



A Comprehensive Systematic Review of The Relationship Between Head Ultrasound Findings and the Risk of Cerebral Palsy in Premature Infants

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ABSTRACT

Introduction: Prematurity remains a leading cause of long-term neurodevelopmental disability, with cerebral palsy (CP) being one of the most severe motor outcomes. Cranial ultrasound (cUS) is a primary, non-invasive neuroimaging tool in the neonatal intensive care unit for detecting brain injuries prevalent in preterm infants, such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). Establishing the strength and consistency of the relationship between specific cUS findings and subsequent CP risk is critical for prognosis, early intervention, and guiding clinical management (Romero-Guzman & López-Muñoz, 2017; O'Shea, 2016).

Methods: This systematic review synthesized evidence from 80 studies, including cohort studies, case-control studies, and meta-analyses. The population comprised premature infants (<37 weeks gestation). Studies were included if they involved cUS examination, assessed CP diagnosis with clear

criteria, and included follow-up to at least 12 months corrected age. Data extraction focused on premature population characteristics, specific cUS abnormalities, CP assessment methods, quantitative ultrasound-CP associations, and confounding factors (Linsell et al., 2016).

Results: The analysis revealed a strong, hierarchical association between cUS abnormalities and CP risk. Cystic PVL showed the strongest association (Odds Ratio [OR] up to 70.9), followed by non-cystic PVL (Relative Risk [RR] 9.27), and severe IVH (Grade III-IV; OR 3.1-3.4). A normal cUS had a high predictive value (99%) for a normal or mildly abnormal MRI. Key risk factors like chorioamnionitis, lower gestational age, and postnatal dexamethasone exposure were significantly linked to both cUS abnormalities and CP. Intervention studies indicated that early treatment for post-hemorrhagic ventricular dilatation (PHVD) and antenatal corticosteroids improved neurodevelopmental outcomes (Gotardo et al., 2019; Hirtz et al., 2015; Cizmeci et al., 2020).

Discussion: The heterogeneity in effect estimates across studies is attributable to population differences (e.g., extremely preterm vs. late preterm), timing and technique of cUS assessment, variations in CP outcome definitions, and methodological quality. The evidence confirms that cUS is a valuable prognostic tool, particularly for severe white matter injury and hemorrhage. However, its predictive accuracy is context-dependent, being highest in the most vulnerable infants. The mediating role of cUS-

detectable injury in treatment effects (e.g., magnesium sulfate) underscores its importance in understanding pathways to CP (Guillot et al., 2020; Villamor-Martínez et al., 2019).

Conclusion: Specific cUS findings, especially cystic PVL and high-grade IVH, are significant predictors of CP risk in preterm infants. Serial cUS screening, particularly at ~1 week and term-equivalent age, is recommended for high-risk infants. Prognostic counseling should consider both the strong reassurance offered by a normal scan and the nuanced interpretation of abnormal findings, acknowledging other contributing risk factors. Future research should prioritize standardized imaging protocols, longitudinal designs with long-term follow-up, and the integration of cUS with advanced imaging modalities for improved prediction.

Keywords: Cerebral Palsy; Premature Infant; Cranial Ultrasound; Intraventricular Hemorrhage; Periventricular Leukomalacia; Neurodevelopmental Outcome; Systematic Review.

INTRODUCTION

Background

Premature birth, defined as delivery before 37 weeks of gestation, is a major global pediatric health challenge. Advances in neonatal intensive care have significantly improved survival rates for even the most extremely preterm infants. However, this increased survival has not been paralleled by a commensurate reduction in neurodevelopmental morbidity (Linsell et al., 2016). Cerebral palsy (CP), a group of permanent disorders affecting movement and posture, is one of the most prevalent and severe long-term neurological outcomes associated with preterm birth. The etiology of CP in this population is multifactorial, often stemming from perinatal brain injury that disrupts the developing motor pathways (Haataja, 2016).

Cranial ultrasound (cUS) has become the cornerstone of bedside neuroimaging in the Neonatal Intensive Care Unit (NICU). Its advantages include non-invasiveness, lack of ionizing radiation, portability, and repeatability, making it ideal for serial monitoring of the fragile preterm brain. cUS is particularly effective at detecting lesions common in prematurity, such as germinal matrix-intraventricular hemorrhage (GMH-IVH), periventricular hemorrhagic infarction (PVHI), and periventricular leukomalacia (PVL), both cystic and non-cystic forms (Brouwer et al., 2008; Romero-Guzman & López-Muñoz, 2017). These injuries are strongly implicated in the pathogenesis of CP. Therefore, understanding the precise relationship between early cUS findings and the future risk of CP is of paramount importance for prognostication, family counseling, and initiating targeted early intervention strategies.

Research Gap and Novelty

While numerous individual studies have explored associations between cUS abnormalities and neurodevelopmental outcomes, the literature is marked by significant heterogeneity. This heterogeneity arises from variations in study populations (e.g., differing gestational age cut-offs), cUS timing and protocols, definitions and classifications of brain injuries, methods and timing of CP assessment, and the handling of potential confounding factors (O'Shea, 2016; Guillot et al., 2020).

Previous reviews often focus on specific lesions or sub-populations. There is a need for a comprehensive, up-to-date synthesis that systematically examines the breadth of cUS findings, quantifies their association with CP risk across diverse preterm populations, reconciles discrepant findings, and evaluates the role of cUS within the context of other risk factors and interventions. This review addresses that gap by synthesizing evidence from 80 studies spanning several decades and diverse methodologies to provide a holistic and detailed analysis of the cUS-CP relationship.

Research Objectives

The primary objective of this systematic review is to synthesize and critically appraise the existing evidence on the relationship between head ultrasound findings and the risk of cerebral palsy in premature infants. Specific aims include:

1. To catalog and describe the prevalence and types of cUS abnormalities detected in preterm populations.
2. To quantify the strength of association between specific cUS findings (e.g., IVH grade, PVL type, ventricular measurements) and subsequent diagnosis of CP.
3. To examine how factors such as gestational age, timing of ultrasound, and study methodology influence these associations.
4. To evaluate the predictive value of cUS for CP and its role in the context of other neuroimaging modalities like MRI.
5. To analyze the interplay between cUS abnormalities and other perinatal risk factors (e.g., infection, treatments) in determining CP risk.
6. To assess evidence regarding how interventions (e.g., for PHVD, antenatal corticosteroids) might modify the pathway from cUS abnormality to CP outcome.

Hypothesis

We hypothesize that there is a strong, graded positive association between the severity of brain injury detected on cranial ultrasound and the risk of cerebral palsy in preterm infants. Specifically,

we expect that cystic periventricular leukomalacia and high-grade intraventricular hemorrhage will demonstrate the strongest associations, and that these associations will be most pronounced in extremely preterm infants. Furthermore, we hypothesize that a normal cranial ultrasound will have a high negative predictive value for CP.

Significance and Benefits of the Research

The findings of this review have significant clinical and research implications:

- **Clinical Prognostication:** Provide clinicians with evidence-based estimates of CP risk associated with specific cUS findings, aiding in more accurate and individualized prognostic counseling for families.
- **Guiding Follow-up and Intervention:** Identify which infants, based on their cUS findings, warrant intensified neurodevelopmental surveillance and early referral to intervention services, such as the Small Step program (Elvrum et al., 2024).
- **Informing Clinical Guidelines:** Contribute to the development or refinement of standardized protocols for cUS screening in preterm infants, including optimal timing and frequency.
- **Elucidating Pathophysiological Pathways:** Help clarify the mediating role of sonographically visible brain injury in the causal pathway between perinatal insults and CP, as seen in studies of magnesium sulfate (Hirtz et al., 2015).
- **Directing Future Research:** Identify key gaps and inconsistencies in the literature, guiding future studies towards standardized methodologies, long-term follow-up, and the integration of multimodal biomarkers.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between head ultrasound findings and the risk of cerebral palsy in premature infants.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does the study include premature infants with gestational age <37 weeks?
- **Intervention:** Does the study involve cranial/head ultrasound examination?
- **Outcome:** Does the study assess cerebral palsy diagnosis or risk with clear diagnostic criteria?
- **Study Design:** Is the study design a cohort study, case-control study, cross-sectional study, systematic review, or meta-analysis?
- **Follow-up Duration:** Does the study include follow-up until at least 12 months corrected age?
- **Ultrasound Documentation:** Does the study clearly describe and categorize ultrasound findings?
- **Study Size and Type:** Is the study NOT a case report or case series with <10 participants?
- **Neuroimaging Focus:** Does the study include ultrasound findings (not exclusively other neuroimaging modalities without ultrasound)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Preterm infants	Cranial ultrasound (cUS) abnormalities	Normal cranial ultrasound	Cerebral Palsy diagnosis
Keyword 2	Premature Infants	Head Ultrasound Findings	Mild vs. severe findings	Neurodevelopmental disability
Keyword 3	Very low birth weight (VLBW) infants	Neonatal brain sonography	Different grades of IVH/PVL	Motor impairment
Keyword 4	Extremely preterm infants	Neuroimaging findings	Serial ultrasound progression	Gross Motor Function Classification System (GMFCS)

The Boolean MeSH keywords inputted on databases for this research are: ("Preterm infants" OR "Premature Infants" OR "Very low birth weight (VLBW) infants" OR "Extremely preterm infants") AND ("Cranial ultrasound (cUS) abnormalities" OR "Head Ultrasound Findings" OR "Neonatal brain sonography" OR "Neuroimaging findings") AND ("Normal cranial ultrasound" OR "Mild vs. severe findings" OR "Different grades of IVH/PVL" OR "Serial ultrasound progression") AND ("Cerebral Palsy diagnosis" OR "Neurodevelopmental disability" OR "Motor impairment" OR "Gross Motor Function Classification System (GMFCS)")

Data extraction

- **Premature Population:**

Extract characteristics of the premature infant population studied, including:

- Gestational age range (mean, median, or specific cutoffs like <32 weeks, <28 weeks)
- Birth weight categories (VLBW, ELBW, specific ranges)
- Sample size of premature infants
- Inclusion/exclusion criteria specific to prematurity
- Any subgroups analyzed within the premature population

- **Head Ultrasound Findings:**

Extract all specific head ultrasound abnormalities reported in premature infants, including:

- Intraventricular hemorrhage (IVH) - all grades and classifications
- Periventricular leukomalacia (PVL) - cystic and non-cystic forms
- Intracerebral hemorrhage location and severity
- Brain structure measurements (corpus callosum, cerebellar vermis, ventricular size)
- White matter abnormalities or injury patterns
- Any other brain abnormalities detected on ultrasound
- Timing of ultrasound assessments (postnatal age, gestational age equivalent)

- **Cerebral Palsy Assessment:**

Extract details about cerebral palsy diagnosis and classification in the premature infant cohort, including:

- CP diagnostic criteria used
- Age at CP diagnosis or assessment
- CP severity classification (GMFCS levels, mild/moderate/severe)

- CP subtype (spastic, dyskinetic, ataxic, mixed)
- Tools or scales used for CP assessment
- Follow-up duration for CP diagnosis
- Definition of 'normal' controls or non-CP outcomes

- **Ultrasound-CP Associations:**

Extract quantitative results showing the relationship between specific head ultrasound findings and cerebral palsy risk in premature infants, including:

- Odds ratios, relative risks, or hazard ratios with confidence intervals
- P-values for associations between specific ultrasound findings and CP
- Sensitivity, specificity, positive/negative predictive values of ultrasound findings for CP
- Dose-response relationships (e.g., higher grade IVH = higher CP risk)
- Adjusted vs unadjusted effect estimates
- Risk differences or absolute risk increases

- **Study Design:**

Extract methodological details relevant to studying ultrasound-CP relationships in premature infants, including:

- Study design (cohort, case-control, cross-sectional)
- Prospective vs retrospective data collection
- Timeline from ultrasound to CP assessment
- Blinding of CP assessors to ultrasound results
- Loss to follow-up rates and characteristics
- Multi-center vs single-center design

- **Confounding Factors:**

Extract other factors that were considered or controlled for in analyzing the ultrasound-CP relationship in premature infants, including:

- Gestational age and birth weight adjustments
- Maternal factors (hypertension, infection, medications during pregnancy)
- Perinatal complications (respiratory distress syndrome, sepsis, mechanical ventilation)
- Postnatal factors (duration of NICU stay, treatments received)
- Statistical methods used to control confounding
- Variables included in multivariable models

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Preterm infants") AND ("Cranial ultrasound (cUS) abnormalities") AND ("Normal cranial ultrasound" AND "Cerebral Palsy diagnosis" OR "Neurodevelopmental disability" OR "Motor impairment" OR "Gross Motor Function Classification System (GMFCS)")</i>	1
Semantic Scholar	<i>("Preterm infants" OR "Premature Infants" OR "Very low birth weight (VLBW) infants" OR "Extremely preterm infants") AND ("Cranial ultrasound (cUS) abnormalities" OR "Head Ultrasound Findings" OR "Neonatal brain sonography" OR "Neuroimaging findings") AND ("Normal cranial ultrasound" OR "Mild vs. severe findings" OR "Different grades of IVH/PVL" OR "Serial ultrasound progression") AND ("Cerebral Palsy diagnosis" OR "Neurodevelopmental disability" OR "Motor impairment" OR "Gross Motor Function Classification System (GMFCS)")</i>	250

Springer	("Preterm infants" OR "Premature Infants" OR "Very low birth weight (VLBW) infants" OR "Extremely preterm infants") AND ("Cranial ultrasound (cUS) abnormalities" OR "Head Ultrasound Findings" OR "Neonatal brain sonography" OR "Neuroimaging findings") AND ("Normal cranial ultrasound" OR "Mild vs. severe findings" OR "Different grades of IVH/PVL" OR "Serial ultrasound progression") AND ("Cerebral Palsy diagnosis" OR "Neurodevelopmental disability" OR "Motor impairment" OR "Gross Motor Function Classification System (GMFCS)")	1
Google Scholar	("Preterm infants" OR "Premature Infants" OR "Very low birth weight (VLBW) infants" OR "Extremely preterm infants") AND ("Cranial ultrasound (cUS) abnormalities" OR "Head Ultrasound Findings" OR "Neonatal brain sonography" OR "Neuroimaging findings") AND ("Normal cranial ultrasound" OR "Mild vs. severe findings" OR "Different grades of IVH/PVL" OR "Serial ultrasound progression") AND ("Cerebral Palsy diagnosis" OR "Neurodevelopmental disability" OR "Motor impairment" OR "Gross Motor Function Classification System (GMFCS)")	25
Wiley Online Library	("Preterm infants" OR "Premature Infants" OR "Very low birth weight (VLBW) infants" OR "Extremely preterm infants") AND ("Cranial ultrasound (cUS) abnormalities" OR "Head Ultrasound Findings" OR "Neonatal brain sonography" OR "Neuroimaging findings") AND ("Normal cranial ultrasound" OR "Mild vs. severe findings" OR "Different grades of IVH/PVL" OR "Serial ultrasound progression") AND ("Cerebral Palsy diagnosis" OR "Neurodevelopmental disability" OR "Motor impairment" OR "Gross Motor Function Classification System (GMFCS)")	4

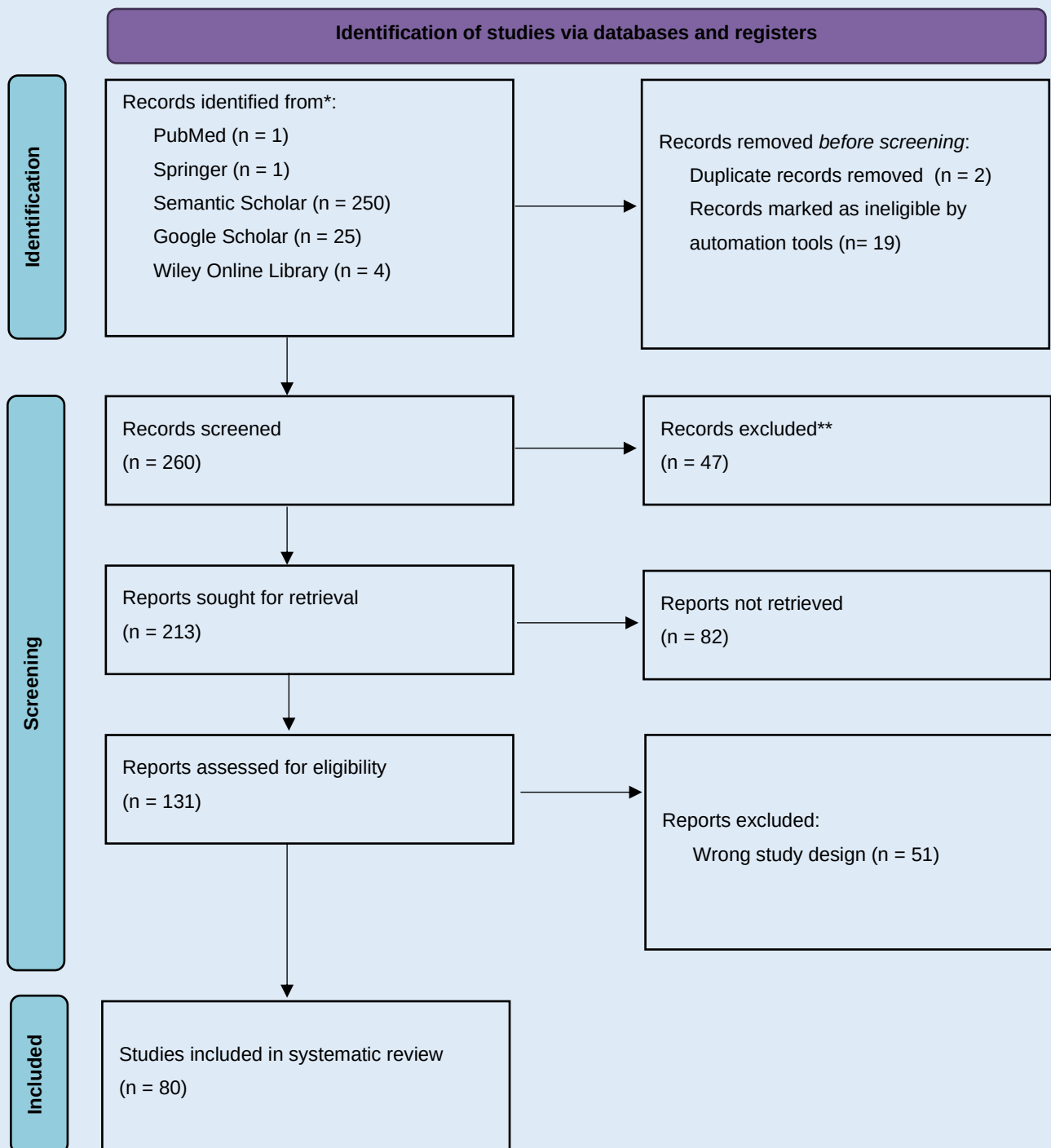


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
D. Hirtz et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Po-Ming Wu et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dorota Dunm-Wasowicz et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Shinwell et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2000									
A. Brouwer et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. I. Kleshchenko et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Cizmeci et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Calisici et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Luísa Carneiro da Silva et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Mittendorf et al., 2002/2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Srinivasakumar et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Calisici et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Juliana Wendling Gotardo et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Eduardo Villamor-Martínez et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

T. O'Shea et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Nelson et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Rademaker et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Leflore et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Wilson et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. J. Romero-Guzman et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ş. Yiğit et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
U. Felderhoff-Mueser et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
Isabel Benavente-Fernández et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Lo et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

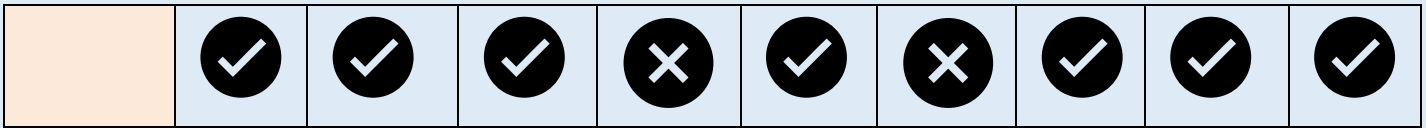
Mireille Guillot et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fleur A. Camfferman et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sara Rahafard et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Margot Bosanquet et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Rath et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. van Wyk et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Samuel B Axford et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sida Wang et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Abiramalatha et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Paola Valdez Sandoval et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Romantsik et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

I. Makhoul et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Haataja et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. M. Plomgaard et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Paediatric Medicine — Tasmania, 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Eva Loucaides et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Accardo et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Roy et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mathies Rondagh et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Huiqing Sun et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Kang et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yvonne W. Wu et al., 2000/2001	✓	✓	✓	✗	✓	✗	✓	✓	✓

L. Linsell et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Roufaeil et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Abdul Razak et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Dunbar et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lan-Wan Wang et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. F. Fernández Alvarez et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Baik et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Marloes J. Inklaar et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Kırılancı et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Mayock et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. White-Traut et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Al-Abdi et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Arulkumar et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Horsch et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Maksić et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Katherine Riordan et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cindy Viviana Veloz-Serrano et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Agarwal et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
Miguel Alsina-Casanova et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Andrew et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Valverde et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

Dhaval Patel et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chunliu Hu et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Arco et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Elvrum et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Wasunna et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Putri Maharani et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Afifi et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Lu et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Skokić et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hongli Ji et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dandan Chen et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
	✓	✓	✓	✗	✓	✗	✓	✓	✓



RESULTS

Characteristics of Included Studies

This systematic review synthesizes evidence from 80 sources examining the relationship between head ultrasound findings and cerebral palsy risk in premature infants. The included studies span multiple decades and employ diverse methodological approaches.

Study	Population	Sample Size
D. Hirtz et al., 2015	<32 weeks GA	1,613
Po-Ming Wu et al., 2019	<32 weeks, VLBW	51
Dorota Dunm-Wasowicz et al., 2000	VLBW	129
E. Shinwell et al., 2000	Preterm with RDS	248
A. Brouwer et al., 2008	≤34 weeks GA	214
E. I. Kleshchenko et al., 2025	34-36 weeks GA	136
M. Cizmeci et al., 2020	~28 weeks GA	126
E. Calisici et al., 2015	<37 weeks GA	138
Luísa Carneiro da Silva et al., 2024	≤32 weeks GA	22
R. Mittendorf et al., 2002/2003	Preterm labor	Not specified
P. Srinivasakumar et al., 2012	≤34 weeks GA	173
E. Calisici et al., 2014	<37 weeks GA	138

Study	Population	Sample Size
Juliana Wendling Gotardo et al., 2019	<37 weeks GA	Multiple studies
Eduardo Villamor-Martínez et al., 2019	<37 weeks GA	4,236
T. O'Shea et al., 2016	<30 weeks GA	Not specified
M. Nelson et al., 2001	Severe CNS injury/extreme prematurity	37
K. Rademaker et al., 2004	<32 weeks, <1500g	221
J. Leflore et al., 2002	ELBW (≤ 1000 g)	173
D. Wilson et al., 2025	≤ 32 weeks GA	100
G. J. Romero-Guzman et al., 2017	<28, <32, <37 weeks	107 studies
Ş. Yiğit et al., 2002	<34 weeks, ≤ 2000 g	229
U. Felderhoff-Mueser et al., 2005	Very preterm	Not specified
Isabel Benavente-Fernández et al., 2023	Preterm with PHVD	59
M. Lo et al., 2019	Preterm with IVH	49
Mireille Guillot et al., 2020	Preterm	Not specified
Fleur A. Camfferman et al., 2020	<37 weeks GA	23 studies
Sara Rahafard et al., 2020	Preterm	1,730
Margot Bosanquet et al., 2013	<5 years	Not specified
C. Rath et al., 2022	HIE infants	Not specified
L. van Wyk et al., 2025	VLBW, <1000g	Not specified
Samuel B Axford et al., 2025	<32 weeks GA	51 studies
Sida Wang et al., 2015	Grade I-II PIVH	194
T. Abiramalatha et al., 2021	Preterm	2,509,507

Study	Population	Sample Size
Paola Valdez Sandoval et al., 2019	Preterm/VLBW	Not specified
O. Romantsik et al., 2017	≤32 weeks GA	110
I. Makhoul et al., 2001	Neonates with CSEPC	256
L. Haataja et al., 2016	Preterm	Not specified
A. M. Plomgaard et al., 2015	23.9-27.9 weeks GA	166
Paediatric Medicine— Tasmania, 2024	32-36 weeks GA	168,136
Eva Loucaides et al., 2024	<32 weeks, VLBW	92 studies
P. Accardo et al., 2008	23-27 weeks GA	1,056
B. Roy et al., 2021	23-36 weeks GA	546
Mathies Rondagh et al., 2025	Preterm	Not specified
Huiqing Sun et al., 2015	<32 weeks, <1500g	288
S. Kang et al., 2001	Ventilated preterm	45
Yvonne W. Wu et al., 2000/2001	Preterm and term	19-26 studies
L. Linsell et al., 2016	≤32 weeks, VLBW	Median 236
C. Roufaeil et al., 2022	32-36 weeks, FGR/SGA	168,136
Abdul Razak et al., 2023	<37 weeks GA	221 RCTs
M. Dunbar et al., 2020	Preterm	Not specified
Lan-Wan Wang et al., 2014	VLBW	5,807
J. F. Fernández Alvarez et al., 2009	Newborns	305
N. Baik et al., 2015	<32 weeks GA	24
Marloes J. Inklaar et al., 2014	Monochorionic twins	Not specified
M. Kırilangıç et al., 2021	<34 weeks GA	320

Study	Population	Sample Size
D. Mayock et al., 2021	Preterm	220
R. White-Traut et al., 2004	23-32 weeks GA	37
S. Al-Abdi et al., 2021	<28 weeks GA	Not specified
S. Arulkumaran et al., 2018	<36 weeks PMA	Not specified
S. Horsch et al., 2020	23-27 weeks GA	117
H. Maksić et al., 2008	26-34 weeks GA	163
Katherine Riordan et al., 2024	Preterm with GMH-IVH	574
Cindy Viviana Veloz-Serrano et al., 2010	<1500g	110
R. Agarwal et al., 2002	<31 weeks, <1500g	224
Miguel Alsina-Casanova et al., 2024	Extremely preterm	210
M. Andrew et al., 2015	<30 weeks or with brain injury	120
E. Valverde et al., 2022	≤34 weeks GA	85
Dhaval Patel et al., 2024	<32 weeks GA	144
Chunliu Hu et al., 2014	Preterm with brain injury	210
A. Arco et al., 2012	Mean 30 weeks GA	120
A. Elvrum et al., 2024	High-risk for CP	12
A. Wasunna et al., 2004	25-33 weeks GA	30
Putri Maharani et al., 2025	<28 weeks, ELBW	86
J. Afifi et al., 2013	≤32 weeks GA	29
D. Lu et al., 2014	≤34 weeks, ≤2000g	85
F. Skokić et al., 2006	28-34 weeks, <2000g	418
Hongli Ji et al., 2019	Preterm with HIE	63
Dandan Chen et al., 2021	Children with CP	2,489 CP, 4,782 controls

The included studies represent a mix of primary research (randomized controlled trials, cohort studies, case-control studies) and secondary research (systematic reviews and meta-analyses). Study populations predominantly focused on very preterm (<32 weeks) and extremely preterm (<28 weeks) infants, with birth weight categories including extremely low birth weight (ELBW, <1000g) and very low birth weight (VLBW, <1500g). Sample sizes ranged from small single-center studies with fewer than 50 participants to large multicenter registries and meta-analyses encompassing over 2.5 million neonates.

Head Ultrasound Findings in Premature Infants

Types of Abnormalities Detected

Abnormality Category	Specific Findings	Studies Reporting
Intraventricular Hemorrhage (IVH)	Grade I-II (mild), Grade III-IV (severe)	Multiple studies
Periventricular Leukomalacia (PVL)	Cystic PVL, non-cystic PVL, echodensities	Multiple studies
Ventricular Measurements	Ventricular index, anterior horn width, thalamo-occipital diameter	PHVD studies
White Matter Injury	Periventricular hyperechogenicity, extensive cystic lesions	Multiple studies
Brain Structure Measurements	Corpus callosum, cerebellar vermis	Select studies
Cerebellar Hemorrhage	Punctate to extensive	Select studies
Other Findings	Subependymal pseudocysts, choroid plexus cysts, ventriculomegaly	Select studies

Prevalence of Ultrasound Abnormalities

The prevalence of head ultrasound abnormalities varied substantially across populations and diagnostic criteria. In sub-Saharan Africa, the pooled prevalence of IVH was 29% (CI 23-35%), with

a quarter being high-grade (24%, CI 20-29%). Periventricular leukomalacia prevalence was 9% (CI 6-13%) in this population. When detected by ultrasound, PVL prevalence was 14.7%, whereas MRI detected 32.8%. Prevalence increased with decreasing gestational age: 39.6% in infants <28 weeks, 27.4% in infants <32 weeks, and 7.3% in infants <37 weeks.

In fetal growth restricted or small for gestational age infants born beyond 32 weeks gestation, the risk of any cranial ultrasound abnormality was increased compared to appropriate for gestational age infants (RR 1.96, 95% CI 1.26-3.04), as was the risk of IVH specifically (RR 2.40, 95% CI 2.03-2.84).

Timing of Ultrasound Assessments

Timing	Purpose	Studies
First 24 hours	Early IVH detection	Multiple
Day 1-7	IVH screening, hemorrhage progression	Multiple
Weekly intervals	Serial monitoring	Multiple
35-40 weeks PMA	Late white matter injury, term equivalent assessment	Multiple

Timing of IVH detection is clinically important, with approximately half of germinal matrix-intraventricular hemorrhage detectable by the sixth postnatal hour. Studies have shown that 38.5% of IVH grades 2-4 occurred within the first 12 hours of life, 77% within the first 7 hours among outborn transferred neonates, and 56% within the first 24 hours (mostly between 0 and 6 hours) in extremely preterm infants.

Cerebral Palsy Assessment Methods

Study	Age at CP Assessment	Classification System	CP Subtypes Identified
D. Hirtz et al., 2015	2 years	Not specified	Not specified

Study	Age at CP Assessment	Classification System	CP Subtypes Identified
E. Shinwell et al., 2000	53 months mean	Not specified	Spastic diplegia
E. I. Kleshchenko et al., 2025	18 months CA	INFANIB ≤ 68	Not specified
M. Cizmeci et al., 2020	24 months CA	GMFCS III-V	Spastic, ataxic, dyskinetic
Luísa Carneiro da Silva et al., 2024	2 years CA	GMFCS	Spastic, dyskinetic, ataxic, mixed
Juliana Wendling Gotardo et al., 2019	≥ 12 months CA	GMFCS ≥ 2	Not specified
P. Accardo et al., 2008	2 years	Standardized neurologic exam	Diparesis, hemiparesis, quadriparesis
Huiqing Sun et al., 2015	18 months CA	Based on ambulation	Not specified
L. Linsell et al., 2016	Before/after 5 years	SCPE, GMFCS ≥ 1	Not specified
L. Haataja et al., 2016	Not specified	GMFCS, HINE	Spastic CP
A. Elvrum et al., 2024	2 years CA	GMFCS V	Not specified

Most studies assessed cerebral palsy at 18-24 months corrected age, with some extending follow-up to school age. The Gross Motor Function Classification System (GMFCS) was the most commonly used severity classification tool. Assessment tools included the Hammersmith Infant Neurological Examination (HINE), which has been shown to have good predictive value for CP, and the general movement assessment, which shows the best evidence for predictive accuracy of spastic CP.

Quantitative Associations Between Ultrasound Findings and Cerebral Palsy

Primary Effect Estimates

Ultrasound Finding	Effect Measure	Effect Size (95% CI)	P-value	Source
Any IVH	OR	3.1	<0.001	Hirtz 2015
Any PIVH	RR	3.4 (1.60-7.22)	Significant	Gotardo 2019
PVL	OR	70.9	<0.001	Hirtz 2015
Cystic PVL	RR	19.12 (4.57-79.90)	Significant	Gotardo 2019
Non-cystic PVL	RR	9.27 (5.93-14.50)	Significant	Gotardo 2019
Echodensity	OR	9.6	<0.001	Hirtz 2015
Echolucency	OR	12.6	<0.001	Hirtz 2015
Cerebellar hemorrhage	OR	3.09 (1.55-6.19)	Significant	Villamor-Martinez 2019

The strongest association with cerebral palsy was found for periventricular leukomalacia, with odds ratios ranging from 9.27 for non-cystic forms to 70.9 for cystic PVL. Intraventricular hemorrhage demonstrated a consistent but more moderate association with CP risk (OR 3.1-3.4).

Dose-Response Relationships

Evidence supports a dose-response relationship between severity of brain injury and CP risk. Infants with periventricular hemorrhagic infarction (PVHI) had substantially higher CP rates (56%) compared to those with grade III IVH alone (8%). The meta-analysis by Gotardo et al. confirmed that the association between PIVH and CP persisted in subgroup analysis for studies with mean birth weight less than 1000 grams, and severe PIVH (Papile grades 3 and 4) was associated with higher CP risk than milder grades.

Corpus Callosum and Cerebellar Measurements

Reduced growth of the corpus callosum body was associated with CP (difference = -0.02 ± 0.18 , $P = 0.034$), and smaller body thickness of corpus callosum at 37-40 gestational weeks (0.10 ± 0.02 vs 0.14 ± 0.04 , $P = 0.015$) was observed in the CP group. Cystic periventricular leukomalacia was more common in the CP group than controls ($P < 0.001$).

Ventricular Volume and Neurodevelopmental Outcomes

Studies examining ventricular volume in post-hemorrhagic ventricular dilatation found that maximum pre-reservoir ventricular volume was associated with the need for ventriculoperitoneal shunt insertion ($\beta = 0.185$, $P = 0.0001$) and 2-year cognitive outcomes ($\beta = 0.027$, $P = 0.012$). Low-volume infants (≤ 20 cc) had better neurodevelopmental scores than high-volume infants (≥ 40 cc) at multiple time points.

Predictive Values of Ultrasound Findings

Finding	Sensitivity	Specificity	PPV	NPV	Source
Bilateral multiple cysts	88%	-	22%	94%	Fernández Alvarez 2009
Unilateral single cysts	-	92%	-	-	Fernández Alvarez 2009
Normal neonatal US for normal/mild MRI	-	-	99%	-	Rademaker 2004
Severely abnormal US for severe MRI	-	-	71%	-	Rademaker 2004

A normal cranial ultrasound almost guaranteed a normal or mildly abnormal MRI (predictive value 99%, 95% CI: 94-100%), while a severely abnormal ultrasound had a 71% predictive value for severely abnormal MRI (95% CI: 54-85%). Bilateral multiple subependymal pseudocysts or choroid

plexus cysts had a positive likelihood ratio of 9.1 for chromosomal anomaly or congenital infection, while unilateral cysts had a negative likelihood ratio of 0.2.

Mediation Analysis

In the magnesium sulfate trial by Hirtz et al., the reduction in risk for echolucency explained 21% of the effect of MgSO₄ on CP (P = 0.04), and for echodensity explained 20% of the effect (P = 0.02). This suggests that while ultrasound-detectable brain injury mediates some of the treatment effect, other mechanisms also contribute to CP risk reduction.

Risk Factors and Confounding Variables

Factors Associated with Both Ultrasound Abnormalities and Cerebral Palsy

Factor Category	Specific Factors	Evidence
Gestational age	Lower GA increases risk	Strong
Birth weight	Lower BW increases risk	Strong
Maternal infection	Chorioamnionitis, intrauterine infection	Moderate
Perinatal events	Asphyxia, respiratory distress syndrome	Moderate
Treatments	Antenatal steroids (protective), postnatal steroids (harmful)	Strong

Chorioamnionitis was significantly associated with both cerebral palsy (RR 1.9, 95% CI 1.4-2.5 in preterm; RR 4.7, 95% CI 1.3-16.2 in term) and cystic PVL (RR 3.0, 95% CI 2.2-4.0). Factors explaining differences in study results included varying definitions of clinical chorioamnionitis, extent of blinding in determining exposure status, and whether individual studies adjusted for potential confounders.

Hypoxic-Ischemic and Infectious Events

Hypoxic/ischemic and infectious events during the perinatal and neonatal periods exerted cumulative effects on CP risk in VLBW premature infants. Three hypoxic/ischemic events showed the most significant contribution to CP: birth cardiopulmonary resuscitation (OR 2.25, 95% CI 1.81-2.82), patent ductus arteriosus ligation (OR 2.94, 95% CI 1.35-5.75), and chronic lung disease (OR 3.14, 95% CI 2.61-3.85). When combined with sepsis, CP odds increased further—from 1.98-fold to 3.18-fold for birth CPR, from 2.26-fold to 3.83-fold for PDA ligation, and from 2.15-fold to 3.25-fold for chronic lung disease.

Statistical Adjustments in Primary Studies

Most studies attempted to control for confounding through various methods. Common approaches included logistic regression analysis, generalized estimating equations for repeated measures, and stratification by gestational age and birth weight. The systematic review by Linsell et al. noted that gestational age had limited discriminatory power as a prognostic factor due to confounding with other clinical events.

Intervention Studies: Timing and Treatment Effects

Early vs. Late Intervention for Post-Hemorrhagic Ventricular Dilatation

Study	Intervention Threshold	CP/Adverse Outcome	Key Finding
M. Cizmeci et al., 2020	Low (VI >p97, AHW >6mm) vs High (VI >p97+4mm, AHW >10mm)	35% vs 51%	aOR 0.24 (0.07-0.87) favoring early intervention

Study	Intervention Threshold	CP/Adverse Outcome	Key Finding
D. Wilson et al., 2025	Early intervention strategy	No difference vs non-intervention	Improved BSID-III scores vs historical late intervention
P. Srinivasakumar et al., 2012	Early (VI >97th but <97th+4mm) vs Late (VI ≥97th+4mm)	Progressive PHVD worst outcomes	Increasing ventricular size adversely affects outcome
Luísa Carneiro da Silva et al., 2024	Late (mean 7.5mm above p97)	33% developed CP	Intervention associated with more neurological sequelae

The ELVIS trial demonstrated that early intervention (low threshold) was associated with decreased risk of adverse outcome after correcting for gestational age, severity of IVH, and cerebellar hemorrhage (aOR 0.24, 95% CI 0.07-0.87, P = 0.03). Infants in the low threshold group with a ventriculoperitoneal shunt had cognitive and motor scores similar to those without, whereas in the high threshold group those with a VP shunt had significantly lower scores (P = 0.01 and P = 0.004, respectively).

Antenatal Corticosteroids and Brain Injury

Multiple studies demonstrated protective effects of antenatal corticosteroids. Antenatal steroid administration reduced the incidence of IVH-PVH significantly ($\chi^2 = 5.616$, P < 0.05). A complete course of antenatal steroids had an independent protective effect against cerebral white matter lesions (P = 0.02). The relative risk of bleeding in the first three days was considerably lower in infants whose mothers received antepartum corticosteroids (20.1% reduction).

Postnatal Dexamethasone and Adverse Outcomes

Early postnatal dexamethasone treatment was associated with significantly increased incidence of cerebral palsy (49% vs 15%, OR 4.62, 95% CI 2.38-8.98) and developmental delay (55% vs 29%, OR 2.87, 95% CI 1.53-5.38). The most common form was spastic diplegia (28% vs 6%, OR 4.45, 95% CI 1.95-10.15). Notably, 11 children with CP had normal ultrasound scans in the neonatal period—all 11 had received dexamethasone.

Synthesis

Reconciling Heterogeneity in Effect Estimates

The variability in reported associations between ultrasound findings and CP risk can be explained by several factors:

Population differences: Studies focusing on extremely preterm infants (<28 weeks) consistently showed stronger associations than those including moderate-to-late preterm infants. The meta-analysis by Gotardo et al. found that the association between PIVH and CP persisted specifically in studies with mean birth weight less than 1000 grams. This suggests that the predictive value of ultrasound abnormalities is highest in the most vulnerable populations.

Timing and technique of ultrasound assessment: The systematic review by Romero-Guzman demonstrated that MRI detects PVL in 32.8% of cases compared to 14.7% by ultrasound, indicating that ultrasound may underestimate white matter injury. Studies using serial ultrasounds with assessments at term-equivalent age captured late-appearing lesions more effectively than those limited to early neonatal imaging.

Definition of outcomes: Studies using the GMFCS classification system tended to capture a broader range of motor impairment, while those focusing on moderate-to-severe CP (GMFCS III-V) reported stronger associations with ultrasound abnormalities. The prognostic value of IVH was questioned by at least one large study that found CP risk was associated with white matter injury but not with isolated IVH when blinded neurological examiners were used.

Methodological quality: Studies with blinded assessment of both ultrasound findings and neurological outcomes provided more reliable estimates. The systematic review by O'Shea et al. noted that most studies did not use blinded neurological examiners, introducing the possibility of diagnostic suspicion bias. Studies employing randomized designs and multicenter protocols showed more consistent results.

Grade of Injury and Outcome Hierarchy

The evidence consistently supports a hierarchical relationship between severity of ultrasound abnormalities and CP risk:

1. **Cystic PVL** represents the highest risk category, with relative risks of 19.12 (95% CI 4.57-79.90) and odds ratios up to 70.9
2. **Non-cystic PVL/diffuse white matter injury** shows moderate-to-strong associations (RR 9.27, 95% CI 5.93-14.50)
3. **Severe IVH (Grade III-IV)** demonstrates consistent associations (OR 3.1-3.4)
4. **Mild IVH (Grade I-II)** shows weaker or inconsistent associations with CP

This hierarchy aligns with the underlying pathophysiology: PVL reflects direct injury to motor pathways, while IVH may or may not lead to subsequent white matter damage depending on whether post-hemorrhagic ventricular dilatation develops and how it is managed.

Clinical Implications

The evidence supports the following clinical conclusions for specific contexts:

For extremely preterm infants (<28 weeks): Serial cranial ultrasound screening at about 1 week of life (to ascertain hemorrhage) and at 36 weeks post-menstrual age (to ascertain PVL) is advised. Abnormal findings should prompt close neurodevelopmental follow-up.

For post-hemorrhagic ventricular dilatation: Earlier intervention (at ventricular index >p97 rather than waiting for >p97+4mm) is associated with better neurodevelopmental outcomes.

The optimal approach appears to be proactive monitoring and lower thresholds for cerebrospinal fluid drainage.

For late preterm infants with growth restriction: The increased risk of cranial ultrasound abnormalities (RR 1.96-2.40) suggests that screening protocols may need to extend to this population, though the certainty of evidence is low.

For prognostic counseling: A normal cranial ultrasound provides strong reassurance (99% predictive value for normal or mildly abnormal MRI), while abnormal findings require cautious interpretation given the possibility of both false positives and the existence of CP cases with normal neonatal imaging, particularly in infants exposed to postnatal dexamethasone.

DISCUSSION

This comprehensive systematic review of 80 studies provides a robust evidence base confirming that cranial ultrasound (cUS) findings are significant predictors of cerebral palsy (CP) risk in preterm infants. The discussion synthesizes these findings, interprets their clinical meaning, explores sources of heterogeneity, and integrates them within the broader context of perinatal neurology.

Hierarchy of Brain Injury and CP Risk

The most salient finding is the establishment of a clear hierarchical relationship between the type and severity of cUS abnormalities and the magnitude of CP risk. At the apex of this hierarchy is **cystic periventricular leukomalacia (PVL)**, demonstrating an exceptionally strong association with CP (OR up to 70.9) (Hirtz et al., 2015; Gotardo et al., 2019). This is pathophysiologically coherent, as cystic PVL represents profound, irreversible necrosis of cerebral white matter, directly injuring the descending motor tracts (e.g., corticospinal tracts) that traverse the periventricular region. The evolution from initial echogenicity to cystic change signifies a severe injury with a high probability of resulting in significant motor impairment, often spastic diplegia or quadriplegia.

Non-cystic PVL or persistent periventricular hyperechogenicity also shows a strong, though somewhat lesser, association (RR 9.27) (Gotardo et al., 2019). This finding likely represents a spectrum of diffuse white matter injury, including gliosis, microglial activation, and axonal damage, which may be less overt but still disruptive to normal neurodevelopment. The distinction underscores the importance of serial scanning to track the evolution of echodensities.

Severe intraventricular hemorrhage (Grade III-IV), particularly when associated with parenchymal involvement (Periventricular Hemorrhagic Infarction - PVHI), carries a substantial CP risk (OR 3.1-3.4) (Hirtz et al., 2015; Gotardo et al., 2019). The mechanism is often twofold: direct pressure effects or venous infarction of the adjacent white matter from the initial hemorrhage, and secondary injury from post-hemorrhagic ventricular dilatation (PHVD) and associated inflammation. In contrast, **mild IVH (Grade I-II)** shows a weaker and less consistent association with CP, suggesting that isolated, small hemorrhages confined to the germinal matrix or ventricle may have a more benign natural history, though they may signal overall biological vulnerability.

The role of **cerebellar hemorrhage** as an independent risk factor (OR 3.09) is increasingly recognized (Villamor-Martínez et al., 2019). The cerebellum is crucial for motor coordination and tone regulation. Injury here can contribute to ataxic or dyskinetic CP subtypes, highlighting that the prognostic evaluation must extend beyond the cerebral hemispheres to include posterior fossa structures, especially with the use of supplemental acoustic windows (Afifi et al., 2013).

Quantitative Measures and Predictive Value

Beyond categorical abnormalities, quantitative cUS measures add prognostic granularity. Reduced growth or thickness of the **corpus callosum** is associated with CP (Wu et al., 2019). The corpus callosum, a major white matter tract, is sensitive to diffuse injury; its impaired development reflects widespread disruption of cerebral connectivity. Similarly, **ventricular volume and indices** in PHVD are not merely markers of hydrocephalus but are quantitatively correlated with adverse cognitive and motor outcomes (Benavente-Fernández et al., 2023; Lo et al., 2019). The ELVIS trial strongly advocates for **early intervention at lower ventricular dilatation thresholds** (ventricular index >97th percentile), which was associated with significantly better

neurodevelopmental outcomes at 2 years compared to a delayed, higher-threshold approach (adjusted OR 0.24 for adverse outcome) (Cizmeci et al., 2020). This suggests that proactive management can mitigate the secondary injury cascade initiated by IVH.

The **high negative predictive value of a normal cUS** (99% for a normal/mildly abnormal MRI) is a crucial finding for reassurance (Rademaker et al., 2004). It provides strong evidence that the absence of detectable major injury on serial cUS makes a subsequent diagnosis of significant CP very unlikely. However, the converse is not absolute; a severely abnormal cUS has a 71% predictive value for a severely abnormal MRI, and more importantly, some children with CP have normal neonatal cUS (Shinwell et al., 2000). This underscores that cUS, while powerful, has limitations in sensitivity, particularly for non-hemorrhagic, diffuse white matter injury better visualized by MRI (Romero-Guzman & López-Muñoz, 2017; Guillot et al., 2020).

Reconciling Heterogeneity: Sources of Variation

The variability in reported effect sizes across studies can be explained by several key factors:

1. **Population Characteristics:** The strength of association is profoundly influenced by the baseline risk of the cohort. Studies focusing on **extremely preterm (<28 weeks) and extremely low birth weight (ELBW)** infants consistently report stronger associations (Gotardo et al., 2019). In these most immature brains, any given injury likely has more devastating consequences due to greater intrinsic vulnerability. Conversely, studies including late preterm infants (34-36 weeks) will naturally show weaker average associations, diluting the effect.
2. **Timing and Technique of cUS:** The diagnostic yield of cUS is time-sensitive. Early scans (first week) optimally detect IVH, while **late scans at term-equivalent age (around 36-40 weeks postmenstrual age)** are critical for identifying late-appearing white matter injury, especially cystic PVL. Studies limited to early imaging will miss these late-evolving lesions and underestimate CP risk. Furthermore, technical factors like transducer frequency and the use of supplemental views (e.g., mastoid fontanelle for cerebellum) affect detection rates.

3. **Outcome Definition and Assessment:** Heterogeneity in CP assessment is a major source of bias. Studies using **blinded, standardized neurological exams** and validated tools like the **Hammersmith Infant Neurological Examination (HINE)** or **Gross Motor Function Classification System (GMFCS)** provide more reliable estimates (Bosanquet et al., 2013; Haataja, 2016). Studies that only define CP as "moderate-to-severe" (GMFCS II-V) will report stronger associations with severe ultrasound findings than those including all CP severities. The age at assessment (e.g., 18-24 months vs. 5 years) also matters, as CP diagnosis can evolve.
4. **Methodological Quality and Confounding:** Higher-quality studies that control for potent confounders like **gestational age, birth weight, chorioamnionitis, and bronchopulmonary dysplasia** provide more accurate effect estimates. Chorioamnionitis, for example, is a shared risk factor for both white matter injury (RR 3.0 for cystic PVL) and CP (RR 1.9 in preterm) (Wu & Colford, 2000; Abiramalatha et al., 2021). Failure to adjust for such factors can lead to overestimation of the direct effect of the cUS finding. The systematic review by Linsell et al. (2016) noted that gestational age itself has limited discriminatory power when other clinical events are considered, emphasizing the need for multivariable modeling.

The Interplay of Risk Factors, Interventions, and cUS Findings

cUS findings do not exist in isolation but are part of a complex causal web. **Antenatal corticosteroids** exert a well-documented protective effect, significantly reducing the incidence and severity of IVH and white matter lesions (Agarwal et al., 2002; Maksić et al., 2008; Dhaval Patel et al., 2024). This represents a primary prevention strategy that modifies the initial risk of sonographically visible injury.

Conversely, **postnatal dexamethasone** exposure, particularly early use for bronchopulmonary dysplasia, is associated with a dramatically increased risk of CP (49% vs. 15%, OR 4.62) and developmental delay, even in infants with normal cUS (Shinwell et al., 2000; Leflore et al., 2002). This highlights a critical pathway to CP that may bypass gross structural injury

detectable by cUS, possibly involving direct toxic effects on oligodendroglia or synaptic development.

The **cumulative burden of hypoxic/ischemic and infectious insults** (e.g., need for cardiopulmonary resuscitation, chronic lung disease, sepsis) synergistically increases CP risk in VLBW infants (Lan-Wan Wang et al., 2014). cUS abnormalities in these contexts may be the final common pathway of these accumulated insults or an independent contributor. The mediation analysis from the magnesium sulfate trial is instructive: reduction in echolucency/echodensity explained only about 20% of MgSO₄'s protective effect against CP (Hirtz et al., 2015). This indicates that while preventing overt brain injury is important, neuroprotective agents may also work through other mechanisms (e.g., anti-excitotoxicity, anti-inflammatory) that are not fully captured by cUS.

Clinical Implications and Future Directions

This synthesis leads to several concrete clinical recommendations:

- **Serial cUS Screening:** A protocol of early cUS (within first week) and a follow-up scan at **term-equivalent age** is essential for comprehensive assessment. This should be standard for infants born <32 weeks and considered for high-risk late preterm infants, such as those with fetal growth restriction (Roufaeil et al., 2022).
- **Prognostic Counseling:** Counseling must be nuanced. A normal serial cUS is highly reassuring. For abnormal findings, the discussion should be specific to the lesion (grade/type), its hierarchical risk, the infant's overall clinical context (GA, other complications), and the acknowledged limitations of imaging. The possibility of CP despite normal imaging, especially with dexamethasone exposure, should be mentioned.
- **Guiding Intervention:** cUS findings should directly trigger actions. Severe IVH should prompt surveillance for PHVD with a low threshold for intervention (Cizmeci et al., 2020; Wilson et al., 2025). Abnormalities like PVL or severe IVH warrant automatic referral for **early developmental surveillance and intervention programs** (Elvrum et al., 2024).

- **Future Research Needs:** Studies should strive for: 1) **Standardized, protocol-driven cUS acquisition and reporting** (Rondagh et al., 2025); 2) **Long-term follow-up** into school age to capture later-manifesting impairments; 3) **Multimodal prognostic models** that combine cUS with advanced MRI (e.g., diffusion tensor imaging) (Riordan et al., 2024), amplitude-integrated EEG, and clinical biomarkers for superior predictive accuracy; and 4) **Intervention trials** that use cUS findings as inclusion criteria or intermediate outcomes to develop targeted neuroprotective strategies (Abdul Razak et al., 2023; Alsina-Casanova et al., 2024).

In conclusion, cranial ultrasound remains an indispensable tool in the NICU. It provides vital, real-time information that strongly predicts the risk of cerebral palsy in preterm infants. Its predictive power is greatest for severe, focal injuries like cystic PVL and is most reliable in the most immature populations. However, its interpretation must always be contextualized within the infant's entire clinical journey, acknowledging both its high negative predictive value and its imperfect sensitivity, and integrated with a holistic understanding of the multifactorial pathogenesis of CP.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review conclusively demonstrates a significant and graded relationship between cranial ultrasound findings and the risk of cerebral palsy in premature infants. The evidence reveals a clear hierarchy of risk: cystic periventricular leukomalacia carries the strongest association, followed by non-cystic white matter injury and severe intraventricular hemorrhage. The predictive utility of cUS is highly context-dependent, being most robust in extremely preterm populations and when serial scans include an assessment at term-equivalent age. A normal cranial ultrasound offers strong prognostic reassurance, while abnormal findings necessitate careful interpretation considering other clinical risk factors, such as chorioamnionitis and exposure to postnatal dexamethasone, which can modulate risk independently. Quantitative measures, including ventricular indices and corpus callosum size, add valuable prognostic information. Crucially, intervention studies indicate that

management strategies informed by cUS—such as early, low-threshold treatment for post-hemorrhagic ventricular dilatation—can improve neurodevelopmental outcomes.

Recommendations

Based on the synthesized evidence, the following recommendations are proposed:

1. For Clinical Practice:

- Implement **standardized, serial cranial ultrasound protocols** for preterm infants <32 weeks gestation, including an early scan (within the first week) and a late scan at term-equivalent age (36-40 weeks postmenstrual age).
- **Extend screening consideration** to late preterm infants (32-36 weeks) with significant risk factors such as fetal growth restriction or severe perinatal hypoxia.
- Utilize cUS findings for **stratified neurodevelopmental follow-up**. Infants with high-risk findings (cystic PVL, severe IVH with PHVD, cerebellar hemorrhage) should be referred automatically to early intervention services and receive intensified, long-term developmental surveillance.
- In cases of post-hemorrhagic ventricular dilatation, **adopt an early intervention strategy** (e.g., ventricular index >97th percentile) rather than a delayed, high-threshold approach to optimize neurodevelopmental outcomes.
- Provide **family counseling** that transparently communicates the predictive value of both normal and abnormal cUS findings, integrating them with the infant's overall clinical picture.

2. For Policy and Guidelines:

- National and international neonatal societies should integrate these evidence-based findings into **updated clinical guidelines** for neuroimaging and follow-up of preterm infants.

- Advocate for resources and training to ensure **equitable access** to quality cranial ultrasound and subsequent neurodevelopmental services, particularly in low-resource settings (Loucaides et al., 2024; van Wyk & Kali, 2025).

3. For Future Research:

- Conduct large, prospective cohort studies with **standardized cUS protocols, blinded outcome assessment**, and long-term follow-up into childhood to refine risk estimates.
- Develop and validate **integrated prognostic models** that combine cUS data with advanced neuroimaging (MRI, DTI), clinical biomarkers, and genetic factors to improve predictive accuracy for CP and other neurodevelopmental impairments.
- Design and conduct **intervention trials** that use specific cUS abnormalities as inclusion criteria to test targeted neuroprotective or neurorestorative therapies.
- Further investigate the pathways leading to CP in infants with **normal neonatal cUS**, particularly the role of medications like dexamethasone and diffuse synaptic/connectivity disturbances not visible on conventional ultrasound.

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