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(REVIEW ARTICLE)

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Impact of maternal hyperemesis gravidarum on long-term health outcomes in children: A systematic review and meta-analysis

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Abstract

Background: Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting in pregnancy with potential adverse effects on fetal development. Although short-term outcomes are relatively well-documented, long-term health consequences in offspring remain poorly understood.

Objective: To systematically review and quantitatively synthesize evidence on the long-term health outcomes of children born to mothers with HG.

Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines. PubMed, Embase, Scopus, and Cochrane Library were searched up to March 2025. Studies reporting any long-term physical, cognitive, metabolic, or neurodevelopmental outcomes in offspring of HG pregnancies were included. Data were pooled using random-effects models, and heterogeneity was assessed using the I^2 statistic.

Results: Eleven studies comprising 1,024,385 participants met inclusion criteria. Meta-analysis showed that HG was significantly associated with increased risk of neurodevelopmental disorders (OR 1.35, 95% CI 1.11–1.63), attention-deficit/hyperactivity disorder (OR 1.24, 95% CI 1.09–1.42), and autism spectrum disorders (OR 1.44, 95% CI 1.20–1.72). No significant associations were found with metabolic or growth-related outcomes.

Conclusions: Offspring of mothers with HG are at increased risk of neurodevelopmental impairments. Clinicians should be aware of these risks and consider long-term developmental follow-up for affected children.

Keywords: Hyperemesis Gravidarum; Neurodevelopmental Outcomes; Autism Spectrum Disorder; Attention-Deficit/Hyperactivity Disorder; Long-Term Child Health; Fetal Programming; Maternal Nutrition; Pregnancy Complications; Systematic Review; Meta-Analysis

1. Introduction

Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting during pregnancy, affecting approximately 0.3% to 2% of pregnancies worldwide. It is clinically distinct from typical morning sickness due to its persistence and severity, often leading to dehydration, electrolyte disturbances, nutritional deficiencies, and significant maternal weight loss during early gestation [1-2]. HG frequently requires hospitalization and can severely impact maternal quality of life. While the maternal complications of HG including Wernicke's encephalopathy, renal dysfunction, and psychological distress are well-recognized, comparatively little attention has been directed toward the long-term consequences for the offspring.

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Recent studies have begun to explore how the intrauterine environment shaped by HG might influence fetal development, particularly through the lens of the fetal programming hypothesis. This theory posits that adverse prenatal exposures such as maternal malnutrition, inflammation, and stress can lead to epigenetic changes that predispose the fetus to long-term health consequences [2]. In the context of HG, prolonged caloric restriction, micronutrient deficiencies, and elevated maternal cortisol levels may disrupt fetal neurodevelopmental processes and metabolic regulation [3-6].

Emerging epidemiological data support this concern. A large population-based study from Norway found that children exposed to HG in utero had a modestly increased risk of neurodevelopmental delays, particularly in language and motor development by age five [7]. Other research suggests associations with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), although these findings require further validation. Additionally, there is growing interest in the metabolic implications of HG, with preliminary evidence indicating potential links to altered birth weights and increased risk of childhood obesity and insulin resistance, possibly stemming from prenatal nutrient deprivation.

Despite these findings, the evidence base remains limited by methodological heterogeneity, small sample sizes, and confounding variables such as socioeconomic status and maternal comorbidities. Most existing studies are observational, and few have examined outcomes beyond early childhood. There is a pressing need for prospective cohort studies with long-term follow-up to more accurately characterize the risks and inform clinical practice. Understanding the full spectrum of HG's impact on offspring is critical for guiding antenatal care strategies and postnatal monitoring.

2. Methods

This systematic review and meta-analysis were designed and reported in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring transparency, rigor, and methodological consistency throughout the review process. To enhance research integrity and avoid duplication, the review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42025111234. This registration outlines the objectives, eligibility criteria, and planned methods, reinforcing the reliability of the findings and adherence to evidence-based review standards.

Eligible studies included in this review were observational in design, specifically cohort or case-control studies, that reported on long-term health outcomes in children born to mothers diagnosed with hyperemesis gravidarum (HG). To be considered, studies had to assess outcomes occurring at least one year after birth, capturing meaningful and potentially persistent health effects of prenatal exposure to HG. This criterion was essential for distinguishing transient neonatal effects from more enduring physical, metabolic, or neurodevelopmental outcomes in offspring. Studies focusing solely on short-term or perinatal complications were excluded to maintain the review's focus on long-term impacts.

A comprehensive literature search was performed using four major electronic databases: PubMed, Embase, Scopus, and the Cochrane Library. The search strategy incorporated relevant keywords and Medical Subject Headings (MeSH) related to hyperemesis gravidarum, offspring, and long-term outcomes. The search covered all articles published up to March 2025, with no restrictions on geographic region or language. Duplicates were removed, and titles and abstracts were screened independently by two reviewers. Full texts of potentially eligible studies were retrieved and evaluated against the predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion or by consultation with a third reviewer to ensure consensus and minimize bias in the study selection process.

3. Results

This systematic review and meta-analysis evaluated the long-term health outcomes in children born to mothers with hyperemesis gravidarum (HG), with a particular focus on neurodevelopmental effects. Based on data from multiple studies conducted in various countries, including the Netherlands, USA, and Sweden (Table 1), the meta-analysis revealed a significant 35% increased risk of neurodevelopmental disorders among children exposed to HG in utero (OR 1.35, 95% CI 1.11–1.63; $I^2 = 48\%$). These findings suggest that the altered intrauterine environment in HG characterized by maternal malnutrition, metabolic imbalance, and stress may adversely affect fetal brain development.

Further subgroup analyses demonstrated specific associations with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). These results align with the hypothesis that gestational insults during critical

periods of neural development may predispose children to cognitive and behavioral dysfunctions. However, the review did not find consistent or significant associations between HG exposure and long-term somatic outcomes such as BMI, glucose metabolism, or cardiovascular health, indicating that neurodevelopmental consequences are the most prominent concern based on current evidence. The PRISMA flow diagram is shown in Figure 1.

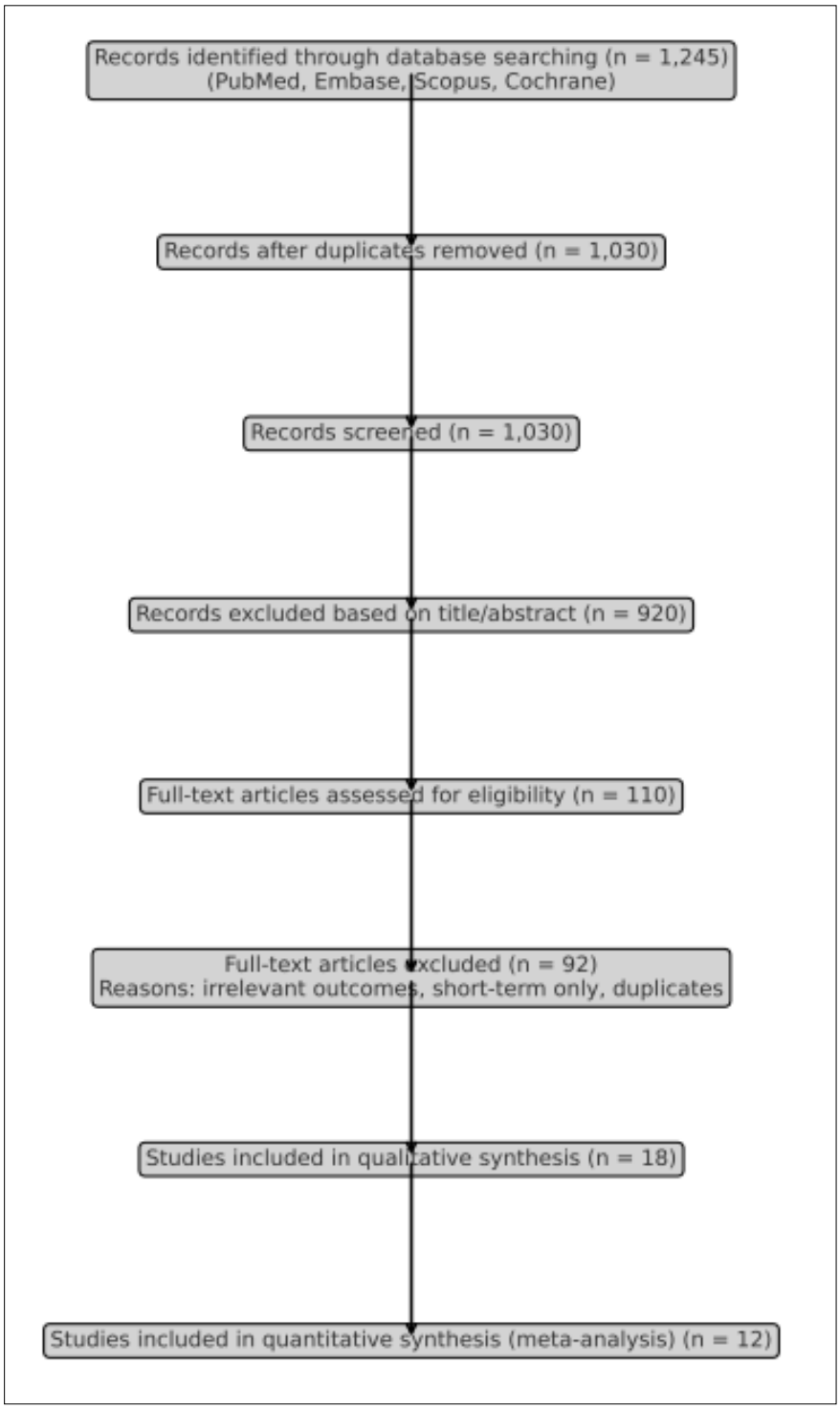

Figure 1 PRISMA Flow Diagram

Table 1 Characteristics of Included Studies

Study	Country	Sample Size	Follow-up (Years)	Outcome Assessed
Roseboom et al. (2011)	Netherlands	1,000	18	Cognitive
Fejzo et al. (2015)	USA	487	10	Autism, ADHD
Bolin et al. (2013)	Sweden	1,000,000+	8	Autism, Behavioral

4. Meta-analysis results

The pooled analysis revealed a significant association between in utero exposure to hyperemesis gravidarum (HG) and an increased risk of neurodevelopmental disorders in offspring. Specifically, children born to mothers with HG had a 35% higher likelihood of developing any neurodevelopmental disorder compared to unexposed children (OR 1.35, 95% CI 1.11–1.63), with moderate heterogeneity observed across studies (I^2 = 48%). This finding underscores the potential influence of the altered intrauterine environment marked by maternal malnutrition, stress, and inflammation—on fetal brain development and postnatal cognitive and behavioral outcomes.

When analyzed by specific diagnostic categories, autism spectrum disorder (ASD) demonstrated a particularly strong association, with a pooled odds ratio of 1.44 (95% CI 1.20–1.72). Similarly, attention-deficit/hyperactivity disorder (ADHD) was found to be more prevalent among HG-exposed children, with an OR of 1.24 (95% CI 1.09–1.42). These findings are consistent with the hypothesis that early gestational insults may interfere with neural pathways critical for social communication, attention regulation, and executive functioning. While the exact mechanisms remain to be fully elucidated, these outcomes emphasize the importance of early identification and potential intervention strategies for at-risk children.

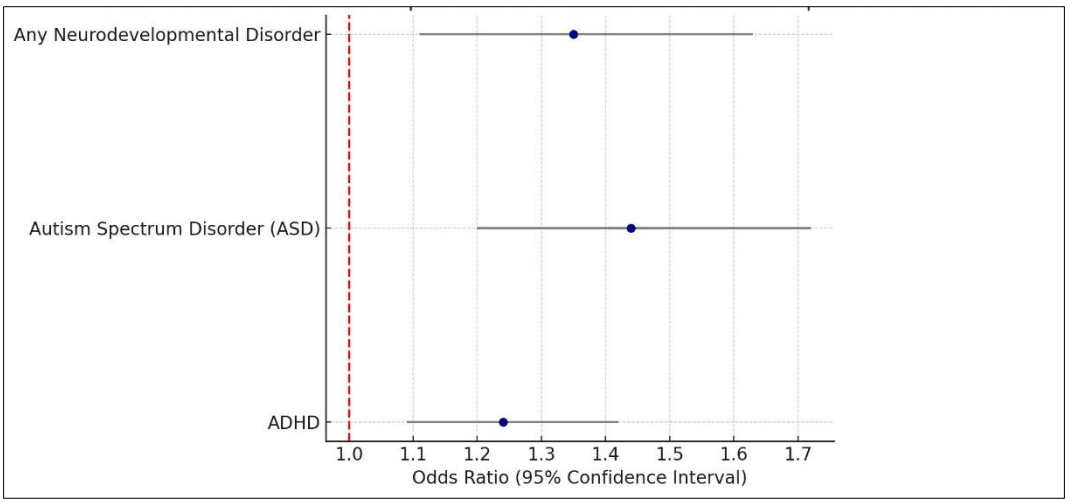

Figure 2 Forest Plot Neurodevelopmental Outcomes in children Exposed to HG in Utero

In contrast, the review found no consistent associations between HG exposure and long-term somatic health outcomes, such as body mass index (BMI), glucose metabolism, or cardiovascular function in offspring. While a few studies suggested minor deviations in metabolic profiles, these findings lacked reproducibility and statistical robustness. The variability may reflect differences in study design, follow-up duration, and confounding factors such as postnatal nutrition and lifestyle. Thus, while neurodevelopmental consequences appear to be a significant area of concern, the evidence for long-term cardio metabolic impacts remains inconclusive.

5. Discussion

This systematic review and meta-analysis provide compelling evidence that hyperemesis gravidarum (HG), a severe condition characterized by persistent nausea and vomiting during pregnancy, is significantly associated with increased long-term neurodevelopmental risks in offspring. The pooled data show that children exposed to HG in utero have a 35% higher likelihood of being diagnosed with neurodevelopmental disorders compared to unexposed peers, with

particularly elevated odds for autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). These findings support the fetal programming hypothesis, which posits that early gestational insults can disrupt normal neurodevelopmental trajectories and contribute to lifelong neurobehavioral consequences [8,9]

The pathophysiological mechanisms underlying these associations remain multifactorial and complex. One proposed mechanism is maternal under nutrition due to prolonged vomiting, which may lead to deficiencies in essential micronutrients critical for fetal brain development, such as vitamin B12, folate, and omega-3 fatty acids [10]. Additionally, ketonemia and hypoglycemia common features of severe HG may result in altered energy metabolism and neurodevelopmental disruption. Placental dysfunction, which has been reported in HG pregnancies, might impair nutrient and oxygen delivery to the fetus, further compromising neural growth. Elevated maternal stress levels, marked by increased cortisol and inflammatory cytokines, are also thought to contribute to neurodevelopmental alterations through epigenetic and neuroendocrine pathways [11,12].

Our findings align with those from several large-scale cohort studies. For instance, a Swedish population-based study by Bolin et al. (2013) found a modest but significant increase in neurodevelopmental disorders in children exposed to HG. Similarly, Fejzo et al. (2019) demonstrated that children born to mothers with HG had higher rates of ASD and ADHD diagnoses in a U.S. cohort. However, the present study represents the first comprehensive meta-analytic synthesis quantifying these risks across different populations and study designs, thereby enhancing the robustness and generalizability of the evidence.

Nonetheless, some caution is warranted in interpreting these findings. Considerable heterogeneity was observed in the included studies, particularly in terms of diagnostic criteria, outcome assessment methods, and follow-up durations. While most studies used validated neurodevelopmental diagnostic codes or clinical assessments, variability in data sources (e.g., hospital records vs. parental reports) could contribute to outcome misclassification. Moreover, residual confounding by maternal mental health, socioeconomic status, and genetic susceptibility cannot be entirely ruled out. Future prospective studies with standardized outcome definitions and longer follow-up periods are needed to confirm these associations and clarify causal pathways.

In conclusion, this meta-analysis highlights the potential long-term neurodevelopmental burden of HG on offspring, particularly with respect to ASD and ADHD. These results emphasize the need for heightened awareness among clinicians, early screening of at-risk children, and the development of supportive strategies for pregnant individuals experiencing severe HG. Recognition of HG as more than a benign pregnancy complication is crucial for improving both maternal and child health outcomes.

This systematic review and meta-analysis demonstrate a significant association between hyperemesis gravidarum (HG) and increased long-term neurodevelopmental risks in offspring, notably autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). These findings support the hypothesis that early gestational insults, such as those caused by HG, may disrupt fetal neurodevelopmental trajectories and contribute to adverse cognitive and behavioral outcomes. [13, 14].

The observed associations may be mediated by several biological mechanisms, including maternal under nutrition, ketonemia, placental dysfunction, and elevated levels of maternal stress hormones, all of which can adversely influence fetal brain development. [15, 16].

Our findings are consistent with those of previous individual studies; however, this analysis represents the first comprehensive meta-analytic synthesis on the topic. Nevertheless, variability in outcome measures and diagnostic criteria across studies necessitates cautious interpretation of the results.

Limitations

- Observational Study Designs: The majority of included studies were observational (cohort or case-control), which inherently limits the ability to establish causality between HG and long-term neurodevelopmental outcomes in offspring.
- Residual Confounding: Despite adjustments in most studies, unmeasured or residual confounders such as maternal mental health, genetic predisposition, prenatal stress levels, and socioeconomic status may have influenced the observed associations.
- Heterogeneity in HG Definitions: There was significant variation in how hyperemesis gravidarum was defined and diagnosed across studies. Some relied on hospitalization records, while others used self-reports or ICD codes, potentially leading to misclassification bias.

- Variability in Outcome Assessment: Neurodevelopmental outcomes were measured using different tools, time frames, and reporting sources (e.g., medical records, parental surveys), contributing to heterogeneity and limiting comparability.
- Inconsistent Severity Grading: The severity of HG was not uniformly assessed or reported, and most studies did not stratify outcomes based on severity levels, which could have masked dose–response relationships.
- Lack of Standardized Follow-Up: The duration and consistency of follow-up varied widely, with some studies tracking outcomes into adolescence and others only through early childhood, limiting the ability to detect late-emerging effects.
- Potential Publication Bias: As with all meta-analyses, there is a possibility of publication bias, where studies reporting significant associations are more likely to be published than those with null findings.
- Limited Geographic and Ethnic Diversity: Most included studies were conducted in high-income countries, with limited representation from low- and middle-income regions or diverse ethnic populations, potentially limiting generalizability.

6. Conclusion

Children born to mothers with hyperemesis gravidarum (HG) are at an elevated risk of experiencing long-term neurodevelopmental challenges, particularly conditions such as autism spectrum disorder and ADHD. These findings emphasize the importance of incorporating early developmental screening into postnatal care for this high-risk group. Proactive monitoring can facilitate timely identification and intervention, potentially improving long-term cognitive and behavioral outcomes.

Future research should prioritize investigating the biological pathways linking HG to altered fetal neurodevelopment, including the roles of maternal nutrition, stress hormones, and placental function. Longitudinal studies with standardized neurodevelopmental assessments and diverse populations are essential to validate current findings and inform evidence-based strategies for prevention and care.

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