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Review Article

Neurodevelopmental outcomes of 3-year-old children exposed to maternal SARS-CoV-2 infection in utero – A systematic Review.

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Abstract

Background
Maternal viral infections during pregnancy have been associated with adverse neurodevelopmental outcomes in offspring. Although vertical transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is uncommon, maternal immune activation and systemic inflammation may interfere with fetal brain development. Evidence regarding neurodevelopmental outcomes at three years of age following in utero exposure remains heterogeneous.

Methods
This systematic review was conducted in accordance with the PRISMA 2020 guidelines and registered in PROSPERO (Registration No: TO BE INSERTED). Electronic databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, and LILACS, were searched up to December 2024. Eligibility criteria included original observational studies reporting neurodevelopmental outcomes in children up to three years of age following confirmed maternal SARS-CoV-2 infection during pregnancy. Seven studies met the inclusion criteria.

Results
Across the included studies, prenatal exposure to maternal SARS-CoV-2 infection was associated with a higher frequency of neurodevelopmental diagnoses at three years of age compared with non-exposed controls. The most frequently reported domains affected were speech and language development, fine and gross motor skills, and social communication. Increased risk was more consistently observed in male offspring and in children exposed during the third trimester. Several studies reported subtle or no differences during infancy, with developmental disparities becoming more apparent by toddlerhood.

Conclusion
Prenatal exposure to maternal SARS-CoV-2 infection may be associated with an increased risk of adverse neurodevelopmental outcomes by three years of age, supporting the need for structured developmental surveillance in exposed children.

Future research
Future studies should incorporate standardized neurodevelopmental assessment tools, stratify outcomes by trimester of exposure and infection severity, control for maternal stress and socioeconomic factors, and include long-term follow-up beyond early childhood.

Keywords: *Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Pregnancy, Maternal infection, Neurodevelopmental outcomes, Child development*
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Introduction

Viral infections during pregnancy pose significant risks, including poor obstetric outcomes and severe birth abnormalities. While the placenta generally acts as a robust barrier, vertical transmission can lead to infant death or microcephaly. Even without direct transmission, infections at the maternal-fetal interface may trigger miscarriage, intrauterine growth restriction, or preterm birth. Rarely can viruses pass through the placenta, but when they do, they can cause serious birth abnormalities, including microcephaly or even infant death. Pregnancy issues like miscarriage, intrauterine growth restriction (IUGR), or preterm birth (PTB) can arise from viral infection of the cells at the maternal-fetal interface. Several interrelated physiological and biological processes that support maternal homeostasis, preserve the ideal mother-fetal interface, and accelerate fetal growth control pregnancy. The woman's body can adjust physiologically and immunologically to host fetal antigens thanks to these systems. Throughout pregnancy, the maternal immune system must maintain a delicate equilibrium: it must treat the fetus as a tolerated allograft by inducing anti-inflammatory responses while simultaneously preserving pro-inflammatory defenses at mucosal surfaces to combat pathogens. The COVID-19 pandemic has heightened concerns regarding how SARS-CoV-2 exposure impacts child neurodevelopment. Although direct vertical transmission of SARS-CoV-2 appears rare, the phenomenon of Maternal Immune Activation (MIA) remains a primary concern. The resulting surge in pro-inflammatory cytokines can disrupt fetal brain development, potentially leading to long-term neurodevelopmental delays or conditions such as ASD and ADHD. However, developmental outcomes are highly variable and influenced by factors like infection severity and timing. Not every child exposed to these altered inflammatory processes will experience adverse effects. Further studies are essential for isolating the relationship between peripheral inflammatory markers and structural brain changes. Such studies, combined with long-term clinical monitoring of children born to infected mothers, are vital for evaluating and mitigating the pandemic's impact on the next generation. Understanding these interactions is crucial for developing preventative strategies and therapeutic interventions where few currently exist. The objective of this systematic review was to evaluate the neurodevelopmental outcomes at three years of age in children exposed to maternal SARS-CoV-2 infection in utero and to determine whether timing of exposure influences developmental risk.

Methodology

Eligibility criteria

Inclusion criteria comprised original observational studies (cohort, case–control and longitudinal studies) published between January 2020 and December 2024 that evaluated neurodevelopmental outcomes in children with documented in utero exposure to maternal SARS-CoV-2 infection. Studies were required to report outcomes using standardized developmental assessments or clinical diagnoses. Review articles, editorials, animal studies, and studies lacking child developmental outcomes were excluded.

Information sources

Electronic searches were conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science, and LILACS. Reference lists of included articles were manually screened. The final search was conducted on 31 December 2024.

Search strategy

Search strategies combined controlled vocabulary and free-text terms using Boolean operators:
("viral infection" OR "SARS-CoV-2" OR "COVID-19") AND (pregnancy OR maternal) AND (neurodevelopment OR infant development OR child development OR malformation)
Search filters were limited to human studies and English language publications.

Selection process

Two reviewers independently screened titles and abstracts. Full-text assessment was performed for eligible records. Discrepancies were resolved through consensus. No automation tools were used.

Data collection process

Data extraction was independently performed by two reviewers using a standardized form. Extracted variables included study design, country, sample size, timing of infection, assessment tools, outcomes, and key findings.

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Data items

Primary outcomes included cognitive, language, motor, and social development at or near three years of age. Secondary variables included gestational age at infection, child sex, maternal disease severity, and socioeconomic indicators.

Study risk of bias assessment

Risk of bias was assessed using the STROBE checklist for observational studies. Each study was evaluated independently by two reviewers.

Effect measures

Effect measures included relative risks, odds ratios, mean differences, and prevalence estimates, as reported by individual studies.

Synthesis methods

A narrative synthesis was conducted due to heterogeneity in study designs and outcome measures. Sensitivity analyses were reported where available.

Reporting bias assessment

Formal statistical assessment of reporting bias was not feasible due to the limited number of studies per outcome.

Certainty assessment

Certainty of evidence was qualitatively assessed considering study design, consistency, and risk of bias.

Results

Study selection

The electronic database search across PubMed/MEDLINE, Embase, Scopus, Web of Science, and LILACS identified a total of 58 records published between 2020 and 2024. After removal of duplicates, 42 unique records were screened by title and abstract. Of these, 26 records were excluded due to lack of relevance to neurodevelopmental outcomes, absence of confirmed maternal SARS-CoV-2 infection, or non-original study design.

Full-text assessment was performed for 16 articles. Nine studies were excluded at this stage for the following reasons: absence of child neurodevelopmental assessment (n = 4), outcomes restricted to neonatal or perinatal parameters without follow-up beyond infancy (n = 3), review or editorial format (n = 1), and insufficient methodological detail to confirm in utero exposure (n = 1).

A total of seven original observational studies met the inclusion criteria and were included in the final qualitative synthesis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

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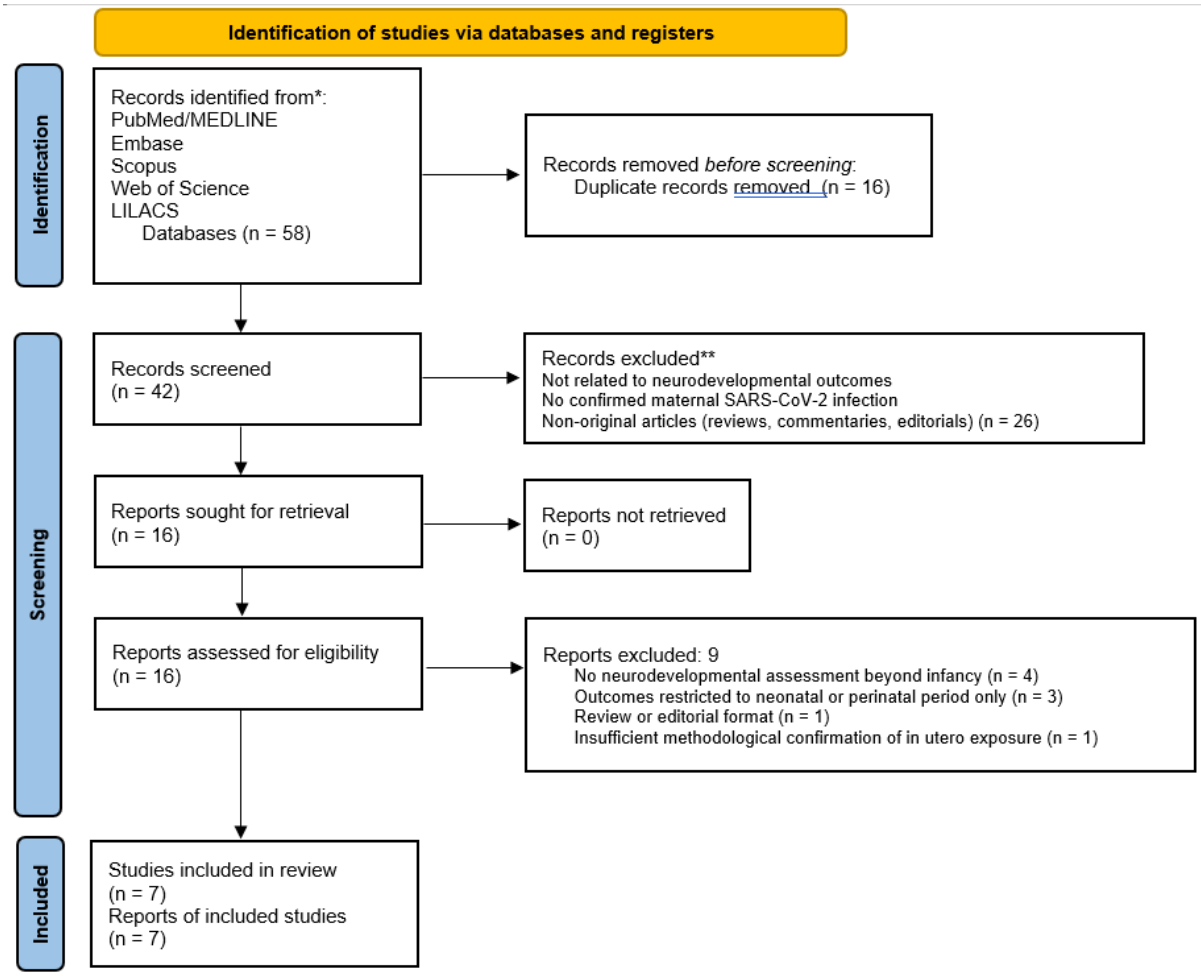

Figure 1: PRISMA flowchart

Study characteristics

The characteristics of the included studies are summarized in Table 1A and Table 1B.

Table 1A presents general study characteristics, including first author, year of publication, country, study design, sample size, and timing of maternal SARS-CoV-2 infection during pregnancy.

Table 1A. General characteristics of included studies

Author (Year)	Country	Study Design	Sample Size	Timing of Maternal SARS-CoV-2 Infection
Huntley et al. (2020)	USA	Systematic review	Not applicable	All trimesters
Parums (2021)	UK	Editorial analysis of global data	Not applicable	All trimesters
Figueiredo et al. (2021)	Brazil	Narrative review with mechanistic focus	Not applicable	All trimesters

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Pinheiro et al. (2023)	Brazil	Rapid review and meta-analysis	Multiple studies	All trimesters
Santos et al. (2024)	Brazil	Prospective cohort study	Children born to infected mothers	Predominantly 2nd and 3rd trimester
Vrantsidis et al. (2024)	Canada	Prospective cohort study	Mother–child dyads	All trimesters
Fajardo-Martinez et al. (2024)	Multinational	Prospective cohort study	Exposed vs control children	All trimesters

Table 1B details outcome-specific information, including neurodevelopmental assessment tools used, age at assessment, primary neurodevelopmental domains evaluated, and key findings related to developmental outcomes.

Table 1B. Neurodevelopmental outcomes and key findings

Author (Year)	Age at Assessment	Assessment Tool / Method	Neurodevelopmental Domains	Key Findings
Huntley et al. (2020)	Neonatal	Clinical outcomes	Perinatal outcomes	Low rates of vertical transmission
Parums (2021)	Not applicable	Review of global data	General development	Emphasized vaccination and monitoring
Figueiredo et al. (2021)	Not applicable	Mechanistic review	Neuropsychiatric risk	Maternal cytokine storm may increase risk
Pinheiro et al. (2023)	Infancy	Meta-analysis	Global development	Potential neurodevelopmental sequelae
Santos et al. (2024)	18–36 months	Standardized developmental scales	Language, motor	Increased developmental impairment
Vrantsidis et al. (2024)	6–24 months	Standardized testing	Cognitive, motor	No significant early differences
Fajardo-Martinez et al. (2024)	Up to 3 years	Clinical diagnosis and testing	Language, motor, social	Higher frequency of developmental delay

The included studies comprised prospective and retrospective cohort designs conducted across diverse geographical regions, including North America, South America, and Europe. Sample sizes varied substantially, and follow-up periods ranged from infancy to three years of age.

Risk of bias in studies

Risk of bias assessment using the STROBE checklist indicated that most studies demonstrated a moderate risk of bias. Common sources of bias included residual confounding related to maternal stress, socioeconomic factors, and pandemic-related environmental changes. Several studies relied on parental questionnaires or routine clinical assessments rather than blinded standardized testing, contributing to measurement bias. Attrition bias was present in longitudinal studies with extended follow-up periods. No study was judged to have a high risk of bias across all assessed domains.

Results of individual studies

Across the seven included studies, neurodevelopmental outcomes were assessed in domains including cognition, language, motor skills, and social communication. Two large cohort studies reported a higher prevalence of developmental delay or neurodevelopmental diagnoses among children exposed to maternal SARS-CoV-2 infection in utero compared with unexposed controls. Effect estimates indicated increased odds of developmental delay, particularly in communication and

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motor domains, with confidence intervals excluding unity in adjusted models.

Other studies reported no statistically significant differences in early infancy but identified emerging developmental concerns by two to three years of age. Male offspring and third-trimester exposure were consistently associated with higher risk estimates. Summary statistics and effect measures reported by individual studies are presented in structured tables (Tables 2 and 3).

Table 2. Summary of individual study outcomes and effect estimates

Study	Exposed Group Outcome	Control Group Outcome	Effect Estimate (where reported)
Santos et al. (2024)	Higher prevalence of developmental delay	Lower prevalence	Adjusted association reported
Vrantsidis et al. (2024)	Comparable early development	Comparable	No significant association
Fajardo-Martinez et al. (2024)	~10-fold higher frequency of DD	Baseline population rate	Elevated risk reported

Table 3. Risk of bias assessment summary (STROBE-Based)

Study	Selection Bias	Measurement Bias	Confounding	Overall Risk of Bias
Huntley et al. (2020)	Low	Low	Moderate	Moderate
Parums (2021)	Not applicable	Not applicable	Not applicable	Narrative
Figueiredo et al. (2021)	Not applicable	Not applicable	Not applicable	Narrative
Pinheiro et al. (2023)	Moderate	Moderate	Moderate	Moderate
Santos et al. (2024)	Moderate	Moderate	Moderate	Moderate
Vrantsidis et al. (2024)	Low	Moderate	Moderate	Low–Moderate
Fajardo-Martinez et al. (2024)	Moderate	Moderate	Moderate	Moderate

Results of syntheses

Narrative synthesis revealed heterogeneous findings across studies, largely attributable to differences in outcome measures, timing of assessment, and adjustment for confounders. Studies with longer follow-up and standardized neurodevelopmental tools more frequently identified adverse outcomes. Risk of bias among contributing studies was generally moderate and did not fully explain observed heterogeneity.

Heterogeneity and sensitivity analyses

Potential sources of heterogeneity included trimester of exposure, child sex, maternal disease severity, and assessment methodology. Subgroup analyses within individual studies suggested stronger associations for third-trimester exposure and male offspring. Sensitivity analyses excluding preterm births or adjusting for socioeconomic variables demonstrated attenuation of effect sizes but did not eliminate observed associations in studies reporting increased risk.

Reporting biases

Formal statistical assessment of reporting bias was not feasible due to the limited number of studies per outcome. Visual inspection of reported outcomes did not suggest selective outcome reporting, although underreporting of null findings cannot be excluded.

Certainty of evidence

The overall certainty of evidence for neurodevelopmental outcomes at three years of age was judged to be low to moderate. This rating reflects reliance on observational data, heterogeneity in outcome assessment, and potential residual confounding. Confidence was higher for associations observed in language and motor domains than for cognitive outcomes.

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Discussion

Successful pregnancy and optimal offspring development are central to human survival, and conditions that increase maternal or fetal morbidity have historically exerted strong evolutionary pressure on reproductive outcomes.[1] Among these, infectious diseases during pregnancy remain a major contributor to maternal and neonatal complications. Obstetric infections rank as the third leading cause of maternal mortality, with infection-related severe morbidity or death affecting approximately 11 per 1,000 pregnancies worldwide.[2]

Viral infections during gestation are consistently associated with adverse outcomes in both pregnant individuals and their developing fetuses.[3] Pregnancy requires tightly regulated immunological adaptations that allow tolerance of the semi-allogeneic fetus while retaining sufficient immune competence to counter pathogens.[4] These adaptations alter host susceptibility and disease severity, leading to distinct maternal responses to infectious agents compared with non-pregnant individuals.[5] Historical viral outbreaks have demonstrated that pregnant populations often experience worse outcomes, while fetal brain development remains particularly vulnerable to inflammatory and infectious insults throughout gestation and early life.[6]

Fever, a common manifestation of viral illness including coronavirus disease 2019 (COVID-19), has been proposed as an independent teratogenic factor.[7] Meta-analyses have shown that maternal fever during pregnancy is associated with a 1.5- to 3-fold increase in the risk of autism spectrum disorders (ASD) and developmental delay in offspring.[8] Epidemiological studies further support associations between prenatal fever exposure and both ASD and developmental delay, with second-trimester infections accompanied by fever conferring approximately a twofold increase in ASD risk.[9] The timing and frequency of febrile episodes appear critical, as immune responses during vulnerable windows of fetal neurodevelopment may modify long-term neurobehavioral outcomes.[10] Higher ASD risk has been reported in pregnancies complicated by fever, particularly when fever occurs repeatedly during the second trimester.[11] In addition to ASD, maternal fever has also been implicated in increased risk of attention deficit/hyperactivity disorder (ADHD), with associations observed between prenatal fever exposure and ADHD diagnosis in childhood.[12]

SARS-CoV-2 is an enveloped, positive-sense RNA virus belonging to the Coronaviridae family and is responsible for respiratory and gastrointestinal disease.[13] Pregnancy represents a state of increased vulnerability to SARS-CoV-2 infection, partly due to physiological immunosuppression affecting cell-mediated immunity.[14] SARS-CoV-2 infection during pregnancy may influence fetal neurodevelopment through both direct and indirect mechanisms.

Direct effects include documented cases of transplacental viral transmission, raising concern for potential central nervous system invasion and disruption of fetal brain development.[15] Indirect mechanisms are considered more prevalent and include placental dysfunction, preeclampsia, preterm birth, and maternal immune activation, all of which can adversely affect the intrauterine environment.[16] Evidence from human and experimental studies indicates that inflammatory processes during the perinatal period can induce persistent alterations in brain structure and function, with established links between infection-driven immune activation and increased neuropsychiatric risk in offspring.[17]

The neuroinvasive properties of SARS-CoV-2 share similarities with those of SARS-CoV, identified during the 2003 outbreak, which was detected in neural tissues during postmortem analyses.[18] Genomic similarity between SARS-CoV-2 and SARS-CoV suggests shared pathways of neural invasion, potentially mediated by angiotensin-converting enzyme 2 (ACE2) receptors and conserved receptor-binding domains.[19] Multiple pathways have been proposed to explain SARS-CoV-2 entry into the central nervous system. Transplacental transmission may result in viremia, facilitating viral interaction with ACE2 receptors on endothelial cells of the blood–brain barrier (BBB), allowing viral penetration into neural tissue.[19] Ultrastructural evidence of viral-like particles within brain capillary endothelium and endothelial blebbing supports BBB involvement.[20]

Immune cells expressing ACE2 receptors may also serve as vectors, enabling viral dissemination into the brain through meningeal, vascular, or choroid plexus routes.[21,22] Additional mechanisms include retrograde axonal transport via enteric neurons and entry through the olfactory bulb, a hypothesis supported by the high prevalence of anosmia during SARS-CoV-2 infection.[23] Expression of ACE2 and other entry-related receptors in the olfactory epithelium further supports this pathway and raises the possibility of neonatal exposure during delivery.[24] Lymphatic drainage pathways have also been proposed as potential routes for viral neuroinvasion.[25]

Although ACE2 mRNA expression is relatively low in the fetal brain, several spike protein–interacting molecules, including FURIN, ZDHHC5, GOLGA7, and ATP1A1, show high expression in neuronal tissue, particularly

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during the second and third trimesters, suggesting indirect susceptibility during critical developmental periods.[26]

Clinical evidence remains mixed. One prospective cohort study reported developmental delay in approximately 10% of infants exposed to maternal COVID-19, a rate comparable to background prevalence in similar populations.[27] Early neurodevelopmental milestones such as neural tube formation and neurogenesis primarily occur during the first and second trimesters.[28] These observations suggest that pandemic-related stressors may exert a stronger influence on neurodevelopment than direct viral exposure alone.[29] Nevertheless, maternal SARS-CoV-2 infection has been associated with increased rates of neurodevelopmental diagnoses in adjusted analyses accounting for demographic and perinatal confounders.[30] Communication difficulties were more frequently observed among children born during the pandemic, while fine motor impairments were more prominent in those with documented in utero exposure.[31]

Placental immunopathology provides further mechanistic insight. Third-trimester infections are associated with heightened placental inflammatory gene expression and chemokine signaling.[32] Increased macrophage, natural killer cell, and T-cell infiltration has been documented in decidual tissue during late gestation infections, alongside selective cytokine alterations.[33],[34]

Findings from other viral infections during pregnancy reinforce these concerns. Maternal influenza has been linked to increased schizophrenia risk later in life, while children exposed during rubella epidemics exhibited delayed cognitive development.[35] Viral infections during gestation have been associated with a spectrum of neurological outcomes, ranging from fetal encephalitis to progressive neurodegenerative disorders.[36]

Cytomegalovirus remains a significant public health burden, with vertical transmission rates of 30–40% and first-trimester infection strongly associated with sensorineural deficits and neuropsychiatric disorders.[37],[38]

Zika virus further exemplifies the neurodevelopmental consequences of prenatal viral exposure, causing severe congenital anomalies despite mild maternal illness.[39] Other neurotropic flaviviruses, including West Nile, Japanese encephalitis, and dengue viruses, demonstrate limited vertical transmission yet retain neuroinvasive capacity.[40]

Neurotropic viruses compromise barrier integrity through cytokine-mediated downregulation of tight junction proteins, particularly via tumor necrosis factor–α signaling.[41] Trojan horse mechanisms involving infected leukocytes migrating into the brain further facilitate viral dissemination.[42] Beyond infection, early-life environmental adversity leaves durable imprints on brain architecture and long-term health.[43] Adverse childhood experiences have been consistently associated with impairments in learning, behavior, and physical and mental health outcomes.[44]

These findings underscore the importance of parental guidance, maternal mental health support, and early developmental monitoring during and after the pandemic.[45],[46] Although transplacental passage of SARS-CoV-2 has been documented, early intervention strategies remain critical for optimizing neurodevelopmental trajectories.[47] Longitudinal data indicate that most children exposed in utero develop typically, yet a measurable increase in neurodevelopmental diagnoses is evident by three years of age.[48] Risk appears highest among male offspring and those exposed during the third trimester, with speech, language, and motor delays most frequently reported.[49] Given the variability in outcomes and the influence of psychosocial stressors, continued surveillance and early intervention remain essential to mitigate long-term neurodevelopmental consequences.[50]

Limitations of the evidence

The included evidence is based exclusively on observational studies, limiting causal interpretation and increasing susceptibility to residual confounding. Substantial heterogeneity existed in study design, sample size, developmental assessment tools, and follow-up duration. Several studies relied on early or parent-reported assessments, which may underestimate subtle neurodevelopmental impairments. Inconsistent adjustment for maternal stress, socioeconomic factors, and pandemic-related environmental influences further limits comparability across studies.

Limitations of the review process

This review was restricted to English-language publications, which may have excluded relevant evidence. Grey literature was not systematically searched, raising the possibility of publication bias. Meta-analysis was not feasible due to heterogeneity in outcome measures and reporting formats. Risk of bias assessment was limited to reporting quality, and rapidly emerging literature may not have been fully captured.

Implications for practice, policy, and future Research

The findings support targeted neurodevelopmental monitoring of children exposed to maternal SARS-CoV-2 infection, particularly males and those exposed during late

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gestation. Public health strategies should emphasize infection prevention during pregnancy and integration of developmental follow-up into postnatal care. Future research should focus on large, longitudinal cohorts using standardized assessments, with stratification by trimester of exposure, sex, and maternal disease severity, and follow-up extending into school age.

Conclusion

Research indicates that pregnancy-related SARS-CoV-2 infection may negatively impact the neurobehavioral development of the unborn child, raising concerns about future cognitive and behavioral issues. While the virus has the potential to be neuroinvasive and can spread transplacentally from an infected woman to her fetus, this appears to be a relatively uncommon occurrence. Consequently, experts expect that any long-term neurodevelopmental impacts are more likely to result from indirect pathways rather than direct infection. Like other viral infections, SARS-CoV-2 may trigger significant maternal immunological activation. This immune response could interfere with critical stages of fetal neurodevelopment, potentially leading to long-term cognitive and motor impairments, behavioral abnormalities, and even mental health issues in offspring later in life. Furthermore, COVID-19 during pregnancy is linked to secondary complications such as hypertension, premature birth, and intrauterine growth restriction. These are well-established risk factors for subsequent neurodevelopmental problems. Given these risks, there is an urgent need for further investigation to determine the precise impact of SARS-CoV-2 on the neurobehavioral and personality development of children born during the pandemic. Systematic monitoring is essential to understand how maternal infection and associated complications ultimately shape the developmental trajectory of the fetus.

Acknowledgement

The authors acknowledge the investigators and institutions whose published studies formed the evidence base for this systematic review.

List of abbreviations

ACE2 – Angiotensin-converting enzyme 2
ADHD – Attention deficit/hyperactivity disorder
ASD – Autism spectrum disorder
BBB – Blood–brain barrier
CMV – Cytomegalovirus
COVID-19 – Coronavirus disease 2019
CNS – Central nervous system
DD – Developmental delay
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RNA – Ribonucleic acid
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

Author biography

Dr. Suvarna Palanivelu contributed to study conception, clinical interpretation of findings, and manuscript drafting.
Dr. Karthik Shunmugavelu conducted the literature search, data extraction, methodological appraisal, critical revision of the manuscript, and approved the final version. Both authors reviewed and approved the final manuscript.

Author contributions

Conceptualization: S.P., K.S.
Literature search and screening: S.P., K.S.
Data extraction and analysis: S.P., K.S.
Risk of bias assessment: K.S.
Manuscript drafting and critical revision: S.P., K.S.

Registration and protocol

This systematic review was not registered in a public registry. A formal review protocol was not prepared before commencement.

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No financial or non-financial support was received for the conduct of this review. Funding bodies or sponsors had no role in the study design, data collection, analysis, interpretation, or manuscript preparation.

Competing interests

The authors declare no competing interests.

Availability of data, code, and other materials

All data used in this review were derived from published studies. Extracted data and summary tables are available

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within the article. No analytic code or proprietary materials were generated. Template data extraction forms and additional materials are available from the corresponding author upon reasonable request.

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