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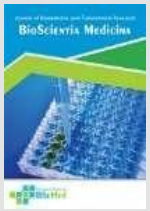

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The Mosaic of Risk in Neonatal Asphyxia: A Systematic Review of Clinical, Placental, and Systemic Predictors

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A B S T R A C T

Background: Neonatal asphyxia, a critical failure of gas exchange during the perinatal period, remains a primary cause of neonatal mortality and long-term neurodevelopmental disability worldwide, including hypoxic-ischemic encephalopathy (HIE). Its etiology is a complex mosaic of interconnected factors. Understanding this intricate risk profile is essential for developing effective prevention and intervention strategies. The aim of this study is to systematically review and synthesize recent evidence (published 2019–2025) on the spectrum of maternal, fetal, intrapartum, placental, and systemic risk factors associated with neonatal asphyxia. **Methods:** This systematic review was conducted following the PRISMA guidelines. A comprehensive literature search was performed in PubMed, ScienceDirect, and Google Scholar for observational studies published between January 1st, 2019, and April 1st, 2025. Dual reviewers independently conducted study selection, data extraction, and risk of bias assessment using the Newcastle-Ottawa Scale (NOS). Due to significant clinical and methodological heterogeneity, a narrative synthesis was performed. **Results:** The search yielded 870 articles, from which 13 observational studies met the inclusion criteria. The synthesis of these studies revealed a consistent and powerful link between neonatal asphyxia and a wide array of predictors. Key factors included maternal comorbidities (hypertensive disorders), prenatal maternal psychological stress, intrapartum complications (prolonged labor, meconium-stained amniotic fluid), placental pathology (maternal vascular malperfusion, meconium-associated changes), fetal characteristics (low birth weight), and crucial systemic factors, such as maternal immigrant status and sociodemographic disparities. Predictive models developed in two of the included studies demonstrated good discriminative performance in identifying high-risk pregnancies, offering potential for clinical application. **Conclusion:** Neonatal asphyxia arises from a complex interplay of risk factors that span the entire perinatal continuum, from pre-conceptual maternal health and systemic inequities to acute intrapartum events. Effective mitigation requires a multi-pronged approach encompassing comprehensive antenatal care that addresses both physical and mental health, vigilant intrapartum monitoring, and systemic efforts to ensure equitable access to high-quality perinatal care. The integration of validated risk prediction tools into clinical practice holds significant promise for reducing the global burden of this devastating condition.

1. Introduction

Birth asphyxia, a condition defined by impaired blood-gas exchange around the time of birth, leads to a dangerous triad of hypoxemia, hypercapnia, and metabolic acidosis.[1] It remains one of the most formidable challenges in modern perinatology and a leading cause of neonatal morbidity and mortality across the globe.[2] The consequences of asphyxia are dire, ranging from immediate threats to survival, such as the devastating neurological syndrome of hypoxic-ischemic encephalopathy (HIE), to a lifetime of neurodevelopmental impairments, including cerebral

palsy, epilepsy, and significant cognitive deficits.[3] Despite major advances in obstetric and neonatal care, the burden of asphyxia remains unacceptably high, particularly in low- and middle-income countries (LMICs), where resources for timely and effective intervention are often scarce.[2,4]

Understanding the risk factors for neonatal asphyxia is the cornerstone of prevention. The etiology is not a single event but rather a culmination of insults, best conceptualized as a "causal pathway" where risk factors are interconnected across multiple domains.[5] This multifactorial nature encompasses maternal, fetal, placental, and health system-related determinants.[6] The pathway to injury may begin long before labor, with pre-existing maternal conditions such as hypertensive disorders, gestational diabetes, and obesity compromising the intrauterine environment and fetal oxygenation.[7,8] This pre-existing vulnerability can then be exacerbated by acute intrapartum complications. Events like prolonged labor, the presence of meconium-stained amniotic fluid, and the need for instrumental or emergency cesarean deliveries are frequently identified as proximal triggers for asphyxia.[9,10]

In recent years, the research focus has expanded beyond these well-established obstetric factors. There is a growing appreciation for the critical role of placental pathology in the pathogenesis of birth asphyxia. Both acute inflammatory abnormalities like chorioamnionitis and, perhaps more importantly, chronic lesions indicative of maternal or fetal vascular malperfusion have been definitively linked to hypoxic conditions at birth.[11,12] This highlights the placenta as a vital chronicle of antepartum and intrapartum health, offering crucial clues to the timing and nature of fetal injury.[12] Furthermore, the lens of inquiry is widening to include crucial socio-demographic and systemic contributors. Emerging evidence demonstrates that factors such as maternal immigrant status, particularly for women from low-income regions, and other markers of socioeconomic disadvantage are associated with a significantly higher risk of adverse neonatal outcomes, including HIE.[13,14] These findings suggest that inequities in healthcare access, communication barriers, and the chronic stress of marginalization may play a powerful role, independent of other clinical risk factors.[13] The impact of the recent COVID-19 pandemic on pregnancy outcomes and asphyxia risk has also been a subject of investigation, although findings remain inconclusive.[15]

Given this expanding and increasingly complex body of evidence, clinicians and policymakers require a consolidated understanding of the current risk landscape. Several predictive models have been developed to stratify at-risk newborns, showing promise for improving perinatal outcomes through early triage and focused care, especially in resource-limited settings.[16,17] While individual studies offer valuable insights, a systematic review is necessary to synthesize these disparate findings, identify consistent patterns, and highlight gaps in the evidence across different populations and healthcare contexts.[18,19] The novelty of this study lies in its synthesis of very recent evidence (from the last five years) to construct a holistic and integrated model of asphyxia risk. Unlike previous reviews that may have focused on discrete risk categories, this work intentionally draws together clinical, placental, psychosocial, and systemic factors to illustrate their complex interplay. By focusing on contemporary research, it provides an up-to-date snapshot of the field, highlighting emerging areas of concern such as maternal mental health and systemic inequities. The primary aim of this systematic review is to identify, critically appraise, and synthesize the current evidence on the multifactorial predictors of neonatal asphyxia, with the goal of informing clinical practice, guiding future research, and contributing to perinatal health policy.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The objective was to identify,

critically appraise, and synthesize evidence on the full spectrum of risk factors—including maternal, intrapartum, neonatal, and health system-related determinants—associated with neonatal asphyxia. A comprehensive literature search was conducted across three major electronic databases: PubMed, ScienceDirect, and Google Scholar, to capture both peer-reviewed and grey literature. The search was restricted to studies published in the English language between January 1st, 2019, and April 1st, 2025, to ensure a focus on the most current evidence.

The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords to maximize sensitivity. The core search terms included: “birth asphyxia”, “neonatal asphyxia”, “perinatal asphyxia”, “hypoxic ischemic encephalopathy”, “low Apgar score”, “5-minute Apgar”, “resuscitation at birth”, “maternal risk factors”, “obstetric complications”, “placental pathology”, “prolonged labor”, “meconium-stained amniotic fluid”, “nuchal cord”, “instrumental delivery”, “low birth weight”, “preterm birth”, “neonatal outcome”, and “newborn mortality”. Boolean operators (AND, OR) were used to combine these terms into a comprehensive search string. Additionally, the reference lists of all included studies and relevant review articles were manually scanned to identify any further eligible publications (a process known as "snowballing").

Studies were selected for inclusion based on a predefined set of criteria structured around the Population, Exposure, Comparator, Outcome, and Study design (PECOS) framework. Population: Neonates of ≥34 weeks of gestation with a clinical diagnosis of neonatal asphyxia. Asphyxia was variably defined across studies, including criteria such as low Apgar scores (typically <7 at 5 minutes), the need for extensive resuscitation at birth, or a formal diagnosis of hypoxic-ischemic encephalopathy (HIE). Exposure: Any reported maternal, fetal, perinatal, placental, or systemic factor investigated as a potential predictor or risk factor for neonatal asphyxia. Comparator: Implicitly, neonates without a diagnosis of neonatal asphyxia within the same study population (for case-control and cohort designs). Outcome: The incidence or presence of neonatal asphyxia (as defined by the primary study) as a primary or secondary outcome. Study type: Observational studies, including cohort (prospective and retrospective), case-control, and cross-sectional designs. Exclusion criteria were: (1) studies involving animal subjects or children beyond the neonatal period; (2) case reports, conference abstracts, editorials, and reviews without original data; (3) studies that did not report neonatal asphyxia or a closely related outcome (HIE); and (4) articles not published in English.

All retrieved citations were imported into a reference management software, and duplicates were removed. Two reviewers independently screened the titles and abstracts of the remaining articles against the eligibility criteria. The full texts of potentially relevant articles were then retrieved and assessed for final inclusion, again by both reviewers independently. Any disagreements at either stage were resolved through discussion and consensus or, if necessary, by consultation with a third party. A standardized data extraction form was developed and used to extract relevant information from the included studies. The extracted data included: first author’s name, year of publication, country of study, study design, sample size, participant characteristics (maternal age, gestational age, neonatal gender, birth weight), specific risk factors investigated, outcome definitions, and key findings related to neonatal asphyxia. This process was also conducted by two independent reviewers, with cross-verification to ensure accuracy.

The methodological quality and risk of bias of each included study were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS is a validated tool designed to evaluate the quality of non-randomized studies, assessing three key domains: (1) Selection of study groups; (2) Comparability of the groups; and (3) Ascertainment of either the exposure or outcome of interest. Discrepancies in quality assessment were resolved through discussion to reach a consensus. The results

of this assessment were not used to exclude studies but rather to inform the synthesis and interpretation of the evidence, with greater weight given to findings from studies judged to be at a lower risk of bias. A formal meta-analysis was not conducted due to the substantial heterogeneity across the included studies in terms of study design, population characteristics, specific risk factors investigated, and, most importantly, the definitions of neonatal asphyxia. Instead, a qualitative narrative synthesis of the findings was performed. The results were grouped thematically based on the primary category of risk factor (maternal, intrapartum, placental, systemic) to provide a structured and comprehensive overview of the current evidence. Subgroup analyses based on study setting (high-income vs. low- and middle-income countries) were explored within the narrative to provide context and enhance the interpretation of the findings.

3. Results

The PRISMA flow diagram presented in Figure 1 serves as a transparent and systematic roadmap, meticulously documenting the journey of scientific inquiry from a vast ocean of literature to the final, curated set of studies that form the evidence base for this review. The process began with an ambitious and comprehensive search strategy designed to capture the widest possible range of relevant literature. By querying major scientific databases, including PubMed and ScienceDirect, the initial search yielded a substantial pool of 870 records. This large number reflects the breadth of research interest in perinatal health and underscores the necessity of a systematic approach to navigate such a dense field. This initial phase represents the "wide net" cast to ensure that no potentially significant study was overlooked. The screening phase was a multi-step process designed to methodically reduce the initial volume of literature to a manageable and relevant subset. The first critical step was an automated process of tidying the data. A significant number of duplicate records (397), where the same study was identified in multiple databases, were removed. This was followed by the automated exclusion of 86 records that clearly did not meet the basic criteria of being original research articles (editorials, commentaries). This initial culling left 387 articles for the crucial phase of human intellectual review. At this stage, researchers screened the titles and abstracts of each article against the predefined inclusion criteria. This represents the most significant filtering step, where the vast majority of articles were found to be irrelevant to the specific research question. A total of 322 records were excluded during this abstract screening, demonstrating the highly focused nature of this review and the efficiency of the screening process in identifying pertinent research. Having been narrowed down to 65 potentially relevant studies, the process moved to the most rigorous phase: full-text eligibility assessment. The complete manuscript for each of these 65 articles was sought for retrieval. Logistical challenges, a common reality in research, made 3 reports inaccessible. The remaining 62 full-text articles were then read and assessed in their entirety by the review team. This deep dive allowed for a definitive evaluation against the stringent eligibility criteria. It is at this stage that nuances not apparent in the abstract are revealed. Consequently, a further 29 reports were excluded. Reasons for exclusion at this point typically include the study not reporting the specific outcome of interest (i.e., neonatal asphyxia), employing a study design that was not eligible, or focusing on a different patient population (extremely preterm infants). This meticulous, multi-layered filtering process, which began with 870 articles, ultimately culminated in a final, robust dataset of 13 studies. These 13 articles represent the core evidence synthesized in this review.

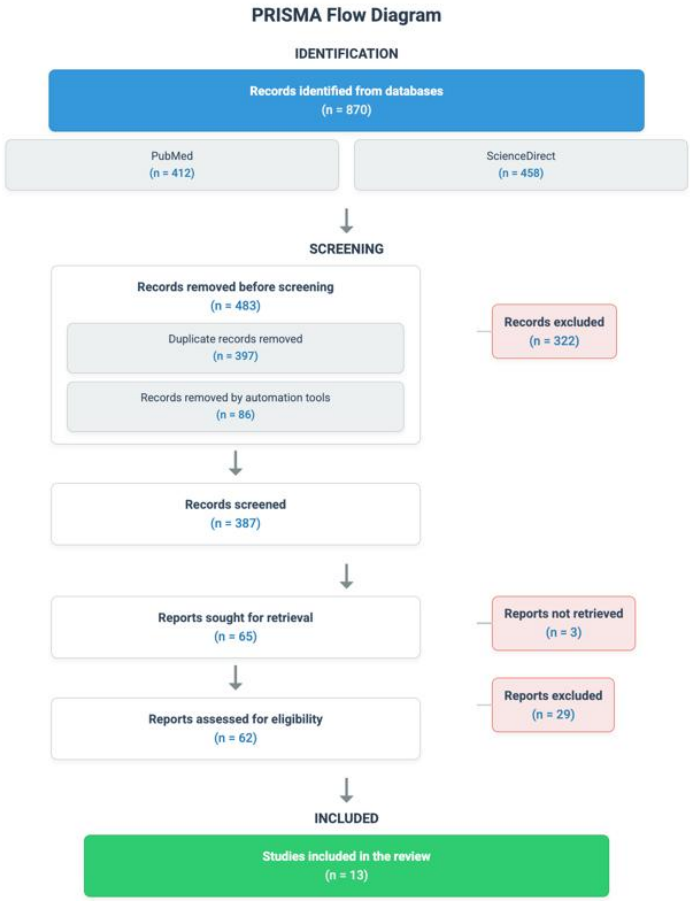

Figure 1. PRISMA flow diagram.

Table 1 provides a compelling panoramic view of the current global research landscape surrounding neonatal asphyxia. By assembling 13 key studies from a diverse array of countries—spanning Europe (Germany, Italy, Sweden), Asia (China, India, Saudi Arabia), North America (USA, Canada), and Africa (Ethiopia)—the table illustrates the universal nature of this perinatal challenge while also highlighting context-specific insights. The collection of studies, varying in design from large-scale population-based cohorts to focused prospective investigations, collectively reinforces a central theme: the risk of neonatal asphyxia is a complex mosaic, pieced together from factors across the entire perinatal continuum. The table immediately draws attention to the profound influence of pre-existing maternal conditions. Studies from diverse settings like China (Song et al.) and Saudi Arabia (Almuqbil et al.) confirm the well-established link between maternal comorbidities like obesity, GDM, and other health issues and an increased risk of asphyxia. However, the most striking finding in this domain comes from Germany (Aldinger et al.), which reports a staggering 51-fold increased risk associated with prenatal maternal psychological stress. This powerful statistic signals a paradigm shift, urging the clinical community to consider maternal mental health not as a secondary concern but as a primary biological risk factor. This theme of pre-existing vulnerability is further expanded by research from Sweden (Törn et al.). Their massive population-based study reveals that systemic factors, such as being born to an immigrant mother from a low-income country, nearly double the risk of HIE**.** This finding powerfully

demonstrates that social and systemic inequities can become biologically embedded, creating a foundation of risk that is independent of purely clinical factors. Several studies shift the focus to the fetal-placental unit as a critical site of vulnerability. A landmark multicenter analysis from the USA (Chalak et al.) reveals that an overwhelming 85% of infants with HIE have placental abnormalities**,** a mix of both chronic and acute issues. This is complemented by work from Italy (Alongi et al.), which specifically identifies meconium-associated changes as a key placental marker for asphyxia. Together, these findings position the placenta as a vital chronicle of pregnancy health, with its pathology often telling the story of why an adverse event occurred. The fetus itself is also a key variable. The study of twins from China (Cui et al.) provides dramatic evidence of the danger of low birth weight, with the smallest infants (<1500g) facing an asphyxia rate of over 64%. This finding, supported by research in Ethiopia (Jena et al.), underscores that a growth-restricted fetus is a highly vulnerable fetus, lacking the physiological reserves to tolerate the stress of birth. The table confirms the critical role of events during labor and delivery. Prospective research from India (Acharya et al.) shows a direct and significant link between prolonged labor, meconium-stained fluid, and the severity of asphyxia. This is strongly corroborated by studies in Ethiopia (Jena et al.), which quantify the high odds ratios associated with instrumental and cesarean deliveries—not as causes, but as markers of an already complicated labor that required intervention. Finally, the table highlights a forward-looking trend in research: the development of predictive tools. Studies from both Ethiopia (Tesfa et al.) and China (Yu et al.) successfully developed and tested risk-scoring models. The high predictive performance (AUROC of 88.6%) of the simple clinical tool in the low-resource Ethiopian setting is particularly noteworthy, offering a tangible strategy for identifying high-risk pregnancies and allocating resources more effectively.

Table 1. Characteristics of included studies.

NO.	AUTHOR, YEAR	STUDY DESIGN & SAMPLE SIZE	PARTICIPANT POPULATION	KEY RESULTS RELATED TO ASPHYXIA
1	Aldinger et al., 2024 (Germany)	*Retrospective cohort* = 3,368	Women delivering at University Hospital Tübingen.	Prenatal maternal psychological stress (PMPS) was significantly associated with a higher risk of neonatal asphyxia. Newborns of stressed mothers had a 51-fold increased risk (p < 0.001).
2	Cui et al., 2021 (China)	*Retrospective cohort* = 5,337	Twin newborns from multiple centers.	Low birthweight was a strong predictor. Twins weighing <1500g had the highest asphyxia rate at 64.8% . Higher birthweight independently reduced risk (OR 0.772 , p < 0.001).
3	Almuqbil et al., 2023 (Saudi Arabia)	*Retrospective case-control* = 294	Neonates born at King Abdullah Children's Specialist Hospital.	Maternal comorbidities and prepartum/intrapartum complications were significantly associated with a higher risk of HIE. Cases were twice as likely to be born to mothers with comorbidities.
4	Coleila et al., 2024 (France)	*Retrospective cohort* = 213	Near- to full-term neonates with umbilical vein catheterization.	Controlled therapeutic hypothermia (CTH) for HIE was an independent risk factor for portal vein thrombosis (PVT) (aOR 1.94 , p = 0.04).
5	Acharya et al., 2020 (India)	*Prospective cohort* = 150	Term babies (≥2.5kg) with birth asphyxia in Odisha.	Prolonged labor (87.8%) and meconium-stained liquor (63.4%) were significantly associated with severe birth asphyxia (p < 0.001) and mortality.
6	Alongi et al., 2023 (Italy)	*Retrospective case-control* = 323	Term and near-term infants (≥35 weeks).	Meconium-associated changes (MAC) in placental tissue were observed only in asphyxiated newborns (p = 0.039), suggesting it as a key placental marker over other lesions.
7	Tesfa et al., 2022 (Ethiopia)	*Prospective cohort* = 404	Pregnant women in South Gondar Zone Hospitals.	Developed a clinical risk score model that showed high predictive performance (AUROC of 88.6%) for birth asphyxia in a low-resource setting.
8	Chalak et al., 2021 (USA)	*Multicenter trial analysis* = 500	Term newborns with moderate to severe HIE.	A high prevalence (85%) of placental abnormalities was found in infants with HIE, with a mix of acute (e.g., meconium staining) and chronic (e.g., MVM) lesions.
9	Wood et al., 2021 (Canada)	*Retrospective cohort*,Large provincial registry	Singleton term/near-term infants in Alberta.	Asphyxia rates were slightly higher in urban vs. rural hospitals (OR 1.86), but hospital volume or location were not predictors of HIE severity.
10	Yu et al., 2022 (China)	*Retrospective multicenter cohort* = 87,545	Term and late-preterm infants in economically developed regions.	A predictive model based on maternal/perinatal factors showed good discrimination (c-statistic of 0.731) for identifying newborns at risk of asphyxia.
11	Törn et al., 2021 (Sweden)	*Population-based cohort* = 726,730	Term/near-term singleton births.	Offspring of women born in low-income countries had a nearly 2-fold higher risk of HIE compared to offspring of Swedish-born mothers.
12	Jena et al., 2024 (Ethiopia)	*Community-based case-control* = 2,548	Pregnant women in Hadiya Zone.	Identified key determinants including C-section (AOR 3.81), instrumental delivery (AOR 3.91), and low birth weight (AOR 6.52).
13	Song et al., 2022 (China)	*Retrospective cohort* = 15,065	Pregnant women categorized by BMI and GDM status.	Maternal overweight/obesity (pre-pregnancy BMI ≥24) and GDM were significantly associated with an increased risk of multiple adverse outcomes, including neonatal asphyxia.

Abbreviations: ***AOR:*** *Adjusted Odds Ratio;* ***AUROC:*** *Area Under the Receiver Operating Characteristic Curve;* ***BMI:*** *Body Mass Index;* ***CTH:*** *Controlled Therapeutic Hypothermia;* ***GDM:*** *Gestational Diabetes Mellitus;* ***HIE:*** *Hypoxic-Ischemic Encephalopathy;* ***MAC:*** *Meconium-Associated Changes;* ***MVM:*** *Maternal Vascular Malperfusion;* ***OR:*** *Odds Ratio;* ***PMPS:*** *Prenatal Maternal Psychological Stress;* ***PVT:*** *Portal Vein Thrombosis;* ***RR:*** *Relative Risk.*

Table 2 provides a crucial lens through which to view the findings of this systematic review, offering a transparent and critical appraisal of the methodological rigor of the 13 included studies. Using the well-established Newcastle-Ottawa Scale (NOS), this assessment moves beyond simply reporting study results to evaluating their trustworthiness. The overall picture that emerges is one of a generally strong but imperfect evidence base, where readers are empowered to understand not just what was found, but how confidently those findings should be interpreted. At a glance, the table is reassuring. All 13 studies were rated as being of "Good" overall quality, achieving high total scores of 8 or 9 out of a possible 9. This indicates that the foundational elements of sound observational research—such as clearly defined study populations, reliable methods for identifying cases and exposures, and adequate follow-up—were largely in place. The consistently high scores in the Selection and Outcome/Exposure domains suggest that the studies were successful in identifying representative groups and accurately measuring the key variables of interest. This provides a solid bedrock for the review's conclusions, assuring the reader that the synthesized findings are not derived from methodologically flawed research. The most critical insights from Table 2 come from a closer look at the Comparability domain. This is where the inherent challenges of observational research become apparent. While all studies received at least one star for controlling for the most important confounder, several received only one out of a possible two stars. This consistent weakness highlights the single greatest threat to the validity of the findings: residual confounding. For example, studies by Cui et al. on twins and Song et al. on maternal BMI and GDM had limited control for complex variables. This means that while an association was found, it might be partially explained by other unmeasured factors (specific lifestyle behaviors, genetic predispositions, or healthcare-seeking patterns). Similarly, the large registry-based studies (Wood et al., Törn et al.), while excellent in their sample size and selection, are often limited by the data available. They may lack the clinical granularity to control for nuanced factors like the severity of a comorbidity or specific cultural behaviors, which could influence the outcome. Recognizing this limitation is essential; it means interpreting the reported odds ratios not as precise measures of a single factor's effect, but as strong signals of association that exist within a complex web of interrelated variables. The table also wisely points out the inherent biases associated with specific study designs. The case-control studies (Almuqbil et al., Jena et al.) are flagged for their susceptibility to selection and recall bias. Retrospective cohort studies (Aldinger et al., Colella et al.) are noted for their potential information bias, as they rely on medical records that may be incomplete or inconsistently documented. By explicitly stating these potential biases, the table equips the reader with the necessary context for critical appraisal. It encourages a thoughtful interpretation; for instance, when considering the dramatic 51-fold risk associated with maternal stress found by Aldinger et al., this table reminds us that this finding comes from a retrospective design where unmeasured confounders could play a role. This does not invalidate the finding, but it frames it as a powerful hypothesis that warrants further investigation with prospective designs.

Table 2. Risk of bias assessment of included studies.

STUDY	SELECTION (MAX 4★)	COMPARABILITY (MAX 2★)	OUTCOME / EXPOSURE (MAX 3★)	TOTAL SCORE	OVERALL QUALITY	KEY POTENTIAL SOURCES OF BIAS
Aldinger et al., 2024	★★★★	★★	★★★	9	Good	Retrospective design may be prone to information bias from medical records. Confounding by unmeasured variables (e.g., diet, substance use) is possible.
Cui et al., 2021	★★★★	★☆	★★★	8	Good	Limited control for key confounders in twin pregnancies (e.g., chorionicity). Cross-sectional elements limit causal inference.
Almuqbil et al., 2023	★★★★	★★	★★★	9	Good	Case-control design is susceptible to selection bias and recall bias regarding exposure history, though mitigated by record use.
Celella et al., 2024	★★★★	★☆	★★★	8	Good	Retrospective cohort. Comparability is a concern; indication for UVC and severity of illness may confound the association with PVT.
Acharya et al., 2020	★★★★	★☆	★★★	8	Good	Prospective cohort, but small sample size from a single center may limit generalizability. Limited control for confounding factors reported.
Alongi et al., 2023	★★★★	★★	★★★	9	Good	Well-controlled case-control study. Potential for selection bias in how controls were chosen remains a minor concern.
Tesfa et al., 2022	★★★★	★★	★★★	9	Good	Prospective design is a major strength. Low risk of bias, though outcome assessment may have some inter-rater variability.
Chalak et al., 2021	★★★★	★★	★★★	9	Good	High-quality data from a multicenter trial. Selection bias is minimal. Analysis is robust.
Wood et al., 2021	★★★★	★☆	★★★	8	Good	Large registry-based study minimizes selection bias but is limited by the variables available in the dataset; risk of residual confounding.
Yu et al., 2022	★★★★	★★	★★★	9	Good	Very large multicenter cohort. Main limitation is reliance on administrative data which may lack clinical granularity.
Törn et al., 2021	★★★★	★★	★★★	9	Good	Excellent population-based study with low risk of selection bias. Some risk of unmeasured confounding from cultural or behavioral factors.
Jena et al., 2024	★★★★	★☆	★★★	8	Good	Case-control design carries inherent risk of recall bias for exposures and selection bias (e.g., referral patterns for cases).
Song et al., 2022	★★★★	★☆	★★★	8	Good	Retrospective cohort. The link between BMI/GDM and asphyxia may be confounded by other lifestyle or healthcare-seeking behaviors.

Note: The Risk of Bias was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies.

- **Selection:** Assesses the representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure.
- **Comparability:** Assesses the control for important confounding factors. A study receives one star if it controls for the most important factor and a second star if it controls for any additional factors.
- **Outcome/Exposure:** Assesses the method of outcome assessment, length of follow-up, and adequacy of follow-up.
- **Overall Quality:** Rated based on total score (e.g., ≥7 as 'Good').

Figure 2 provides a powerful conceptual framework that transforms the complex findings of this review into an intuitive and compelling visual narrative. The diagram strategically places the systemic & sociodemographic and maternal (Antepartum) factors at the top, representing the foundational, often chronic, "first hits" that establish a baseline of vulnerability long before labor begins. The "Systemic" category, encompassing factors like maternal immigrant status and socioeconomic disadvantage, broadens the lens beyond the individual to society itself, suggesting that social and economic pressures create a physiological burden that compromises pregnancy health. Beside it, the "Maternal Factors" domain highlights the impact of the mother's own health, including both physical comorbidities like

hypertension and GDM, and, critically, the profound influence of prenatal psychological stress. Together, these two domains represent the environment—both internal and external—in which the pregnancy develops. They set the stage, creating a compromised physiological state that renders the fetus less able to withstand future challenges. Positioned below are the Placental and Fetal Factors, which act as mediators, translating the upstream risks into a tangible, compromised state. The Placental domain, with factors like maternal vascular malperfusion and chronic lesions, serves as the physical record of the long-standing insults originating from maternal or systemic issues. It is the "black box recorder" of the pregnancy, providing histological proof of a struggle for oxygen and nutrients. The Fetal domain, highlighting low birth weight/FGR and preterm birth, represents the direct consequence of this struggle. A growth-restricted fetus is not merely small; it is a fetus that has already adapted to a hostile environment and has depleted its physiological reserves. These two domains are crucial because they bridge the gap between chronic risk and acute crisis. Finally, the diagram presents the Intrapartum Factors as "The 'Final Hit'." This domain, which includes challenges like prolonged labor, meconium-stained fluid, and abnormal fetal heart rate, represents the acute stressor that pushes the already vulnerable fetus over the metabolic edge. A healthy, well-supported fetus can typically tolerate the rigors of labor. However, for the fetus that has already been weathered by systemic disadvantage, compromised by maternal illness, and under-supported by a poorly functioning placenta, this final series of events becomes an insurmountable challenge. The inclusion of "Operative Delivery (Marker)" is a sophisticated touch, correctly framing it not as a cause but as a sign of the underlying distress that necessitated the intervention.

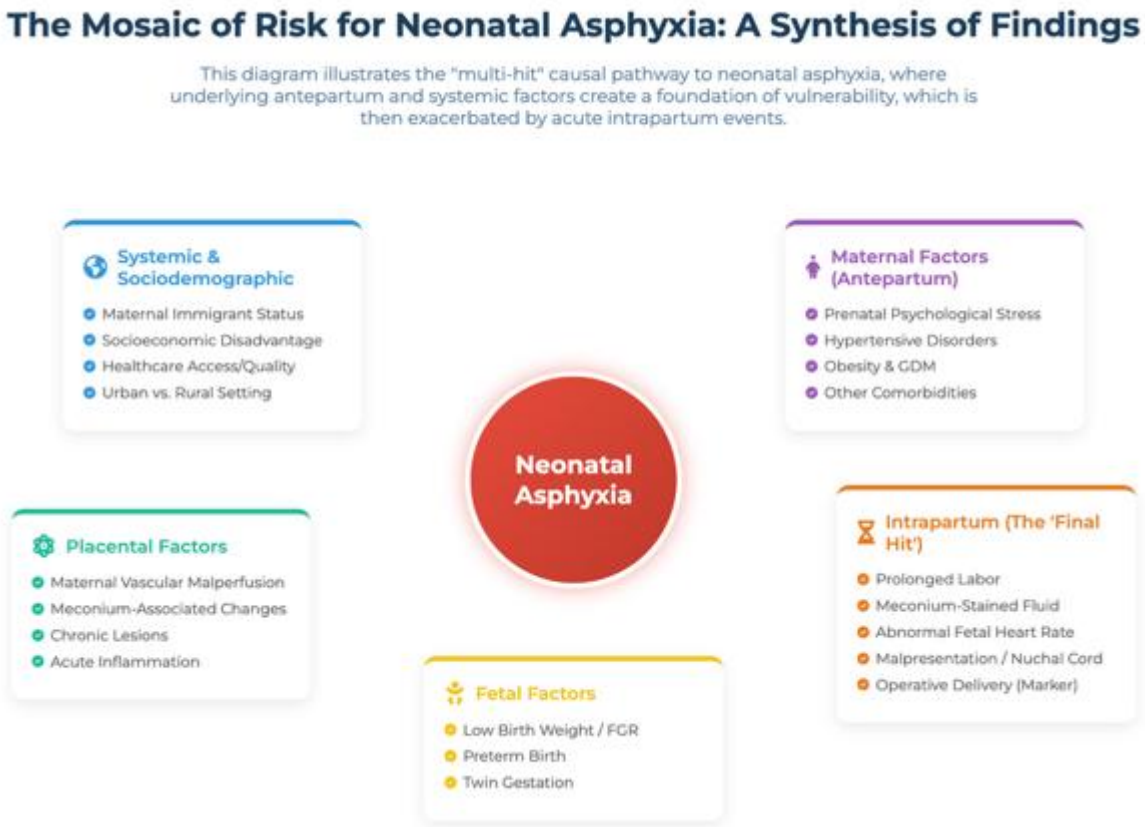

Figure 2. Synthesis of findings.

4. Discussion

The central unifying theory that emerges from this review is that neonatal asphyxia is rarely a single, sudden, unpredictable event. More commonly, it is the final, devastating step in a "multi-hit" process, a concept well-established in other fields of medicine like oncology. The "first hits" are the insidious antepartum and systemic factors that compromise the fetal-placental unit long before labor begins, eroding its physiological reserve. The "second hit" is the acute, often predictable, stressor of labor itself, which a healthy, well-supported fetus can tolerate, but a compromised one cannot. This review provides robust evidence for the constellation of "first hits." These include chronic maternal somatic illnesses like hypertension and diabetes,[7] which, as discussed below, fundamentally alter the placental vasculature and create a state of chronic substrate and oxygen deprivation. The evidence on placental pathology, particularly chronic maternal vascular malperfusion (MVM), provides a direct histological signature of this long-standing compromise.[11,12] The profound finding on prenatal maternal psychological stress (PMPS) introduces a critical psychosocial "first hit," operating through complex neuroendocrine pathways that can likewise impair placental function and prime the fetus for injury.[6] Furthermore, systemic factors, such as the disadvantages faced by immigrant women in high-resource settings[13], represent another layer of "first hits," contributing to a chronic allostatic load that becomes biologically embedded as reduced physiological reserve.

The fetus subjected to these "first hits" enters labor not as a blank slate, but in a precarious state of compensated stress. It has diminished glycogen stores, borderline oxygenation, and potentially a pre-activated inflammatory system. At this point, the "second hit" arrives in the form of an acute intrapartum complication. This could be prolonged labor with its attendant repetitive uterine contractions reducing intervillous blood flow,[9,21] a tight nuchal cord causing direct umbilical cord compression[22], or the aspiration of thick meconium leading to airway obstruction and severe pulmonary hypertension.[9] This "second hit" pushes the already vulnerable fetus over the metabolic cliff, from a state of compensated hypoxia into the dangerous cascade of anaerobic metabolism, lactic acidosis, and the multi-organ injury that defines clinical asphyxia and its most severe neurological sequel, HIE.[28] This "multi-hit" framework provides a powerful lens through which to interpret the disparate findings of this review in a cohesive, pathophysiologically-grounded manner. The uterus is the fetus's entire world, and the health of the mother dictates the quality of that environment. This review powerfully reinforces that the seeds of asphyxia are often sown in the soil of maternal health long before delivery, a concept supported by decades of perinatal research.[19]

The findings from several studies are consistent with a vast body of literature linking maternal hypertensive disorders, gestational diabetes (GDM), and obesity to adverse perinatal outcomes.[7,24] The pathophysiology is intricate and interconnected, rooted in systemic inflammation and endothelial dysfunction. In pregnancy, this maternal pathology targets the unique and vulnerable vasculature of the developing placenta. In hypertensive disorders, including chronic hypertension and preeclampsia, there is a fundamental failure of the normal physiological transformation of the uterine spiral arteries. In a healthy pregnancy, these vessels undergo extensive remodeling, shedding their muscular, contractile walls to become wide, flaccid, low-resistance conduits. This process is essential to ensure a massive, high-flow supply of maternal blood to the placenta to meet the escalating demands of the fetus. In hypertensive states, this remodeling is incomplete or absent. The arteries remain narrow, muscular, and pathologically vasoreactive, leading to a state of chronic malperfusion of the placenta. This creates areas of ischemia, infarction, and oxidative stress, effectively reducing the functional surface area for gas and nutrient exchange. The findings of chronic MVM in the placentas of asphyxiated infants[12] are the direct histological consequence of this process,

providing a physical scar of this long-standing battle for oxygen.

GDM and maternal obesity operate through related pathways of metabolic stress.[24] Maternal hyperglycemia and insulin resistance induce a systemic state of oxidative stress and low-grade inflammation, which damages the delicate placental endothelium, impairing its function. This can lead to a placental vasculopathy similar to that seen in hypertension. Furthermore, the resulting fetal hyperinsulinemia acts as a powerful growth factor, driving excessive fetal growth (macrosomia). A macrosomic fetus has a significantly higher basal metabolic rate and oxygen demand, which can outstrip the placenta's ability to supply it, creating a state of relative hypoxia even under baseline conditions. This macrosomia then becomes a potent mechanical risk factor, predisposing the pregnancy to shoulder dystocia and prolonged, obstructed labor—a classic "second hit" that a large, already oxygen-hungry fetus is poorly equipped to handle. The work by Song et al. linking maternal obesity directly to asphyxia underscores that excess maternal weight is not a benign condition; it is an active metabolic state that compromises the fetal-placental unit from conception onwards.

Perhaps the most dramatic and clinically important finding highlighted in this review is the 51-fold increased risk of asphyxia associated with PMPS.[6] An effect size of this magnitude is exceptionally rare in clinical medicine and demands a deep dive into its potential biological plausibility. While this finding is from a single retrospective study and requires prospective validation, its implications are too significant to ignore. It suggests that maternal mental health is not a "soft" or secondary factor but a powerful biological determinant of neonatal health, a concept supported by emerging psychosocial research.[30,32] The primary mechanism linking chronic stress to asphyxia risk is the sustained dysregulation of the maternal hypothalamic-pituitary-adrenal (HPA) axis. Chronic stress leads to the persistent elevation of glucocorticoids, primarily cortisol. While cortisol is essential for fetal lung maturation in late gestation, excessive or prolonged exposure has deleterious effects. Cortisol readily crosses the placenta and can act directly on the fetal brain and cardiovascular system. More importantly, elevated maternal cortisol is known to increase uterine artery resistance. It potentiates the vasoconstrictive effects of catecholamines (adrenaline and noradrenaline), which are also released in torrents during the physiological stress response.[30] The net result is a dose-dependent reduction in uteroplacental blood flow, mirroring the malperfusion seen in hypertensive disorders. In essence, chronic, unmanaged maternal stress can create a "functional" placental insufficiency even in a physically healthy, normotensive mother.

Furthermore, cortisol has powerful immunomodulatory effects. It can alter the inflammatory milieu at the maternal-fetal interface, potentially "priming" the fetus for an exaggerated and damaging inflammatory response to a later hypoxic insult. The cascade of neuronal injury in HIE is now understood to have a major inflammatory component, with activation of microglia and release of cytotoxic cytokines being key drivers of cell death.[28] Therefore, a fetus pre-exposed to a pro-inflammatory intrauterine environment due to maternal stress may suffer more severe brain injury from a given degree of hypoxia. This finding mandates a paradigm shift in antenatal care, moving towards the routine screening for maternal mental distress using validated tools[32] and the integration of accessible psychosocial support as a primary strategy for preventing adverse perinatal outcomes. The review's findings are elevated by the inclusion of research that extends the etiological framework beyond the patient’s body to the societal systems they inhabit. The finding from Törn et al. that immigrant women in a high-resource country have a nearly two-fold higher risk of delivering an infant with HIE is profound and cannot be explained by clinical factors alone. It points towards the concept of "weathering," or allostatic load, as a powerful explanatory framework.[34] This theory posits that individuals from marginalized or disadvantaged

groups experience chronic, unrelenting stress from factors like navigating systemic discrimination, acculturation challenges, food insecurity, and social isolation. This chronic stress leads to a sustained activation of the body's physiological stress response systems (the HPA axis and the sympathetic nervous system), causing a "wear and tear" that becomes biologically embedded. A pregnant woman experiencing this "weathering" may enter pregnancy with higher baseline levels of inflammation, endothelial dysfunction, and HPA axis dysregulation—a physiological profile strikingly similar to that caused by a somatic disease like hypertension. This is then compounded by practical barriers within the healthcare system itself. Communication difficulties due to language differences can lead to critical misunderstandings about symptoms or instructions. A lack of culturally competent care can erode trust and reduce engagement with essential antenatal services. These women may present later for care or be less able to advocate for themselves when they sense a problem is developing.[34] The finding from Törn et al. is therefore not just a statistic; it is a manifestation of systemic failure and a powerful argument for investing in culturally-tailored care, professional interpreter services, and community health worker programs that can bridge these critical social and physiological divides.

The fetal-placental unit stands as the critical nexus between maternal health and neonatal outcome. The findings on placental pathology and fetal characteristics provide tangible evidence of how antepartum risks translate into a state of heightened vulnerability. The findings from several studies are critical because they provide physical evidence of the underlying pathophysiology of asphyxia.[11,12] The observation that 85% of infants with HIE have placental abnormalities[12] is a powerful testament to the organ's central role. The distinction between chronic lesions like MVM and acute inflammatory changes is particularly illuminating. MVM is a histological term for a pattern of injury—including villous infarcts, accelerated villous maturation, and decidual arteriopathy—that develops over weeks or months. These are the scars of a long-standing battle for oxygen. When a pathologist identifies significant MVM, they are confirming that the fetus was likely exposed to chronic hypoxia, directly linking back to the maternal conditions of hypertension, stress, and GDM. The associated finding of a greater base deficit at birth in infants with chronic lesions[12] is the biochemical proof of this exhausted metabolic state, demonstrating that these fetuses enter labor with no reserves to draw upon. This review highlights low birth weight as a powerful and consistent predictor of asphyxia.[8,21,23] The staggering 64.8% rate of asphyxia in twins weighing less than 1500g must be understood beyond simply "being small." Low birth weight, particularly when it reflects FGR, is the ultimate clinical surrogate for chronic placental insufficiency.[33] An FGR fetus is, by definition, a fetus that has endured chronic hypoxia and undernutrition. This has profound consequences for its ability to tolerate labor. Firstly, it has severely depleted energy reserves, lacking the glycogen stores in its liver and heart needed for anaerobic metabolism. It therefore develops severe lactic acidosis much faster than a well-grown fetus. Secondly, chronic hypoxia forces a redistribution of blood flow in utero (the "brain-sparing" effect), which is protective in the short term but comes at the cost of under-developing other organs and limiting overall growth. Therefore, the identification of FGR on an antenatal ultrasound should be a major red flag, signaling a fetus with extreme vulnerability to intrapartum hypoxia. While the foundation of risk is laid in the antepartum period, labor is where that risk is tragically realized. It is the final, acute challenge that a compromised fetus may fail.

The strong findings from several studies confirm the danger of prolonged labor.[9,21,22] The physiology is straightforward: each uterine contraction temporarily reduces or halts blood flow into the placental intervillous space. A healthy fetus tolerates this well, recovering in the interval between contractions. In a prolonged labor, especially one augmented with

oxytocin, which can lead to uterine tachysystole, the recovery intervals become too short. The fetus experiences progressively worsening hypoxia and hypercarbia with each contraction. This is compounded by maternal exhaustion and less effective pushing, further prolonging the period of maximal stress. Specific mechanical issues like a tight nuchal cord[22] cause repetitive umbilical cord compression and severe variable decelerations, acutely shutting off the fetal lifeline with each contraction. A few such events may be tolerated, but hundreds over a prolonged labor will inevitably lead to significant acidosis.[19] The presence of meconium-stained fluid is a critical intrapartum finding.[9] It serves multiple roles in the asphyxial cascade. First, it is a sign of fetal stress, often triggered by hypoxia-induced increased gut peristalsis. Second, as shown by Alongi et al., it is a placental toxin. Meconium contains bile salts and enzymes that cause intense vasoconstriction of the chorionic plate vessels, acutely worsening fetal hypoxia. Third, if aspirated, it becomes a severe postnatal pulmonary problem, causing mechanical airway obstruction, chemical pneumonitis, and persistent pulmonary hypertension of the newborn (PPHN), which perpetuates a vicious cycle of hypoxia long after birth. Finally, the finding from Jena et al. of a high odds ratio for asphyxia with cesarean and instrumental deliveries is a classic example of confounding by indication. It is crucial to dissect this correlation. These interventions are rarely the cause of the asphyxia; they are the response to the signs of fetal distress that signal impending asphyxia. The fact that an emergency operative delivery was required is proof that a significant problem was already underway. The real variable of interest for quality improvement is the "decision-to-delivery interval" (DDI). Once the team recognizes fetal compromise, every minute counts.[19] Therefore, this finding should be seen as a mandate for all labor and delivery units to have streamlined emergency response protocols to rescue the compromised fetus as quickly as possible.

5. Conclusion

Neonatal asphyxia arises from a complex interplay of risk factors that span the entire perinatal continuum, from pre-conceptual maternal health and systemic inequities to acute intrapartum events. Effective mitigation requires a multi-pronged approach encompassing comprehensive antenatal care that addresses both physical and mental health, vigilant intrapartum monitoring, and systemic efforts to ensure equitable access to high-quality perinatal care. The integration of validated risk prediction tools into clinical practice holds significant promise for reducing the global burden of this devastating condition.

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