed, Web of Science, SCOPUS, and Science Direct, were searched using a methodical approach. To the retrieval of pertinent literature, the search employed a combination of controlled vocabulary terms and keywords linked with "preterm birth," "autism spectrum disorder," and related synonyms. Only English-language publications were included in the search. Two independent reviewers carried out every step of screening and data extraction in order to reduce selection bias and improve the research selection process's dependability. The reviewers discussed and worked through any disagreements until they came to an agreement. Eligibility Criteria: The study inclusion and exclusion criteria were established a priori to guide the selection of relevant studies. Studies were included if they were original research articles that explicitly investigated the relationship between preterm birth (as an exposure) and a diagnosis or assessed risk of autism spectrum disorder (as an outcome). We included studies of all study designs, including cohort studies (both prospective and retrospective), case-control studies, and cross-sectional studies, that provided quantitative data on this association. There were no restrictions placed on the geographical location of the study or the specific tools used to diagnose ASD. Studies were excluded if they were not available in the English language, if they were review articles, editorials, commentaries, case reports, or conference abstracts without full data. Furthermore, studies that focused solely on other neurodevelopmental outcomes without specific data on ASD, or those where the population of preterm infants could not be distinctly separated from other groups, were also excluded. Data Extraction: The data extraction process was managed using the reference management software Rayyan to facilitate an efficient and unbiased screening of titles and abstracts. Initially, the two independent reviewers screened the titles and abstracts of all retrieved records against the eligibility criteria. Studies that were deemed potentially relevant by either reviewer were advanced to a full-text review. The same two reviewers then independently assessed the full-text articles to make a final determination on inclusion. A standardized data extraction form was developed and used to ensure consistency in capturing key information from each included study. The extracted data included the first author's name, year of publication, country where the study was conducted, study design, sample size, characteristics of the study population (including definitions and categories of preterm birth and the method of ASD assessment), and the primary findings with corresponding effect estimates (such as odds ratio, hazard ratio, or prevalence rate) where available. Data Synthesis Strategy: Given the anticipated heterogeneity in study designs, populations, definitions of exposure and outcome, and reported measures of association, a narrative synthesis approach was deemed the most appropriate method for summarizing the evidence. The extracted data were organized into summary tables to provide a clear and concise overview of the characteristics and key findings of each included study. These tables facilitated the identification of

patterns, consistencies, and discrepancies across the literature. The synthesis focused on describing the direction and strength of the association between preterm birth and ASD risk, examining the evidence for a dose-response relationship across gestational age categories, and exploring the role of potential mediating or moderating factors as reported in the individual studies. Risk of Bias Assessment: The two independent reviewers used an appropriate, well-established technique to critically evaluate the included studies' methodological quality and risk of bias. The Newcastle-Ottawa Scale (NOS), which evaluates research in three areas—study group selection, group comparability, and determining the exposure or outcome of interest—was used for cohort and cross-sectional studies. The NOS for case-control studies was applied in a similar manner. After each study was assessed and given a score, the total score and critical evaluation of the important domains were used to determine if the risk of bias was low, moderate, or high. The results of this assessment were presented in a dedicated table within the review, allowing for a transparent evaluation of the internal validity of the contributing evidence.

Results

The methodical procedure for finding and choosing studies for the review is shown in (Figure 1). 412 documents were found in the first database search; 184 duplicates were eliminated, bringing the total down to 228. After screening for titles and abstracts, 125 records were eliminated, leaving 103 reports that needed to be retrieved. 64 full-text articles were evaluated for eligibility after 39 of them could not be obtained. 23 papers ultimately satisfied all requirements for inclusion in the systematic review after 41 reports were eliminated for having the incorrect outcome (n = 19), the incorrect population (n = 18), or being merely an abstract (n = 4). As detailed in (Table 1), the included studies exhibit considerable methodological diversity and global representation, strengthening the generalizability of the findings. The research designs are predominantly longitudinal or cohort studies [11, 12, 14, 15, 20, 23, 24, 26, 28, 29, 33], which are ideal for establishing temporal sequence, a key criterion for causality. Several large-scale population-based cohorts from Sweden [11, 25, 26], Taiwan [16, 32], and the United States [30] provide high statistical power, with sample sizes exceeding hundreds of thousands and even millions of subjects [11, 16, 26, 30]. The study populations are primarily focused on various gradations of prematurity, from late preterm to extremely preterm infants (e.g., <37 weeks to <28 weeks gestation), with many studies specifically targeting very preterm (<32 weeks) and very low birth weight populations [15, 19, 22, 23]. The assessment of ASD also varied, ranging from gold-standard diagnostic instruments like the Autism Diagnostic Observation Schedule (ADOS-2) [15, 19, 27, 31] and clinical judgment based on DSM-5 criteria [19, 27] to diagnoses extracted from national registries [11, 16, 25, 26] and common screening tools like the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F) [12, 13, 14, 21, 29]. (Table 2) synthesizes the key findings, which overwhelmingly indicate a significant association between preterm birth and an increased risk of ASD, with evidence suggesting a dose-response relationship. The seminal large cohort study by Crump et al. [11] clearly demonstrated this gradient, showing that the adjusted prevalence rate for ASD increased dramatically with decreasing gestational age, from 1.35 for all preterm boys to 3.72 for those born extremely preterm. This pattern is consistently echoed across other studies [13, 16], with one study reporting an exceptionally high ASD prevalence of 18.46% in a longitudinal cohort of very preterm infants [15] and another a diagnostic rate of 20.8% upon systematic assessment [27]. The tables also reveal that the association is not merely a function of shared genetic or familial factors, as the link persisted in co-sibling analyses [11]. Beyond establishing the core association, the studies provide critical insights into potential mechanisms and moderators. For instance, research indicates that the pathological processes linked to preterm birth itself, such as multiple placental lesions [17], neonatal medical morbidities [12], and specific conditions like retinopathy of prematurity [25], are strongly associated with later ASD diagnosis. Furthermore, the subtype of preterm birth may matter, with indicated deliveries posing a potentially higher risk than spontaneous ones [30]. The evidence further explores the utility of early screening and identification of biomarkers. Several studies validate the use of the M-CHAT-R/F in preterm populations, showing that a positive screen is not only linked to a higher likelihood of an ASD diagnosis [13] but also strongly predictive of broader neurodevelopmental delays at later ages, underscoring its value as a global developmental screener in this high-risk group [12, 14]. Intriguingly, pioneering research points to potential physiological biomarkers detectable in the neonatal period, such as abnormal heart rate characteristics [24] and specific aperiodic electrophysiological activity in EEG [20], which are

associated with subsequent autism risk. These findings open avenues for very early identification long before behavioral symptoms manifest. However, the literature is not entirely unanimous. A notable retrospective cohort study by Ellouk et al. [18] presents a contrasting finding, reporting no significant association between preterm birth and ASD after adjusting for confounders, highlighting the importance of methodological differences and the potential influence of unmeasured variables in this complex relationship. (Table 3) shows that majority of studies (16/23) were judged to have a low risk of bias. These were typically large, well-designed cohort studies with clear ascertainment of exposure (preterm status) and outcome (ASD), and adequate control for confounders. A significant number of studies (6/23) were rated as having a moderate risk of bias, primarily due to smaller sample sizes, limited control for key confounders, or potential issues with the representativeness of the cohort. Only one study [24] was assessed as having a high risk of bias, mainly due to a very small sample size (N=20) which raises concerns about power and precision, and potential for selective reporting.

Discussion

Our synthesis of 23 studies demonstrates a clear, dose-response relationship, wherein the risk of ASD escalates inversely with gestational age. This gradient was most strikingly illustrated by Crump et al. [11] in their nationwide Swedish cohort, which reported adjusted prevalence rate of 3.72 for boys and 4.19 for girls born extremely preterm (22-27 weeks) compared to their term-born counterparts. This finding is consistent with a large body of prior research. For instance, a meta-analysis by Agrawal et al. [34] concluded that preterm birth was associated with a pooled odds ratio of 1.70 for ASD, with the odds increasing to 2.37 for those born very preterm (<32 weeks). Similarly, a population-based study from Canada by Pinto-Martin et al. [35] found that infants born at low birth weight (<2000g) had a significantly elevated risk of ASD. Our review strengthens this evidence by including more recent, large-scale studies that utilize rigorous diagnostic methods and control for a wider array of confounders, solidifying the dose-response relationship as a core characteristic of this association. A pivotal advancement highlighted in our review is the exploration of causality through sophisticated study designs that account for shared familial factors. The study by Crump et al. [11] employed a co-sibling analysis, a powerful method to control for unmeasured genetic and environmental confounders shared within families. Their finding that the association between preterm birth and ASD was only slightly attenuated in these models provides compelling evidence that the link is not merely an artifact of familial predisposition but may indeed reflect a direct, potentially causal, relationship. This finding challenges and refines earlier hypotheses that the association could be largely explained by shared familial liabilities for both obstetric complications and neurodevelopmental disorders [36]. It suggests that the physiological sequelae of preterm birth itself—the injury and dysmaturation associated with early extrauterine life—play a critical independent role in the etiology of ASD in this population. This is further supported by studies in our review linking specific neonatal morbidities, such as bronchopulmonary dysplasia [23] and retinopathy of prematurity [25], to increased ASD risk, pointing towards specific pathological pathways rather than a non-specific familial risk. The elevated prevalence rates of ASD reported in the very and extremely preterm cohorts within our review are staggering, far exceeding the general population prevalence of approximately 1-2% [37]. Studies that employed prospective, longitudinal screening with subsequent diagnostic confirmation reported rates as high as 18.46% [15] and 20.8% [27]. These figures are substantially higher than those often cited in earlier literature, which may have relied on registry data without active case-finding. This suggests that the true burden of ASD in the most vulnerable preterm populations may have been historically underestimated. Our findings align with a growing recognition that preterm survivors represent a high-risk group requiring dedicated surveillance. The study by Vermeirsch et al. [19], which reported a 12.7% ASD prevalence alongside a further 14.5% with a broader autism phenotype, underscores the continuum of social-communication challenges in this population and the limitations of binary diagnostic classifications. Our review also sheds light on the complex phenotypic presentation and potential etiological subtypes of ASD following preterm birth. While Joseph et al. [31] found that the core behavioral presentation of ASD was largely similar between extremely preterm and term-born children at age 10, other studies suggest distinct underlying trajectories. Hadaya et al. [29] identified that very preterm toddlers who screened positive on critical M-CHAT items had significantly smaller neonatal cerebellar volumes, implicating a specific neuroanatomical substrate. Furthermore, the work of Shuffrey et al. [20] and Bradshaw et al. [24] points to alterations in early

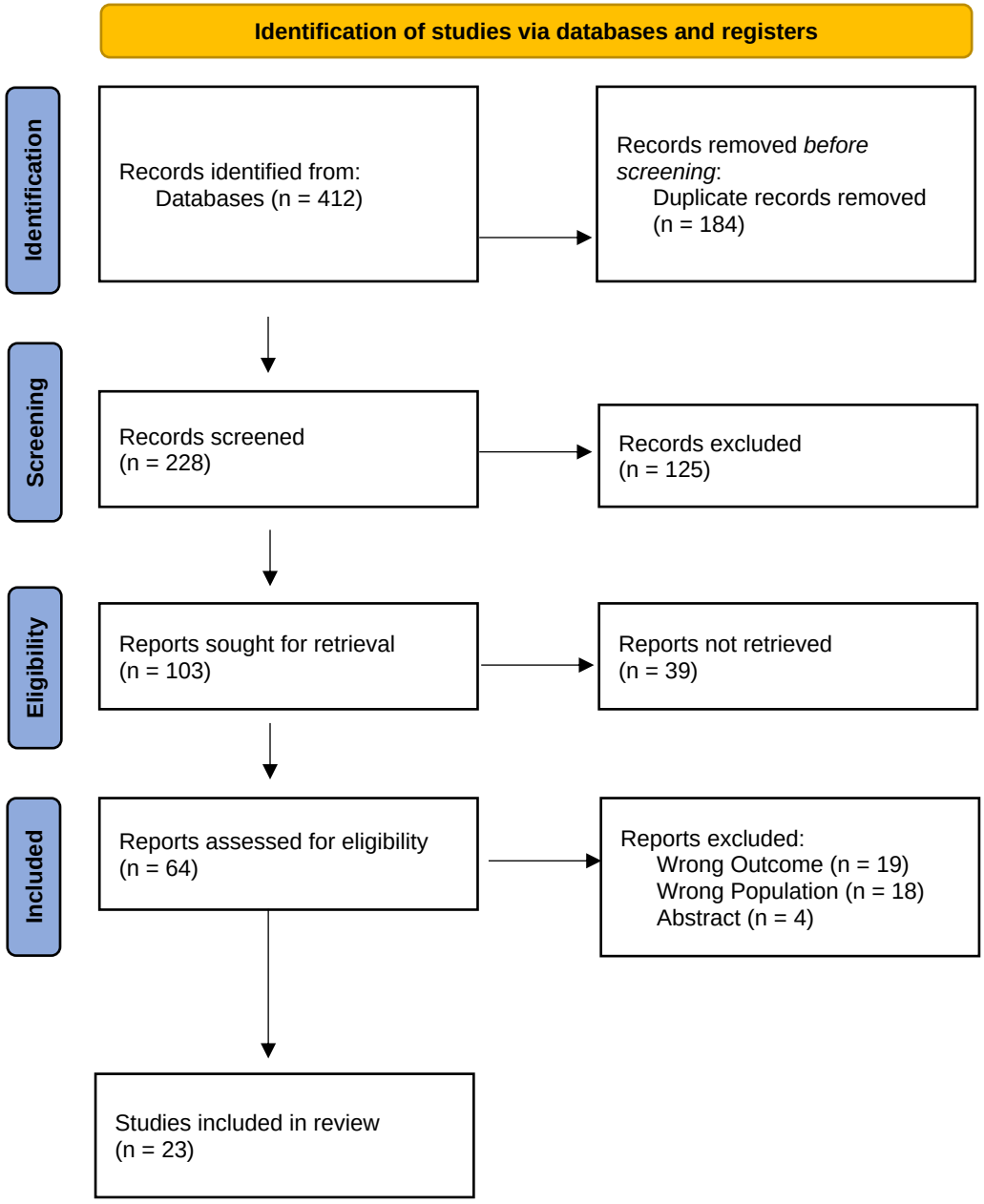

Figure 1: PRISMA 2020 Flow Diagram for Study Selection.

Table 1: Demographic and Methodological Characteristics of Included Studies.

Study (Author, Year) [Ref]	Country	Study Design	Sample Size	Study Population	Preterm Definition (GA)	ASD Assessment Method
Crump et al., 2021 [11]	Sweden	National Cohort	4,061,795	All singleton births	<37 weeks (All Preterm), 22-27w (Extreme), 28-33w (Very-Mod), 34-36w (Late)	National patient registers (ICD diagnoses)
Shuster et al., 2023 [12]	USA (Multi-site)	Longitudinal Cohort	466	Infants born <30 weeks GA	<30 weeks	M-CHAT-R/F (Screener)
Hamner et al., 2025 [13]	USA	Cross-sectional	9,725 (Screening) 435 (Evaluation)	Toddlers at well-child visits	<28w (Extreme), 28-31w (Very), 32-36w (Moderate)	M-CHAT-R/F & Diagnostic Evaluation
Shuster et al., 2024 [14]	USA (Multi-site)	Longitudinal Cohort	467	Infants born <30 weeks GA	<30 weeks	M-CHAT-R/F (Screener)
Marín Soro et al., 2024 [15]	Spain	Prospective Longitudinal	133	Infants <32w GA or <1500g	<32 weeks or BW <1500g	M-CHAT & ADOS-2
Chang et al., 2023 [16]	Taiwan	Population-based Cohort	916,315	National birth cohort	Analyzed as a continuum: <28w, 28-30w, 31-33w, 34-36w	National health records (ICD codes)
Mir et al., 2021 [17]	USA	Matched Case-Control	64 (16 cases, 48 controls)	Infants born ≤28 weeks GA	≤28 weeks	Clinical diagnosis (DSM-5)
Ellouk et al., 2025 [18]	Israel	Retrospective Cohort	114,975	Singleton deliveries	<28w, 28-32w, 32-37w	Not Specified (Medical records)
Vermeirsch et al., 2021 [19]	Belgium	Cross-sectional	55	Children born very preterm (VP)	<32 weeks	Clinical judgment (DSM-5), ADOS-2
Shuffrey et al., 2022 [20]	South Africa	Prospective Cohort	71	Preterm infants (25-36w GA)	25-36 weeks (Mean GA: 34.6w)	BITSEA (Autism risk screener)
Ontiveros Perez et al., 2025 [21]	USA	Retrospective Cohort	NM	Infants born <32 weeks GA	<32 weeks	M-CHAT-R/F (Screener)
Magán-Maganto et al., 2023 [22]	Spain	Cross-sectional	57	Children born VLBW (7-10 years old)	VLBW (<1500g)	Neuropsychological assessment & diagnostic referral
Marín Soro et al., 2025 [23]	Spain	Prospective Longitudinal	133	Infants <32w GA or <1500g	<32 weeks or BW <1500g	M-CHAT & ADOS-2 (Suspected ASD)

Bradshaw et al., 2023 [24]	USA	Prospective Cohort	20	Infants born very preterm (VPT)	VPT (GA range NM)	Assessment of social communication & ASD symptoms at 12m
Lundgren et al., 2025 [25]	Sweden	Regional Cohort	143 (from 266)	Extremely preterm children <28w GA without brain injury	<28 weeks	Clinical diagnosis (ICD codes)
Persson et al., 2023 [26]	Sweden	National Cohort	1,406,650	National birth cohort	Preterm (<37 weeks)	National patient registers (ICD diagnoses)
Nagai et al., 2022 [27]	Japan	Cross-sectional	77	Children born <32 weeks GA	<32 weeks	ADOS-2 & DSM-5 criteria
Ghosn et al., 2022 [28]	Spain	Prospective Follow-up	158 (111 TPL, 47 control)	Infants after threatened preterm labour (TPL)	TPL group (irrespective of final GA)	AOSI (at 6m), ADOS-2 & CSBS-DP (at 30m)
Hadaya et al., 2024 [29]	UK	Longitudinal Cohort	371	Toddlers born very preterm (VPT)	<33 weeks	M-CHAT (Screener), SRS-2 (Childhood traits)
Peltier et al., 2025 [30]	USA	Retrospective Cohort	337,868 (maternal-child dyads)	Singleton pregnancies	<37 weeks (Subtyped: Spontaneous & Indicated)	Electronic Health Record diagnosis (ICD)
Joseph et al., 2023 [31]	USA	Matched Case-Control	118 (59 EP, 59 Term)	Extremely Preterm (EP) and term-born children with ASD	<28 weeks	ADOS, ADI-R
Wang et al., 2023 [32]	Taiwan	Propensity-score Matched Cohort	108,786 (18,131 HDP, 90,655 control)	Children of mothers with/without HDP	<37 weeks	National health insurance data (ICD codes)
Bradshaw et al., 2025 [33]	USA	Longitudinal Cohort	137	Infants (EL-ASD, LL, PT)	Preterm (PT group)	Developmental evaluation for ASD outcome at 24m

GA: Gestational Age; w: weeks; BW: Birth Weight; VLBW: Very Low Birth Weight; HDP: Hypertensive Disorders of Pregnancy; M-CHAT-R/F: Modified Checklist for Autism in Toddlers, Revised with Follow-Up; ADOS-2: Autism Diagnostic Observation Schedule, Second Edition; BITSEA: Brief Infant Toddler Social Emotional Assessment; SRS-2: Social Responsiveness Scale, Second Edition; AOSI: Autism Observation Scale for Infants; CSBS-DP: Communication and Symbolic Behavior Scales Developmental Profile; EL-ASD: Elevated Likelihood for Autism Spectrum Disorder; LL: Low Likelihood; NM: Not Mentioned.

Table 2: Key Findings and Outcomes Related to Preterm Birth and ASD Risk.

Study (Author, Year) [Ref]	Main Findings Related to Preterm Birth and ASD	Key Metrics (e.g., OR, HR, RR, Prevalence)	Notes / Subgroup Analysis
Crump et al., 2021 [11]	Preterm & early term birth associated with increased ASD risk. Association largely independent of familial factors.	aPR (vs. term): Extreme PT: 3.72 (Boys), 4.19 (Girls); All PT: 1.35 (Boys), 1.53 (Girls); Early Term: 1.11 (Boys), 1.16 (Girls)	Strong dose-response relationship. Cosibling analysis slightly attenuated results.
Shuster et al., 2023 [12]	Positive M-CHAT-R/F screen at 2y associated with neonatal medical morbidities and neurobehavioral profiles.	OR for positive screen: Hypoaroused profile: 2.76; ≥2 medical morbidities: 2.65	Positive screen linked to poorer developmental and behavioral outcomes at 2y.
Hamner et al., 2025 [13]	Screen-positive rates and ASD prevalence increased with earlier preterm birth. M-CHAT-R/F performance acceptable in preterm toddlers.	ASD Prevalence: Extreme PT: 16.05%; Very PT: 2.00%; Mod PT: 2.89%; Full Term: 1.49%	PPV highest for extreme PT and full term groups.
Shuster et al., 2024 [14]	Positive M-CHAT-R/F at 2y associated with significant developmental delays at 3y in very preterm infants.	aOR for scores ≤84 / ≥64 at 3y: Cognitive: 4.03; Language: 5.38; Motor: 4.74; CBCL-PDD: 3.77	Supports M-CHAT-R/F as a meaningful global developmental screener in this population.
Marín Soro et al., 2024 [15]	High estimated prevalence of ASD in very preterm infants using a longitudinal screening protocol.	Estimated ASD Prevalence: 18.46% (24/130 confirmed)	Average age of detection was 25.4 months.
Chang et al., 2023 [16]	Lower GA and degree of SGA associated with increased risk of ASD with and without ID. A dose-response relationship was observed.	aOR for ASD with ID: <28w: 4.26; 28-30w: 2.80; 31-33w: 1.63; 34-36w: 1.39. Male infants showed a stronger GA-ASD gradient.	Analyzed GA and SGA as continuous risk factors.
Mir et al., 2021 [17]	Extremely preterm infants with ASD had a 2-fold greater incidence of multiple placental pathologic lesions.	69% of ASD cases had multiple placental lesions vs. 33% of controls (p=0.01)	Suggests a role of cumulative antenatal insults in ASD etiology in EP infants.
Ellouk et al., 2025 [18]	Found no significant association between PTB and ASD diagnosis after adjusting for confounders.	Adjusted HR for ASD: <28w: 0.74; 28-32w: 0.99; 32-37w: 1.07	Presents a negative association, contrasting with most literature.
Vermeirsch et al., 2021 [19]	High prevalence of ASD and broader autism phenotype in a very preterm cohort.	ASD Prevalence: 12.7%; Broader Phenotype: 14.5%	Highlights challenges in identifying ASD with standard tools in preterm children.
Shuffrey et al., 2022 [20]	Aperiodic EEG activity in preterm neonates associated with subsequent increased autism risk at 3 years.	NM (Significant correlation reported)	Suggests a potential early electrophysiological biomarker for ASD risk.
Ontiveros Perez et al., 2025 [21]	High prevalence of positive autism screens in preterm children; lower GA was the primary associated factor.	Positive Screen Prevalence: 12.2%	Language difficulties were common in both screen-positive and screen-negative groups.

Magán-Maganto et al., 2023 [22]	Confirmed high ASD prevalence in VLBW children. Lower GA and BW weakly correlated with ASD.	ASD Prevalence: 7.02% (4/57)	Weak correlations: GA (τb=-0.23), BW (τb=-0.25).
Marín Soro et al., 2025 [23]	Identified specific prenatal, perinatal, and postnatal factors associated with suspected ASD in VP/VLBW infants.	Factors: Lower GA, BPD, longer NICU stay (↑ risk); Cesarean delivery, full steroids (↓ risk)	Some risk factors may differ from the general population.
Bradshaw et al., 2023 [24]	Neonatal abnormal heart rate characteristics (HRC) strongly predicted ASD symptoms at 12 months.	Correlation between HRC & ASD symptoms: r=0.81	Very small sample size (N=20). Promising but preliminary.
Lundgren et al., 2025 [25]	Moderate-to-severe ROP associated with a threefold increased likelihood of ASD in extremely preterm children.	Adjusted OR for ASD with ROP ≥ stage 2: ~3.0 (p=0.011)	Association independent of GA and sex in children without major brain injury.
Persson et al., 2023 [26]	Maternal T1D increased offspring ASD risk; ~20% of this effect was mediated through preterm birth.	HR for ASD with T1D: 1.40; Mediation via PTB: RR=1.06 (22% of total effect)	HbA1c level was not associated with ASD risk beyond T1D itself.
Nagai et al., 2022 [27]	Very high diagnostic rate of ASD when systematically assessing a cohort of very preterm children.	ASD Diagnostic Rate: 20.8% (16/77)	Suggests true prevalence in VP children may be higher than previously reported.
Ghosn et al., 2022 [28]	Infants after threatened preterm labour (TPL) had higher autistic symptom load at 30m, irrespective of final GA.	NM	Suggests the TPL event itself, not just prematurity, is a risk factor.
Hadaya et al., 2024 [29]	VPT toddlers with positive M-CHAT (critical items) had smaller neonatal cerebellar volumes. Distinct trajectories to high ASD traits.	NM	Links early brain structure to later social traits, suggesting heterogeneity in etiology.
Peltier et al., 2025 [30]	Both spontaneous and indicated PTB increased ASD risk, with a stronger effect for indicated PTB.	adj.HR: Spontaneous PTB: 1.69; Indicated PTB: 2.68	No association found in non-Hispanic Black children.
Joseph et al., 2023 [31]	ASD phenotypic presentation was largely similar between EP and term-born children with ASD at age 10.	EP group had less severe stereotyped language and RRBs per ADI-R.	Focused on phenotype comparison, not risk.
Wang et al., 2023 [32]	Preterm birth and SGA potentiated the association between maternal hypertensive disorders and childhood ASD.	HDP itself was not a significant contributor after adjustment; PTB and SGA were key moderators.	Supports a multiple-hit hypothesis.
Bradshaw et al., 2025 [33]	Infants later diagnosed with ASD showed elevated resting RSA from 9-24 months, unlike TD infants.	NM	Contrasts with lower RSA typically found in older children with ASD, highlighting development.

aPR: Adjusted Prevalence Rate; OR: Odds Ratio; HR: Hazard Ratio; RR: Risk Ratio; GA: Gestational Age; PT: Preterm; EP: Extremely Preterm; VPT: Very Preterm; SGA: Small for Gestational Age; ID: Intellectual Disability; BPD: Bronchopulmonary Dysplasia; ROP: Retinopathy of Prematurity; T1D: Type 1 Diabetes; CBCL-PDD: Child Behavior Checklist - Pervasive Developmental Problems scale; NM: Not Mentioned

Table 3: Risk of Bias Assessment for Included Studies Using the Newcastle-Ottawa Scale (NOS) for Cohort Studies.

Study (Author, Year) [Ref]	Selection (Max 4 stars)	Comparability (Max 2 stars)	Outcome (Max 3 stars)	Total Score (Max 9)	Overall Risk of Bias
Cohort Studies					
Crump et al., 2021 [11]	★★★★	★★	★★★	9	Low
Shuster et al., 2023 [12]	★★★☆	★★	★★★	8	Low
Hamner et al., 2025 [13]	★★★★	★★	★★★	9	Low
Shuster et al., 2024 [14]	★★★☆	★★	★★★	8	Low
Marín Soro et al., 2024 [15]	★★★☆	★☆	★★★	7	Moderate
Chang et al., 2023 [16]	★★★★	★★	★★★	9	Low
Ellouk et al., 2025 [18]	★★★☆	★★	★★★	8	Low
Shuffrey et al., 2022 [20]	★★★☆	★☆	★★☆	6	Moderate
Ontiveros Perez et al., 2025 [21]	★★★☆	★☆	★★☆	6	Moderate
Magán-Maganto et al., 2023 [22]	★★★☆	★☆	★★★	7	Moderate
Marín Soro et al., 2025 [23]	★★★☆	★☆	★★★	7	Moderate
Bradshaw et al., 2023 [24]	★★☆☆	★☆	★★☆	5	High
Lundgren et al., 2025 [25]	★★★☆	★★	★★★	8	Low
Persson et al., 2023 [26]	★★★★	★★	★★★	9	Low
Nagai et al., 2022 [27]	★★★☆	★☆	★★★	7	Moderate
Ghosn et al., 2022 [28]	★★★☆	★★	★★★	8	Low
Hadaya et al., 2024 [29]	★★★☆	★★	★★★	8	Low
Peltier et al., 2025 [30]	★★★★	★★	★★★	9	Low
Bradshaw et al., 2025 [33]	★★★☆	★★	★★★	8	Low
Case-Control Studies	**Selection (Max 4)**	**Comparability (Max 2)**	**Exposure (Max 3)**	**Total Score (Max 9)**	
Mir et al., 2021 [17]	★★★☆	★★	★★★	8	Low
Joseph et al., 2023 [31]	★★★☆	★★	★★★	8	Low
Wang et al., 2023 [32]	★★★★	★★	★★★	9	Low
Cross-Sectional Studies	**Selection (Max 4)**	**Comparability (Max 2)**	**Outcome (Max 3)**	**Total Score (Max 9)**	
Vermeirsch et al., 2021 [19]	★★★☆	★☆	★★★	7	Moderate

neurophysiological functioning, such as aperiodic EEG activity and abnormal heart rate characteristics, as potential biomarkers of subsequent ASD risk. These findings suggest that the "preterm ASD" phenotype may be the behavioral endpoint of a heterogenous group of disruptions to early brain development, involving the cerebellum, autonomic nervous system, and cortical electrophysiology. This heterogeneity may explain why some studies find subtle phenotypic differences, such as less severe stereotyped language [31], and why screening tools like the M-CHAT-R/F, while useful, may require population-specific interpretation [13, 14]. The utility of early autism screening in preterm populations is a critical practical implication of our findings. Multiple studies in this review [12, 13, 14, 21] validate the use of the M-CHAT-R/F in preterm toddlers, demonstrating its ability to identify children at high risk for not only ASD but also significant global developmental delays. Shuster et al. [14] powerfully demonstrated that a positive M-CHAT-R/F screen at age 2 was strongly predictive of cognitive, language, and motor deficits at age 3, with adjusted odds ratio ranging from 4.03 to 5.38. This positions the M-CHAT-R/F not just as an autism-specific screener but as a valuable tool for identifying broader neurodevelopmental vulnerability in this high-risk group. However, the studies also caution that screen-positive rates are high and do not always equate to a definitive ASD diagnosis, emphasizing the necessity of a two-stage process involving screening followed by comprehensive diagnostic evaluation by specialists [13, 19]. Beyond the simple metric of gestational age, our review identifies several important modifiers and mediators of the preterm birth-ASD relationship. The study by Peltier et al. [30] made a crucial distinction by demonstrating that the subtype of preterm birth matters; indicated preterm deliveries (often due to conditions like preeclampsia or fetal growth restriction) were associated with a significantly higher risk of ASD (adj.HR=2.68) compared to spontaneous preterm deliveries (adj. HR=1.69). This suggests that the underlying maternal or fetal pathology necessitating early delivery may contribute independently to neurodevelopmental risk. Furthermore, the interaction between preterm birth and other perinatal insults is critical. Wang et al. [32] and Persson et al. [26] showed that preterm birth and SGA act as potent effect modifiers, significantly amplifying the ASD risk associated with maternal hypertensive disorders and type 1 diabetes, respectively. This supports a "multiple-hit" model of pathogenesis, where the initial insult of prematurity increases the brain's vulnerability to subsequent adversities. The search for very early, pre-symptomatic biomarkers is a frontier explored in our review. The findings of Shuffrey et al. [20], who linked aperiodic EEG activity in the neonatal period to autism risk at 3 years, and Bradshaw et al. [24], who found abnormal heart rate characteristics in the NICU to predict ASD symptoms at 12 months, are particularly provocative. These studies move beyond behavioral markers to identify physiological signatures of risk that are present long before the classic symptoms of ASD emerge. This aligns with a growing body of research, such as the work by Schendel et al. [38], which emphasizes the importance of the prenatal and perinatal period in the etiology of ASD. If validated in larger cohorts, these biomarkers could revolutionize early identification, allowing for the initiation of preemptive interventions during periods of peak neuroplasticity. It is important to acknowledge the contrasting finding by Ellouk et al. [18], which reported no significant association between preterm birth and ASD after adjusting for confounders. This outlier underscores the methodological complexities inherent in this field. Differences in population characteristics, the definition and ascertainment of ASD, the specific confounders controlled for, and the duration of follow-up can all influence the observed association. For example, if a study does not actively screen for ASD and relies solely on clinical diagnoses, it may miss a significant number of cases, particularly those with average cognitive abilities, leading to an underestimation of the true risk. The divergent result from Ellouk et al. [18] highlights the need for continued research with standardized methodologies but does not invalidate the overwhelming consensus from the majority of high-quality studies included in this and other reviews. Limitations: Despite the robust findings, this systematic review is subject to several limitations. First, the included studies exhibited heterogeneity in their definitions of preterm birth (e.g., varying gestational age cut-offs) and, most notably, in their methods of ASD ascertainment, which ranged from gold-standard diagnostic assessments like the ADOS-2 to registry-based ICD codes. This heterogeneity complicates direct comparisons and meta-analysis. Second, while many studies controlled for key confounders such as sex and socioeconomic status, residual confounding by unmeasured factors (e.g., detailed genetic risk, specific environmental exposures) remains a possibility. Third, the

generalizability of findings from high-income countries with advanced neonatal care may be limited to settings with similar medical resources, as the outcomes for extremely preterm infants are heavily influenced by the quality of perinatal and neonatal care. Finally, the focus of most studies was on establishing association and prevalence; there is a relative paucity of research delving into the specific mechanistic pathways linking preterm brain injury and dysmaturation to the development of core ASD symptoms, representing a critical area for future investigation.

Conclusion

In conclusion, this systematic review provides a comprehensive and contemporary synthesis of evidence firmly establishing preterm birth as a major, independent risk factor for autism spectrum disorder. The association is characterized by a strong dose-response relationship, is evident across diverse populations and study designs, and appears to be mediated through distinct neurodevelopmental pathways involving autonomic regulation, brain structure, and specific neonatal morbidities. The alarmingly high prevalence of ASD in extremely preterm cohorts underscores the non-negotiable need for integrating systematic, longitudinal screening and developmental surveillance into the standard of care for these children.

Conflict of Interest

None

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