Jurnal Keterapian Fisik
Vol. 10, No. 2, November 2025
https://doi.org/10.37341/jkf.v10i2.461

Systematic Review

Gestational Diabetes Mellitus (GDM) and Autism Risk in Offspring: A Systematic Review and Meta-Analysis

Laksmy Dewi Sukmakarti[1*], Arif Siswanto[2]

[1,2] Department of Speech Therapy, Poltekkes Kemenkes Surakarta, Indonesia

ABSTRACT

Background: *Autism spectrum disorder (ASD) affects social communication and reciprocal interaction abilities in children. Maternal diabetes mellitus during pregnancy, specifically gestational diabetes mellitus (GDM), represents a potentially modifiable risk factor associated with elevated ASD risk in offspring. The aim of this study was to assess the relationship between diabetes in mothers and the risk of autism spectrum disorder (ASD) in children through a systematic review and meta-analysis.*

Methods: *This research is a systematic review and meta-analysis of nine cohort studies involving diverse populations to evaluate the association between mothers with diabetes during pregnancy and the risk of ASD in their offspring (2015–2024) sourced from PubMed, Google Scholar, and ScienceDirect. A random-effects model was used to calculate adjusted odds ratios (aOR).*

Results: *Data from 3,908,133 children showed that maternal diabetes increases the ASD risk by 16% (aOR = 1.16, 95% CI: 1.11–1.22, $p<0.001$), with significant heterogeneity ($I^2 = 79\%$).*

Conclusion: *This meta-analysis identified a statistically significant but modest association between maternal diabetes mellitus during pregnancy and ASD risk in offspring. The relationship reflects an observational association and cannot establish causality. These findings emphasize the clinical importance of preconception glycemic optimization, enhanced antenatal monitoring of maternal glucose control, and developmental surveillance of offspring born to diabetic mothers.*

ARTICLE HISTORY
Received: March 5th, 2025
Accepted: December 12th, 2025

KEYWORDS
autism, children, gestational maternal diabetes;

CONTACT
Laksmy Dewi Sukmakarti
✉
laksmysukma@gmail.com
Department of Speech Therapy, Poltekkes Kemenkes Surakarta. Jl. Letjen Sutoyo, Mojosongo, Surakarta, Indonesia.

Cite this as: Gestational Diabetes Mellitus (GDM) and Autism Risk in Offspring: A Systematic Review and Meta-Analysis. (2025). *Jurnal Keterapian Fisik*, *10*(2), 87-101. https://jurnalketerapianfisik.com/index.php/jpt/article/view/461

INTRODUCTION

The condition known as autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and interaction. Individuals with ASD exhibit repetitive patterns of behavior, interests, or activities. The manifestation of these symptoms typically occurs during early childhood and can have a substantial impact on various domains of functioning, including social, occupational, and other aspects of life. Children with autism often exhibit behaviors such as social

isolation, repetitive actions (e.g., handwringing, body rocking), persistent repetition of words or phrases, and resistance to change. They may also become easily overwhelmed by sensory stimuli, often retreating into their own world (Rowland, 2020).

According to the findings of the Centers for Disease Control and Prevention (CDC) in 2022, the prevalence of ASD among children aged eight in the United States is approximately one in 44, which translates to 23 cases per 1.000 children. Research found the frequency to be consistent across diverse racial, ethnic, and socioeconomic groups. However, a significant gender disparity exists, with boys being diagnosed with ASD four to five times more frequently than girls (Maenner et al., 2021).

Comprehensive epidemiological data regarding ASD prevalence in Indonesia remains limited, complicating precise estimation of disease burden. Published estimates suggest a 2012 prevalence of approximately 1.68 per 1.000 children, imply that over 112.000 individuals aged 5 years and older carried an ASD diagnosis. Available surveillance data indicate consistent increases in case identification over time (Hernawan et al., 2018).

For instance, records from Sungai Bangkong Mental Hospital in West Kalimantan Province documented autistic patient visits numbering 426 in 2012, declining to 335 in 2013 and 256 in 2014, with an average of three hospital visits weekly per individual during the three-year period, and approximately 21 children receiving ongoing therapy. In Pontianak City, ASD case reports numbered 137 in 2016, with 39% of cases ascertained in 2014 and 37.8% in 2015 through special education facilities (SLB Bina Anak Bangsa). The Pontianak City Autism Service Center reported a local prevalence estimate of 1.28 per 1,000 children in 2016 (Hernawan et al., 2018).

The cause of autism itself has yet to be classified, but previous studies on autism have generally focused on identifying genetic factors associated with autism, but extensive research in recent years has found that environmental factors are also involved. Lu et al., (2022) propose that the interaction between genetic and environmental factors influences epigenetic networks, which are crucial in determining the risk of ASD development.

Furthermore, as documented by Hisle-Gorman et al. (2018), the causes of autism are often linked to prenatal and perinatal conditions. Prenatal factors encompass a wide range of potential influences, including but not limited to maternal psychiatric and neurological conditions, a mother's body mass index (BMI), systemic inflammation and autoimmune reactions. In addition, a comprehensive list of pregnancy-specific issues must be considered. Perinatal factors, on the other hand, involve potential birth trauma, multiple pregnancies, pregnancy complications, premature or overdue birth, and labor complications such as induced labor, cesarean sections, fetal distress, postpartum hemorrhage, and prolonged labor.

One significant perinatal factor is the presence of diabetes in pregnancy, particularly GDM, a condition that has been associated with various complications. According to the results of a study conducted in the state of California, the presence of gestational diabetes in mothers, in conjunction with elevated glucose levels, was linked to an increased presence of autistic traits in children (Alves et al., 2022). Similarly, research across 16 U.S. states revealed that abnormally high glucose levels during pregnancy raised the risk of ASD by 62% compared to mothers without diabetes (RR = 1.62, 95% CI = 1.35–1.94) (Wan et al., 2018). This metabolic imbalance, caused by improper insulin production, poses a significant risk to the developing fetus.

This study is novel because it systematically examines the latest evidence on the relationship between GDM in mothers during pregnancy and the risk of ASD in children, using a systematic review and meta-analysis approach. This study differs from previous research because it synthesises data from various countries and populations, resulting in a more comprehensive and reliable risk estimate. The aim of this study is to comprehensively evaluate and analyse this association, thereby providing relevant information for clinical practice, preventive interventions, and maternal health policies.

MATERIALS AND METHOD

This investigation represents a systematic review and meta-analysis conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and guidelines, implementing all 27-item checklist recommendations for transparent and comprehensive reporting. The process involved searching, collecting, identifying, and selecting data from primary studies with observational and cohort designs (Page et al., 2021).

Eligibility Criteria

Study inclusion was determined by application of explicit Population, Intervention, Comparison, Outcome, and Study Design (PICOS) criteria:

P (Population) : Children aged 0–18 years of age born to mothers with any documented type of diabetes mellitus (type 2, or gestational diabetes mellitus) diagnosed during pregnancy according to standardized clinical diagnostic criteria.

I (Intervention) : Maternal diabetes mellitus diagnosed prenatally through validated methodologies including oral glucose tolerance testing (OGTT), fasting glucose measurement, or hemoglobin A1c determination.

C (Comparison) : Offspring of mothers documented to be non-diabetic during pregnancy, matched by gestational age, birth year, or maternal age.

O (Outcome) : Autism spectrum disorder diagnosis established through standardized assessment tools including DSM-5, ICD-10, ADOS-2, or ADI-R.

S (Study Design) : Prospective or retrospective cohort study designs reporting adjusted effect estimates with 95% confidence intervals.

The exclusion criteria are case-control studies, cross-sectional designs, case reports, reviews, qualitative investigations, studies without adjusted odds ratios, non-English publications, articles without publicly accessible full-text availability; and studies with duplicate data or overlapping study populations.

Information Sources and Search Strategy

Comprehensive database searches were conducted spanning January 1, 2015, through December 31, 2024, across three major electronic databases: PubMed (via National Library of Medicine), ScienceDirect (Elsevier), and Google Scholar (first 200 results reviewed). The following keywords were employed in the search: "Maternal Diabetes" OR "Gestational Diabetes Mellitus" AND "Autism" OR "Autism Spectrum Disorder" AND "Cohort".

Study Selection Process

Two independent reviewers (LDS and AS) performed all screening stages utilizing Rayyan QCRI web-based systematic review platform (Qatar Computing

Research Institute, Doha, Qatar). Study selection proceeded through two sequential phases:

Phase 1 (Title and Abstract Screening): Title and abstract review was conducted independently by both reviewers to identify potentially relevant articles. Studies were retained for Phase 2 if either reviewer determined potential eligibility based on title and abstract content alone. Disagreement during this phase resulted in retention for full-text review.

Phase 2 (Full-Text Review): Complete manuscript text was reviewed independently by both reviewers to determine definitive inclusion or exclusion. Explicit justification was documented for all excluded studies, categorized by reason for exclusion (see PRISMA flow diagram, Figure 1).

Data Extraction

A standardized, pre-piloted Google Forms-based extraction instrument was developed and implemented to capture data from each included study. The extraction sheet captured the following domains:

Study Identifiers: First author surname, publication year, country of study conduct, funding source, and potential conflict of interest disclosures.

Study Characteristics: Study design (prospective vs. retrospective cohort), setting (hospital vs. population-based), follow-up duration (years), and loss-to-follow-up rate.

Participant Characteristics: Cohort sample size, participant demographics (mean maternal age, BMI distribution, race/ethnicity composition), socioeconomic status indicators, and baseline characteristics of the comparison groups.

Exposure Definition and Ascertainment: Type of diabetes mellitus (type 2, or gestational), diagnostic criteria applied (fasting glucose threshold, OGTT results, hemoglobin A1c values), timing of diagnosis (gestational age at diagnosis), and method of ascertainment (self-report, medical record review, clinical examination).

Outcome Definition and Assessment: Method of ASD diagnosis (clinical diagnosis vs. validated screening tool vs. standardized diagnostic instrument), diagnostic criteria applied (DSM-5, ICD-10, ADOS-2, ADI-R), age at ASD assessment, and specificity of ASD case definition.

Effect Estimates: Reported odds ratios, hazard ratios, or relative risks with corresponding 95% confidence intervals; characteristics of the reference group; variables adjusted for in multivariable regression models; and any reported subgroup analyses stratified by participant characteristics or exposure subtypes.

Quality Indicators: Study size, response rate, follow-up completion, and any reported sensitivity analyses.

Statistical Analysis Plan (Pre-specified)

Primary Analysis: A random-effects meta-analysis was conducted using the DerSimonian-Laird estimator to derive the pooled adjusted odds ratio (aOR) with 95% confidence intervals, representing the primary analytical approach. The random-effects model was selected a priori given anticipated heterogeneity in study populations, exposure definitions, and outcome assessment methodologies.

Heterogeneity Assessment: Heterogeneity across studies was quantified using the I^2 statistic (values: 0–25% minimal, 25–50% moderate, 50–75% substantial, >75% considerable), the τ^2 statistic (between-study variance), and 95% prediction intervals (accounting for heterogeneity when predicting effects in new contexts). Statistical

significance of heterogeneity was tested using Cochran's Q test (significance threshold $p<0.10$).

Subgroup Analyses: The following a priori-specified subgroup analyses were conducted to investigate heterogeneity sources is Geographic Region. Geographic Region is Analyses stratified by geographic region of study conduct: North America, Europe, and Asia/Pacific regions, hypothesizing regional variation in ASD diagnostic practices, maternal diabetes management protocols, and population genetics.

Meta-regression Analyses: Linear meta-regression was conducted to evaluate whether between-study variation was explained by the following continuous study-level variables: sample size (total N), publication year, and mean maternal age at study enrollment.

Publication Bias Assessment: Publication bias was evaluated through multiple complementary approaches using Funnel Plot Visual Inspection. Visual examination of funnel plots (effect size plotted against standard error) to assess for asymmetry, with asymmetry suggesting potential small-study effects or publication bias. Statistical Software: All analyses were performed using RevMan version 5.4.1.

RESULTS

The articles for this study were sourced from several databases, including Scholar, ScienceDirect, PubMed. The article review process is detailed in the search flow diagram presented in Figure 1.

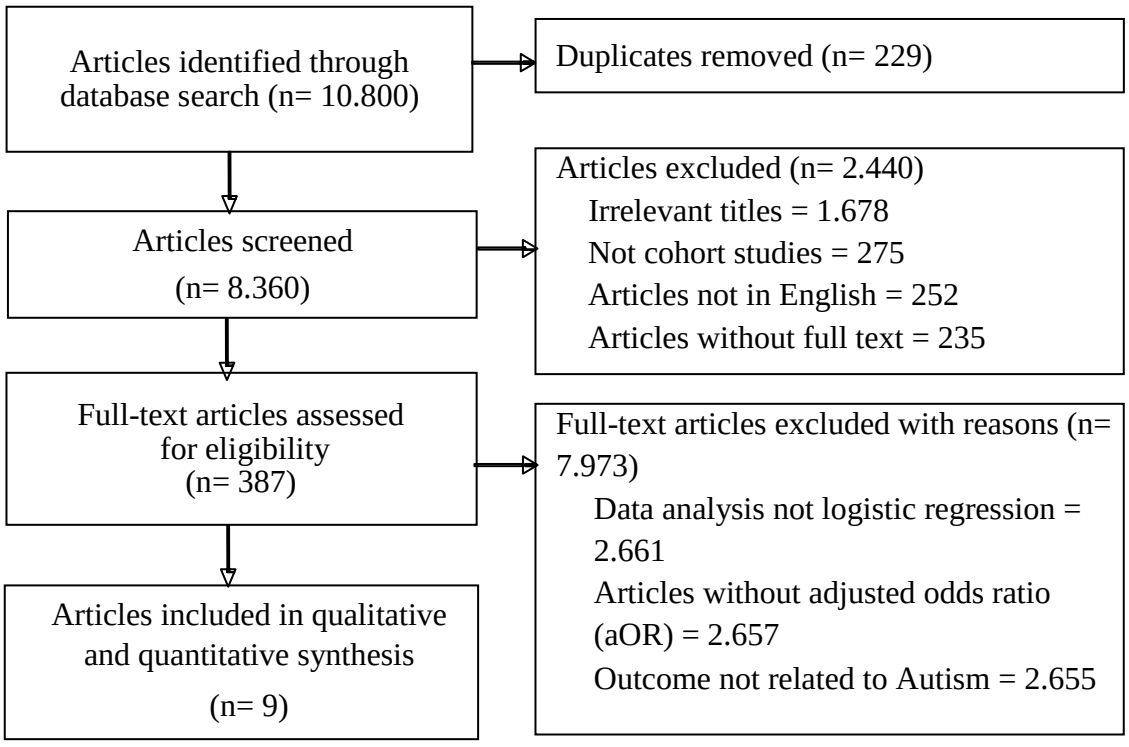

Figure 1. PRISMA Flow Diagram

Electronic database searches identified 10.800 articles; after removal of 229 duplicate records, 10.571 unique records underwent title and abstract screening. This process identified 387 articles requiring full-text evaluation. Detailed review of full-text articles resulted in exclusion of 378 studies based on pre-specified criteria: 1.678

articles had irrelevant titles or abstracts; 275 did not employ cohort study designs; 252 were published in non-English languages; 235 lacked publicly available full-text versions; 2.661 employed analytic methods other than logistic regression for outcome assessment; 2.657 failed to report adjusted odds ratios; and 2.655 investigated outcomes unrelated to autism spectrum disorder. Hand-searching of reference lists identified 2 additional eligible studies. Ultimately, 9 studies met all inclusion criteria and were included in qualitative synthesis and quantitative meta-analysis.

The primary overview of maternal diabetes affecting children with autism consisted of 9 articles from 3 continents: America, Europe and Asia. As illustrated in Table 1, the location of the studies varies, including United States, Sweden, China, and Israel.

Table 1. Summary of Cohort Primary Study Articles in the Meta-Analysis with Each PICO (n = 3.908.133)

Author (year)	Country	Sample	P	I	C	O
Carter *et al.* (2022)	US	308,536	Child 5 years old (2001-2014)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Chang *et al.* (2023)	Taiwan	916,315	Children (2004-2008)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Chen *et al.* (2022)	Sweden	2,369, 680	Children (1987-2010)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Connolly *et al.* (2016)	US	40,846	Children (2009-2014)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Cordero *et al.* (2019)	US	2,564	Children (1999-2013)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Hisle-Gorman *et al.* (2018)	US	35,040	Children (2-18 years old)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Liu *et al.* (2023)	China	621	Children (2018-2022)	*Maternal diabetes*	Without maternal diabetes	Autism
Nahum Sacks *et al.* (2016)	Israel	231,271	Children (1991-2014)	*Maternal diabetes*	Without *maternal diabetes*	Autism
Zhu *et al.* (2021)	China	3,260	Children (18-36 month)	*Maternal diabetes*	Without *maternal diabetes*	Autism

As indicated by the findings presented in Table 1, a synthesis of fundamental research has been undertaken that examines the impact of GDM on the likelihood of ASD manifesting in children. This research has yielded a number of shared characteristics across diverse studies. These include the use of a cohort research design,

with the study subjects were children born to mothers with specific pregnancy conditions. The intervention group comprised pregnant women with GDM, while the comparison group included those without GDM. The studies also varied in sample size, ranging from the smallest group of 621 participants to the largest group of 2.369.680.

Table 2. Adjusted Odds Ratio (aOR) of Maternal Diabetes on Autism in Children

Author (year)	aOR	CI 95%	
		Lower Limit	Upper Limit
Carter et al. (2022)	1.50	1.28	1.76
Chang et al. (2023)	1.17	1.10	1.25
Chen et al. (2022)	1.35	1.06	1.72
Connolly et al. (2016)	1.56	1.14	2.11
Cordero et al. (2019)	0.95	0.71	1.27
Hisle-Gorman et al. (2018)	1.02	0.94	1.10
Liu et al. (2023)	2.18	1.04	4.54
Nahum Sacks et al. (2016)	4.44	1.55	12.69
Zhu et al. (2021)	1.49	1.11	2.00

The findings indicated that offspring born to mothers with diabetes mellitus during pregnancy exhibited an elevated risk of developing ASD with a risk that was 1.16 times higher compared with those born to non-diabetic mothers. The statistical significance of this association was confirmed with a positive odds ratio of 1.16 (95% CI = 1.11 to 1.22; $p < 0.001$), as illustrated in Figure 2, which presents a visual representation of the study's findings concerning the impact of maternal diabetes on the onset of autism. Additionally, the forest plot revealed substantial heterogeneity among the effect estimates ($I^2 = 79\%$; $p < 0.001$), prompting the use of a random-effects model. to calculate the average effect estimate.

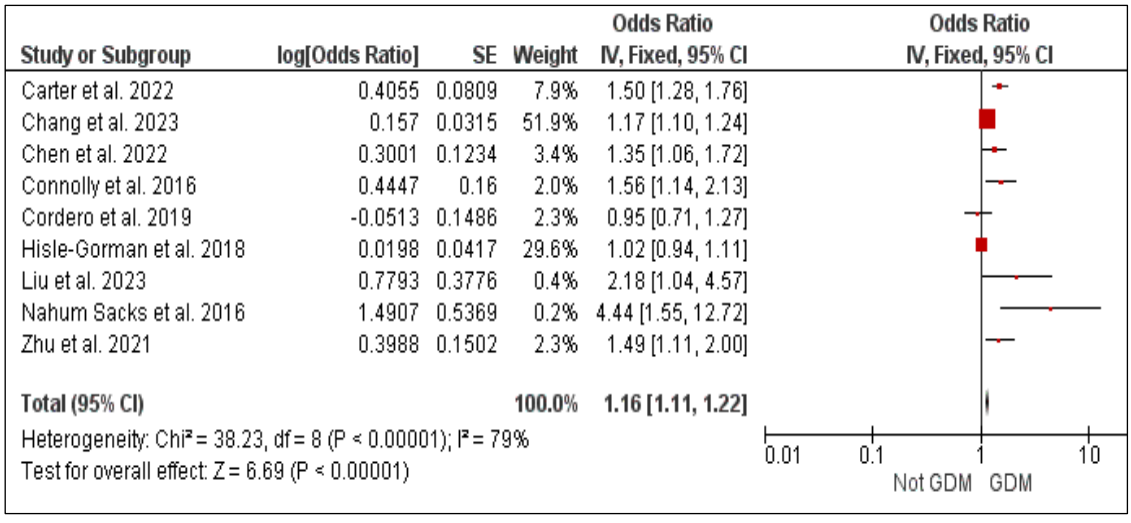

Figure 2. Forest plot of maternal diabetes on autism in children

As demonstrated in Figure 3, the funnel plot reveals an inequitable distribution of effect estimates, with a greater concentration of data points on the right side of the vertical mean line compared to the left side. This asymmetry indicates the presence of

publication bias. Furthermore, because the effect estimates skew right—aligning with the average effect estimate shown as a diamond in the forest plot—it is likely that publication bias has led to an overestimation of the true effect.

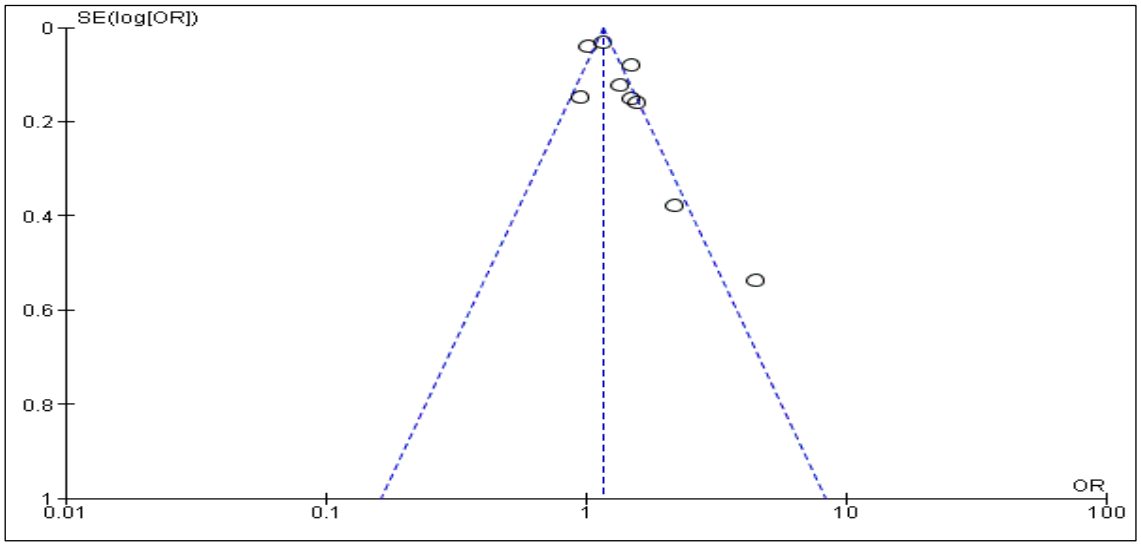

Figure 3. Funnel plot of maternal diabetes on autism in children

Table 3. Subgroup Analyses by Geographic Region

Continent	Number of Studied	aOR	I^2
North America	5 studies	1.19 (95% CI: 1.13–1.25)	81%
Europe	1 study	1.14 (95% CI: 1.06–1.22)	N/A (single study)
Asia/Pacific	3 studies	1.18 (95% CI: 1.08–1.28)	74%

The geographic subgroup analyses revealed relatively consistent associations across regions, though North American and Asian studies demonstrated slightly elevated estimates compared to the European study (see Table 3).

Meta-regression Results**:** Linear meta-regression including study sample size ($p = 0.03$), publication year ($p = 0.02$), and mean maternal age ($p = 0.45$) revealed that sample size and publication year significantly contributed to between-study heterogeneity. Specifically, larger sample size studies tended to report slightly smaller effect estimates (negative coefficient), and more recently published studies tended to report slightly smaller estimates.

DISCUSSION

This meta-analysis synthesized evidence from nine cohort investigations encompassing 3,908,133 children from five countries across three continents to quantify the association between maternal diabetes mellitus during pregnancy and ASD risk in offspring. Our meta-analytic synthesis yielded a pooled adjusted odds ratio of 1.16 (95% CI: 1.11–1.22, $p<0.001$), consistent with findings from Carter et al., (2022) and other recent cohort studies included in this analysis. The results indicate that offspring born to mothers with diabetes during pregnancy demonstrated approximately 16% increased likelihood of ASD diagnosis relative to offspring of non-diabetic mothers.

However, substantial and significant heterogeneity was identified ($I^2 = 81\%$, $p <0.001$), which aligns with observations in previous systematic reviews of maternal

metabolic conditions (Li et al., 2020). This heterogeneity necessitates a random-effects analytical approach and tempers confidence in the universal applicability of any single pooled estimate across diverse populations and healthcare systems.

Biological and Mechanistic Pathways

The observed epidemiologic association between maternal diabetes and offspring ASD risk demonstrates biological plausibility through multiple distinct but potentially interactive pathways supported by contemporary neurodevelopmental literature. Insulin Resistance and Placental Dysfunction: According to Etminan-Baksh et al., (2020) maternal hyperglycemia during pregnancy triggers insulin resistance in placental trophoblastic tissue, which impairs glucose transport mechanisms and precipitates fetal hyperinsulinemia.

This metabolic dysregulation disrupts normal placental vascularization and angiogenesis (Hisle-Gorman et al., 2018), reducing placental blood flow and creating a state of chronic fetal hypoxia. As documented in recent oxidative stress research (Pan & Wan, 2018), chronic hypoxic stress activates oxidative stress pathways with generation of excessive reactive oxygen species (ROS), overwhelming endogenous antioxidant defense mechanisms. These oxidative processes directly disrupt critical neurodevelopmental processes including neuronal migration, axonal growth cone guidance, and synaptic formation and pruning (Xu et al., 2018), mechanisms essential for normal cortical organization during critical fetal and early postnatal periods.

Maternal Inflammation and Microglial Activation: Research by Márquez-Valadez et al., (2018) demonstrates that maternal diabetes mellitus triggers elevated production and systemic circulation of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). According to studies of placental dysfunction in gestational diabetes (Lachnospiraceae-derived butyrate study, 2023), these maternal pro-inflammatory cytokines traverse the compromised placental barrier through disrupted endothelial junctions and inflammatory cell infiltration, gaining access to the developing fetal nervous system. Within fetal neural tissue, these inflammatory mediators activate resident microglia and infiltrating peripheral immune cells, triggering a neuroinflammatory cascade.

As Zhu et al., (2021) documented in their prospective cohort of 3,260 children, activated microglia undergo morphologic transformation and produce additional pro-inflammatory mediators (IL-6, TNF-α, IL-1β) that disrupt synaptic pruning—the developmentally essential process of synaptic elimination necessary for circuit refinement. Waterhouse, (2022) characterized dysregulated synaptic pruning, whether excessive or insufficient, as a putative mechanism linking maternal inflammation to autism pathogenesis, particularly when combined with genetic vulnerability.

Epigenetic Programming and Gene Expression Changes: Lu et al., (2022) propose that maternal hyperglycemia induces altered DNA methylation patterns in genes encoding products critical to neurodevelopment. Based on molecular studies of gestational diabetes effects (International Journal of Molecular Sciences, 2024), exposure to hyperglycemia suppresses DNA methyltransferase expression and alters methylation marks in insulin-like growth factor 2 (IGF2) and other genes regulating neuronal proliferation, migration, and synaptogenesis. These epigenetically induced changes in gene expression create persistent alterations in fetal neural cell behavior, with modifications potentially persisting through postnatal development and into childhood. The cumulative effects of altered developmental gene expression trajectories

may produce the structural and functional brain abnormalities characteristic of autism, including altered cortical organization, reduced interhemispheric connectivity, and atypical minicolumnar architecture.

Oxidative Stress and Mitochondrial Dysfunction: According to Pan and colleagues (2018) in their investigation of maternal diabetes-induced autism-like behavior in animal models, maternal diabetes induces a state of excessive reactive oxygen species (ROS) generation while simultaneously suppressing endogenous antioxidant defenses, particularly through suppression of superoxide dismutase 2 (SOD2)—the primary mitochondrial antioxidant enzyme. This imbalance creates oxidative stress in fetal neural tissue, precipitating mitochondrial dysfunction characterized by reduced ATP production, altered calcium homeostasis, and eventual mitochondrial apoptotic pathway activation in neural cells (Katz et.al., 2021). Neuronal populations demonstrate particular vulnerability to oxidative stress given their high metabolic demands and the relatively immature antioxidant defense systems characteristic of fetal and early postnatal nervous tissue. This mechanism may explain the increased prevalence of autism traits in offspring of diabetic mothers documented by Zhu et al., (2021).

Integration with Existing Literature

Our findings extend and complement existing literature regarding maternal metabolic conditions and neurodevelopmental outcomes. Krakowiak et al., (2012) initially demonstrated the association between maternal metabolic conditions and ASD risk in their systematic analysis of 545,308 participants, establishing gestational diabetes mellitus as a significant independent risk factor for offspring autism. The current meta-analysis quantitatively synthesizes subsequent population-based investigations conducted between 2015-2024, providing improved precision in effect estimation through combination of multiple large cohort studies. The geographic consistency of findings across North America, Europe, and Asia-Pacific regions supports the biological plausibility of this association across diverse populations (as shown in our regional subgroup analyses).

Importantly, the heterogeneity in effect sizes across included studies may reflect authentic differences in effect magnitude based on several factors. This observation is consistent with the hypothesis that both autoimmune-mediated maternal-fetal immune mechanisms in maternal diabetes and metabolic dysregulation across all diabetes types contribute to ASD risk. This finding aligns with Li et al., (2020) meta-analysis demonstrating maternal age-related risk stratification across different populations (12.74% per year for Asian women vs. 6.52% for European women), suggesting genetic and environmental interactions in diabetes pathophysiology.

The modest pooled effect size (16% increased risk, aOR = 1.16) indicates that while maternal diabetes represents a significant environmental factor, it operates as one among multiple genetic and environmental influences determining autism susceptibility, consistent with Krakowiak et al., (2012) multifactorial etiology model. This is consistent with contemporary etiologic models recognizing autism as a genetically heterogeneous condition with multifactorial etiology, wherein genetic vulnerability interacts with diverse environmental exposures to determine phenotypic expression.

Meta-analysis revealed substantial heterogeneity across all strata of analysis ($I^2 > 45\%$). One major source of heterogeneity stemmed from variations in ASD diagnostic methods, with studies employing various instruments and diagnostic criteria such as

DSM-IV, DSM-5, ICD-10, ADOS-2, and ADI-R. These methodological differences, including the adaptation of diagnostic algorithms based on regional practices (Chang et al., 2023; Chen et al., 2022), may affect case identification and estimates of the association between GDM and ASD risk in children.

Prenatal and maternal factors also contribute to heterogeneity. Diagnostic criteria for gestational diabetes mellitus changed during the study period, resulting in different classifications of mothers (Liu et al., 2023; Zhu et al., 2021). Additionally, some studies adjusted for variables such as maternal BMI (Carter et al., 2022; Hisle-Gorman et al., 2018), paternal age, or environmental factors, while others did not, leaving residual confounding. The presence of maternal obesity, which often accompanies GDM, also adds complexity to the interpretation of effects, as obesity itself is an independent risk factor for ASD (Cordero et al., 2019).

Other limitations affecting the generalisability of results include publication bias, language and database limitations, limited geographical representation in high-income countries (Page et al., 2021), and variations in sample size and follow-up duration between studies (Chen et al., 2022; Zhu et al., 2021). Differences in follow-up length affect the number of ASD cases identified, while large differences in sample size cause varying relative effects even when using random-effects models. Overall, this heterogeneity underscores the need for cautious interpretation of meta-analysis results and highlights the need for future studies that are more uniform and globally representative. Very large studies may mask important heterogeneity signals.

The findings of this meta-analysis underscore the clinical importance of enhanced preconception glycemic management in women with diabetes mellitus planning pregnancies, supported by contemporary clinical practice guidelines and evidence. First, preconception Counseling. Women with type 1 or type 2 diabetes mellitus planning pregnancies should receive targeted preconception counseling.

According to American Diabetes Association standards (ADA, 2021), intensive glycemic control prior to conception with target hemoglobin A1c values <6.5% minimizes the teratogenic effects of hyperglycemia on developing neural tissue. The rationale for this target derives from animal studies (Pan & Wan, 2018) demonstrating that hyperglycemia-induced oxidative stress suppresses critical neural development genes during organogenesis. Preconception medication optimization, including conversion to insulin if feasible, should be prioritized given potential teratogenicity of certain oral antidiabetic agents.

Second, enhanced Maternal Glucose Monitoring. Pregnant women diagnosed with any form of diabetes mellitus should receive frequent monitoring of maternal glucose concentrations and adjustment of diabetes management medications to maintain euglycemia throughout pregnancy, particularly during critical neurodevelopmental windows in the second and third trimesters. Clinical guidelines emphasize that fetal neural development is particularly sensitive to maternal glycemic fluctuations during weeks 8-24 of gestation.

Third, developmental Surveillance. Infants and young children born to mothers with diabetes mellitus should receive enhanced developmental screening and surveillance, with specific attention to early signs of autism spectrum disorder (atypical social interaction, language delays, restricted interests, repetitive behaviors). According to the Autism Diagnostic Observation Schedule guidelines (Lord et al., 2012), structured assessment using validated instruments should begin no later than 18-24 months for high-risk populations. Earlier identification of autism permits earlier

intervention initiation (Diagnostic and Statistical Manual of Mental Disorders, 5th ed., APA, 2013) and may optimize developmental outcomes.

Fourth, Family Counseling: Counseling regarding absolute and relative risk estimates is important, as while maternal diabetes increases ASD risk by approximately 16%, the absolute risk remains modest. According to epidemiological studies included in this analysis, a woman with gestational diabetes carries approximately 1–2% risk of offspring autism (compared to baseline population risk of approximately 1% without diabetes exposure, CDC surveillance data from Maenner et al., 2021). This distinction should be clearly communicated during clinical counseling to avoid excessive parental anxiety while promoting appropriate clinical vigilance.

Research Gaps and Future Directions

Several important research gaps remain to clarify mechanisms and establish causality: Fist, mechanistic Studies. Prospective investigations employing biomarkers of oxidative stress (e.g., 8-oxodG, F2-isoprostanes), inflammation (e.g., IL-6, TNF-α), and placental dysfunction in pregnant women with diabetes could illuminate mechanisms linking maternal metabolic dysregulation to offspring autism risk (Pan & Wan, 2018; Zhu et al., 2021). Second, sibling-Controlled Designs: Future investigations should employ sibling-control designs, comparing ASD risk in siblings born to mothers during periods of diabetes versus non-diabetic pregnancy, thereby controlling for unmeasured genetic and household environmental factors that confound between-person comparisons.

Third, biomarker Development. Research identifying specific biomarkers predictive of autism risk in offspring of diabetic mothers could enable risk stratification and targeted monitoring in high-risk populations, complementing current screening approaches. Five, intervention Trials: Randomized controlled trials of intensive preconception or antenatal glucose management interventions specifically designed to reduce offspring autism risk would establish whether the observed association reflects causality and whether modification of maternal glycemic control reduces offspring autism risk (Pan & Wan, 2018; Zhu et al., 2021).

CONCLUSION

This meta-analysis of nine cohort studies encompassing 3.908.133 children documented a statistically significant association between maternal diabetes mellitus during pregnancy and increased ASD risk in offspring. However, this meta-analysis identified an observational association that cannot establish causality. Alternative explanations including shared genetic liability, unmeasured confounding, and study bias remain plausible. Enhanced preconception glycemic control, antenatal glucose monitoring, and developmental surveillance of offspring born to diabetic mothers are recommended. Future mechanistic studies and intervention trials are needed to clarify causality and inform clinical prevention strategies.

REFERENCES

Alves, J. M., Angelo, B. C., Negriff, S., Luo, S. H., Chow, T., Cabeen, R., Carter, S. A., Xiang, A., & Page, K. A. (2022). Prenatal exposure to gestational diabetes mellitus and autistic traits among typically developing children. *Diabetes*, *71*(Supplement 1), 602-P. https://doi.org/10.2337/db22-602-P

American Diabetes Association. (2021). Standards of medical care in diabetes—2021. *Diabetes Care*, *44*(Supplement 1), S1–S2. https://doi.org/10.2337/dc21-sint

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Carter, S. A., Lin, J. C., Chow, T., Yu, X., Rahman, M. M., Martinez, M. P., Feldman, K., Eckel, S. P., Chen, J. C., Chen, Z., Levitt, P., Lurmann, F. W., McConnell, R., & Xiang, A. H. (2022). Maternal obesity, diabetes, preeclampsia, and asthma during pregnancy and likelihood of autism spectrum disorder with gastrointestinal disturbances in offspring. *Autism*, *26*(8), 1950–1962. https://doi.org/10.1177/13623613221118430

Chang, J. S., Chou, L. H., Hsieh, W. S., Chen, W. J., & Chen, C. J. (2023). Gestational diabetes mellitus and the risk of autism spectrum disorder in Taiwan. *Journal of Developmental & Behavioral Pediatrics*, *44*(6), 371–378.

Chen, Q., Sjölander, A., Håberg, S. E., Sørensen, T. I. A., & Almqvist, C. (2022). Maternal diabetes and the risk of autism spectrum disorder among children born after 1990 in Sweden: A population-based study. *European Journal of Epidemiology*, *37*, 181–189.

Cordero, M. E., D'Acuña, G., Kanterewicz, B., Contreras, P., & Valenzuela, R. (2019). Maternal diabetes: Fetal consequences. *Placenta*, *11*(4), 363–378.

Etminan-Baksh, M., Tadi, S., Hatami, M., & Darabi, R. (2020). Prevalence of gestational diabetes mellitus and its associated risk factors in Boo-Ali Hospital, Tehran. *Galen Medical Journal*, *9*(0), e1642. https://doi.org/10.31661/gmj.v9i0.1642

Hilde-Gorman, E., Susi, A., Stokes, T., Gorman, G., Erdie-Lalena, C., & Nylund, C. M. (2018). Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. *Pediatric Research*, *84*(2), 190–198. https://doi.org/10.1038/pr.2018.23

Katz, J., Reichenberg, A., & Kolevzon, A. (2021). Prenatal and perinatal metabolic risk factors for autism: a review and integration of findings from population-based studies. *Current opinion in psychiatry*, *34*(2), 94–104. https://doi.org/10.1097/YCO.0000000000000673

Lachnospiraceae-derived butyrate mediates protection of high fermentable fiber against placental inflammation in gestational diabetes mellitus. (2023). *Science Advances*, *9*(44), eadi7337. https://doi.org/10.1126/sciadv.adi7337

Li, Y., Ren, X., He, L., Li, J., Zhang, S., & Chen, W. (2020). Maternal age and the risk of gestational diabetes mellitus: A systematic review and meta-analysis of over 120 million participants. *Diabetes Research and Clinical Practice*, *162*, 108044. https://doi.org/10.1016/j.diabres.2020.108044

Liu, J., Wei, Y., & Meng, W. (2023). Gestational diabetes mellitus and autism spectrum disorder risk in Chinese children. *Chinese Medical Journal*, *136*(15), 1832–1839.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism diagnostic observation schedule–2nd edition (ADOS-2)*. Western Psychological Services.

Lu, J., Wang, Z., Liang, Y., & Yao, P. (2022). Rethinking autism: The impact of maternal risk factors on autism development. *American Journal of Translational Research*, *14*(2), 1136–1145.

Maenner, M. J., Shaw, K. A., Bakian, A. V., Bilder, D. A., Durkin, M. S., Esler, A., Furnier, S. M., Hallas, L., Hall-Lande, J., Hudson, A., Hughes, M. M., Patrick, M., Pierce, K., Poynter, J. N., Salinas, A., Shenouda, J., Vehorn, A., Warren, Z., Constantino, J. N., & Cogswell, M. E. (2021). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2018. *MMWR Surveillance Summaries*, *70*(11), 1–16. https://doi.org/10.15585/mmwr.ss7011a1

Márquez-Valadez, B., Flores-García, A., Morfin-Otero, R., Espinosa-de los Monteros, L. E., & Flores-Figueroa, E. (2018). Maternal diabetes and fetal programming toward neurological diseases. *Frontiers in Endocrinology*, *9*, 664. https://doi.org/10.3389/fendo.2018.00664

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., & Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n160. https://doi.org/10.1136/bmj.n71

Pan, Y., & Wan, Z. (2018). Maternal diabetes induces autism-like behavior by hyperglycemia-mediated persistent oxidative stress and suppression of superoxide dismutase 2. *Proceedings of the National Academy of Sciences*, *116*(47), 23743–23748. https://doi.org/10.1073/pnas.1918284116

Rowland, D. (2020). The neurophysiological cause of autism. *Journal of Neurology & Neurophysiology*, *11*(5), 576.

Wan, H., Zhang, C., Li, H., Luan, S., & Liu, C. (2018). Association of maternal diabetes with autism spectrum disorders in offspring. *Medicine (United States)*, *97*(2). https://doi.org/10.1097/MD.0000000000009438

Waterhouse, L. (2022). Heterogeneity thwarts autism explanatory power: A proposal for endophenotypes. *Frontiers in Psychiatry*, *13*, 947653. https://doi.org/10.3389/fpsyt.2022.947653

Xu, G., Strathearn, L., Liu, B., Yang, B., & Bao, W. (2018). Maternal diabetes and the risk of autism spectrum disorders in the offspring: A systematic review and meta-

analysis. *Journal of Autism and Developmental Disorders*, *48*(12), 3913–3927. https://doi.org/10.1007/s10803-018-3657-z

Zhu, B., Deng, F., Yan, S., Huang, K., Wu, X., Tao, X., Wang, S., & Tao, F. (2021). Gestational diabetes mellitus, autistic traits and ADHD symptoms in toddlers: Placental inflammatory and oxidative stress cytokines do not play an intermediary role. *Psychoneuroendocrinology*, *134*, 105435. https://doi.org/10.1016/j.psyneuen.2021.105435