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Risk of schizophrenia in the offspring of mothers with diabetes during pregnancy: systematic review and meta-analysis

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Risk of schizophrenia in the offspring of mothers with diabetes during pregnancy: systematic review and meta-analysis

Short Title: Schizophrenia Risk in the Offspring of Mothers Whith Diabetes

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ABSTRACT

Objectives: Hyperglycemia during pregnancy is related to adverse obstetric, neonatal, and long-term health outcomes for both mothers and the offspring. This study aimed to conduct a systematic review and meta-analysis of the global literature evaluating the association between maternal diabetes (DM) during pregnancy and the incidence of schizophrenia in the offspring.

Methods: Following PRISMA guidelines and registered in PROSPERO (CRD42024545505), a comprehensive search was conducted across major databases up to November 2024. Three retrospective cohort studies, including 2,603,889 individuals, met the inclusion criteria.

Results: Three studies were included in the quantitative synthesis. Meta-analysis of hazard ratios showed that maternal DM during pregnancy was associated with an increased risk of schizophrenia in the offspring (HR = 1.58; 95% CI: 1.22–2.03; P = 0.0004), with no heterogeneity (I^2 = 0%). Analysis based on odds ratios showed a similar trend but did not reach statistical significance (OR = 2.15; 95% CI: 0.13–34.69; P = 0.59).

Conclusion: Maternal DM during pregnancy may be associated with an increased risk of schizophrenia in the offspring. Although maternal hyperglycemia may influence fetal neurodevelopment through inflammatory and

metabolic mechanisms, the observational nature and limited number of included studies preclude causal inference, and these findings should be interpreted with caution.

Keywords: Diabetes Mellitus; Pregnancy; Schizophrenia; Offspring.

INTRODUCTION

The prevalence of diabetes mellitus (DM) during pregnancy has increased significantly worldwide over the past decades. This phenomenon is largely attributable to the obesity epidemic, the increased incidence of DM among women of childbearing age, and the greater frequency of pregnancies in older women. The disease can be classified as gestational diabetes mellitus (GDM) or pre-gestational diabetes mellitus (PGDM), with GDM accounting for around 90% of cases. Among PGD cases, it is estimated that approximately 60% corresponds to type 2 DM and 40% to type 1 DM[1].

The presence of hyperglycemia during pregnancy is associated with a series of adverse outcomes, including obstetric complications, neonatal risks and unfavorable long-term health consequences for the mothers and their offspring[2-3]. For example, women diagnosed with GDM have a higher risk of developing type 2 DM, obesity, hypertension and metabolic syndrome during their lifetime. In addition, children born to mothers with GDM are two to eight times more likely to develop obesity, glucose intolerance, and metabolic syndrome during childhood and early adulthood, compared to children born to mothers without GDM[3-4].

In addition, it has been shown that intrauterine exposure to maternal DM is related to an increased risk of cognitive impairment, psychomotor alterations and the development of neuropsychiatric disorders such as schizophrenia[1]. Schizophrenia is a chronic and debilitating psychiatric disorder, characterized by psychotic symptoms, emotional and cognitive dysfunctions, which affect approximately 1% of the global population[5]. Although the etiology of schizophrenia is multifactorial, involving genetic and environmental factors, exposure to adverse conditions *in utero*, such as maternal DM, may be linked to the development of this disease[6].

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The current evidence suggests that GDM may increase the risk of schizophrenia through two parallel and potentially synergistic neurodevelopmental pathways. The first is a direct intrauterine pathway, in which maternal hyperglycemia promotes oxidative stress, placental inflammation, and maternal immune activation, leading to fetal microglial priming and persistent neuroinflammation that interferes with key neurodevelopmental processes such as neuronal differentiation, synaptic pruning, and myelination. The second is an indirect perinatal pathway, in which GDM increases the likelihood of fetal macrosomia, predisposing to obstetric complications such as shoulder dystocia, prolonged labor, and birth trauma, which in turn raise the risk of perinatal asphyxia and hypoxic-ischemic injury[7]. Perinatal hypoxia activates microglia, impairs oligodendrocyte maturation, disrupts white matter development, and alters the maturation of dopaminergic circuits—changes that are widely implicated in the pathophysiology of schizophrenia. Taken together, these findings support a two-hit neurodevelopmental model, in which prenatal metabolic and inflammatory insults sensitize the developing brain, while perinatal hypoxic events act as secondary triggers that amplify microglial activation and increase lifetime susceptibility to schizophrenia[8].

Cognitive deficits, considered endophenotypes of schizophrenia, correspond to early neurodevelopmental alterations and are recognized as markers that may precede the full clinical manifestation of the disorder[9]. Sapienza et al. (2025) indicate that immunometabolic mechanisms, such as neuroinflammation and neurotransmission dysfunction, may play a central role in the pathophysiology of schizophrenia. Metabolic syndrome, characterized by insulin resistance, central obesity, dyslipidemia, and hypertension, promotes, via activation of the kynurenine pathway, a state of chronic low-grade systemic inflammation, with increased production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, leading to neurotransmission alterations, microglial activation, and cognitive impairment[10]. Maternal DM shares pathophysiological mechanisms with metabolic syndrome, including insulin resistance, hyperglycemia, and systemic inflammation, exposing the fetus to a pro-inflammatory environment capable of interfering with neurodevelopment. This early immunometabolic programming may induce persistent microglial

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activation, alterations in synaptogenesis and synaptic pruning, and increased vulnerability to schizophrenia in the offspring[11].

Supporting this hypothesis, evidence shows an association between metabolic syndrome and cognitive impairment in schizophrenia. Cuoco et al. (2022) observed that patients with schizophrenia and metabolic syndrome exhibited worse cognitive performance, reduced functional mobility, and poorer quality of life, suggesting that metabolic dysregulation contributes to the progression of cognitive decline[12]. Complementarily, Bosia et al. (2021) demonstrated that the interaction between metabolic syndrome and inflammatory variants of the IL-1β gene modulates cognitive performance in patients with schizophrenia, reinforcing the role of chronic inflammation as a link between metabolic dysfunction and brain alterations[13].

The association between maternal DM during pregnancy and the risk of schizophrenia in the offspring has been the subject of increasing research, although the evidence remains inconclusive. In light of this literature gap, the present study aimed to conduct a systematic review and meta-analysis on the incidence of schizophrenia in the offspring of women with DM during pregnancy.

OBJECTIVES

The objective of this study was to conduct a systematic review and meta-analysis of data published in the global literature on the risk of incidence of schizophrenia in the offspring of women with DM during pregnancy.

METHODS

Design

This is a systematic review and meta-analysis, conducted in accordance with the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] methodological tool. The research was registered in the PROSPERO database on May 10, 2024, with the approval number CRD42024545505.

To help construct the research question, the acronym PICo (population, interest and context) was used in which "P" corresponds to the offspring of women who had DM during pregnancy; "I" to identify the risk of incidence of

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schizophrenia in the exposed offspring; "Co" available studies in the medical literature. The guiding question of this study was: what is the risk of incidence of schizophrenia in the offspring born to women with DM during pregnancy?

Eligibility criteria

The established inclusion criteria were: observational studies, including cohort and case-control studies, estimating the risk of incidence of schizophrenia in the offspring of women with DM before or during pregnancy. The diagnosis of schizophrenia in the offspring had to be made according to the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) or the "International Statistical Classification of Diseases and Related Health Problems" criteria. Selected studies had to be published in English, Portuguese and Spanish and had to present complete data evaluating maternal DM exposure and the presence of schizophrenia in the offspring.

Non-original studies or research articles, such as literature reviews, studies that did not relate schizophrenia in the offspring to maternal DM during gestation, animal studies, studies involving women with DM outside the gestational context, or that addressed psychiatric diagnoses other than schizophrenia, or did not objectively distinguish the condition, were excluded. Otherwise, studies with a Newcastle-Ottawa Scale (NOS)[15] score below 7, were considered to be of low methodological quality, and were also excluded, as well as meta-analyses, letters to the editor, case reports, duplicate publications without additional information or papers available only in abstract form were also not included.

In case of multiple studies using data from the same cohort, priority was given to the study with the longest follow-up or the largest number of participants.

Data source and searches

The descriptors were selected using the "Medical Subject Headings" (MeSH) resource and free-text keywords. The MeSH terms included “Diabetes Mellitus, Type 1”, “Diabetes Mellitus, Type 2”, “Diabetes, Gestational”, and “Schizophrenia”, while the free-text keyword “offspring” was also incorporated. These terms were combined using the Boolean operators OR and AND as

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follows: (“Diabetes Mellitus, Type 1” OR “Diabetes Mellitus, Type 2” OR “Diabetes, Gestational”) AND “Schizophrenia” AND “offspring”. Broader terms related to psychosis, severe mental illness, intrauterine exposure, maternal hyperglycemia, or gestational metabolic disorders were not included because the review was specifically designed to identify studies evaluating schizophrenia as the primary outcome in the offspring of women with DM during pregnancy. Literature searches were conducted between September and November 2024 in PubMed, Embase, Web of Science, Scopus and SciELO. The search included studies published from the inception of each database through November 18, 2024.

Study selection and data extraction

Two reviewers applied the descriptors to the databases and independently screened the literature, following the previously established inclusion and exclusion criteria. The studies were exported to the Mendeley tool[16] in order to exclude duplicate articles. After reading the titles and abstracts, papers that did not meet the inclusion criteria were excluded. Subsequently, the full texts of the articles considered potentially eligible were retrieved and rigorously assessed to identify the appropriate studies. A third reviewer resolved disagreements between the two reviewers.

Data extraction was performed by four reviewers following the PRISMA guidelines[8] for systematic reviews and meta-analyses.

Following standardized forms, information on the name of the first author, year of publication, country, type of study, sample size, years of follow-up, year of data collection, number of women with and without DM in pregnancy, number of exposed and unexposed children to maternal DM during pregnancy, number of children with and without schizophrenia and the adjustments made for confounding factors, were collected as shown in Tables 1 and 2.

Statistical analysis

To estimate the risk of schizophrenia incidence in the offspring of mothers with DM during pregnancy, a meta-analysis was conducted using two complementary approaches according to the type of effect measure reported in the included studies. For studies reporting adjusted time-to-event estimates,

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hazard ratios (HR) and HR ratios (HRR) with their corresponding 95% confidence intervals (CIs) were extracted and synthesized using the generic inverse variance method. These estimates were transformed into logarithmic scale (log HR) and pooled using a random-effects model. For studies reporting raw event data, odds ratios (OR) were calculated using the Mantel-Haenszel method based on 2×2 contingency tables and were also pooled using a random-effects model.

Statistical heterogeneity was assessed using the Chi-square (χ^2) test and quantified using the I^2 statistic. A P value greater than 0.10 and $I^2 \leq 50\%$ indicated low heterogeneity, while I^2 values above 50% indicated substantial heterogeneity. Given the anticipated clinical and methodological variability among studies, random-effects models were applied for all analyses.

Given the differences in study designs and effect measures, analyses were conducted separately for adjusted HRs (HR/HRR) and crude OR, and results were not pooled across these metrics.

No additional data conversions were required beyond standard logarithmic transformation for HRs. All included studies provided sufficient numerical data for effect estimation.

A sensitivity analysis using a leave-one-out approach was planned to assess the robustness of the findings. The certainty of evidence was evaluated according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, as summarized in Table 3. Because only three studies met the inclusion criteria, publication bias was not assessed. According to the Cochrane Handbook[17], funnel plot asymmetry and statistical tests such as Egger's regression test are not recommended when fewer than 10 studies are included, as they have insufficient power to reliably detect publication bias.

All statistical analyses were performed using Review Manager (RevMan) version 5.4.

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Table 3. GRADE assessment of the certainty of evidence for the association between maternal diabetes during pregnancy and the risk of schizophrenia in offspring.

Outcome	No. of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
Maternal diabetes → schizophrenia	3 studies (2,603,889)	Not serious	Not serious	Not serious	Not serious	Not assessable	⊕⊕◯◯ Low

Legend: GRADE: Grading of Recommendations Assessment, Development and Evaluation. Risk of bias was assessed using the Newcastle–Ottawa Scale. Inconsistency was evaluated based on statistical heterogeneity (I^2), overlap of confidence intervals, and consistency of effect estimates. Indirectness was assessed according to the applicability of the population, exposure, comparator, and outcome to the review question. Imprecision was evaluated based on the precision of the pooled effect estimate and confidence intervals. Publication bias could not be formally assessed because fewer than 10 studies were included in the meta-analysis.

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Registration and protocols

This study was registered in the PROSPERO database (International Prospective Register of Systematic Reviews) on May 10, 2024, under registration number CRD42024545505. Prospective registration of the protocol promotes methodological transparency and minimizes reporting bias by ensuring that the objectives, inclusion criteria, and methods were predefined before data collection and analysis.

No amendments were made to the protocol after its registration in the PROSPERO platform.

RESULTS

Bibliographic research

The systematic search on the databases resulted in a total of 1,008 articles. Of these, 210 articles were excluded by being duplicated (Figure 1). After reading the titles and abstracts of the selected studies, by two independent authors (MZM and BYFH), 13 studies were selected by being potentially relevant to the topic. After reading these articles in full, only 3 studies aligned with the proposed question and met the inclusion criteria. The selected articles had their data extracted and analyzed. Figure 1 provides a concise summary of the research results, explaining the reasons for article exclusion.

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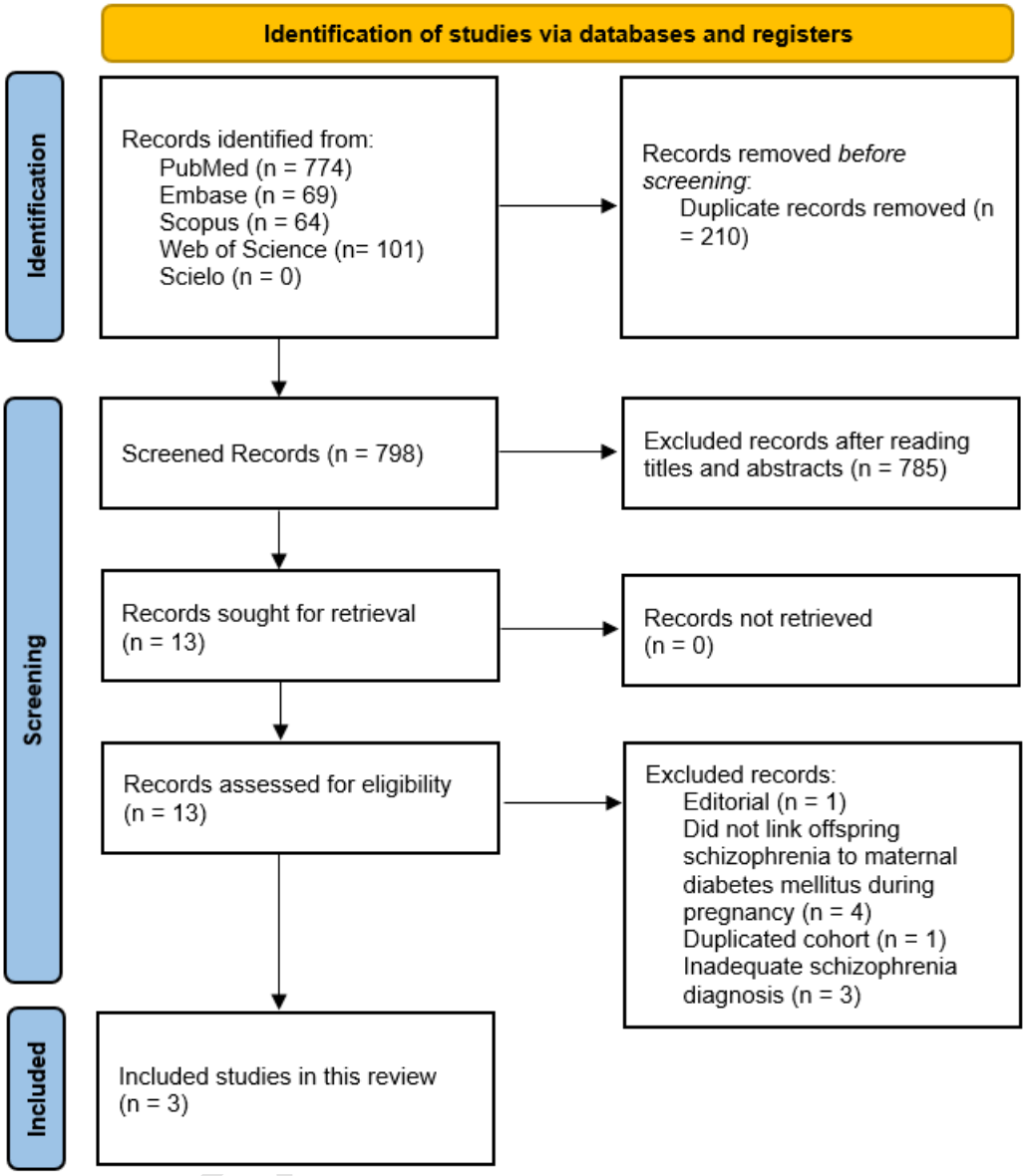


Figure 1 – Flowchart of study selection according to the PRISMA 2020 guidelines. Illustrates the process of database searching, screening, eligibility assessment, and final inclusion of studies in the systematic review.

Quality assessment

After applying the NOS[15] to assess the methodological quality of the studies, the average score was approximately 8.6. This indicates the high methodological quality of the studies included in this meta-analysis. All the studies included in this systematic review and meta-analysis were cohort studies.

Study characteristics

The included studies were conducted between 2003 and 2021, using similar methodologies, and evaluated retrospective cohorts. Follow-up duration ranged from 23 to 40 years, with most studies adjusting for confounding factors such as maternal and paternal history of psychiatric disorders, maternal age and offspring sex. In all studies, schizophrenia diagnoses followed the ICD and DSM criteria. However, the same was not true for maternal DM diagnosis, since only one study adopted uniform criteria. Methodological quality was assessed with scores ranging from 8 to 9 in the NOS[15] indicating a high methodological quality of the included studies. The characteristics of the included studies are summarized in Table 1 and diagnostic criteria for DM and schizophrenia and confounding factors in Table 2.

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TABLE 1 – Characteristics of the included studies evaluating the incidence of schizophrenia in offspring exposed to maternal diabetes during pregnancy.

Title	Author	Type of study	Year	Country	Data collection period	Follow-up duration	N	Healthy mother + schizophrenic offspring	Mothers with diabetes + schizophrenic offspring	Newcastle Ottawa Scale
Associations of Maternal Diabetes During Pregnancy With Psychiatric Disorders in Offspring During the First 4 Decades of Life in a Population-Based Danish Birth Cohort[1]	Nogueira Avelar e Silva R, Yu Y, Liew Z, Vested A, Sørensen HT, Li J	Retrospective cohort	2021	Denmark	01/10/2019 - 15/06/2021	40 years	2.413.335	3780	45	9
An association between high birth weight and schizophrenia in a Finnish schizophrenia family study sample[13]	Asko Wegelius, Annamari Tuulio-Henriksson, Maiju Pankakoski, Jari Haukka, Ulriika Lehto, Tiina Paunio, Jouko Lönnqvist, Jaana Suvisaari	Retrospective cohort	2011	Finland	2011	36 years	33.731	115	20	9
Patterns of Fetal and Childhood Growth and the Development of Psychosis in Young Males: A Cohort Study[14]	David Gunnell, Finn Rasmussen, Dimitris Fouskakis, Per Tynelius, Glynn Harrison	Retrospective cohort	2003	Sweden	NR	23 years	246.655	80	0	8

Legend: Details include study title, authors, study type, year, country, data collection period, follow-up duration, sample size, number of schizophrenia cases among exposed and unexposed offspring, and Newcastle–Ottawa Scale score.

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Table 2 Diagnostic criteria for diabetes and schizophrenia, and confounding factors considered in the included studies.

Title	Diagnostic criteria for diabetes	Diagnostic criteria for schizophrenia	Confounding factors
Associations of Maternal Diabetes During Pregnancy With Psychiatric Disorders in Offspring During the First 4 Decades of Life in a Population-Based Danish Birth Cohort[1]	(1) Diagnosis of diabetes coded as: ICD-10*: E10-E11, H36.0, O24 excluding O24.4 and O24.9; ICD-8: 249, 250; (2) receipt of chiropody for diabetic conditions; (3) two redeemed prescriptions for insulin (ATC* code: A10A); or (4) two redeemed prescriptions for oral antidiabetics (ATC code: A10B). Blood glucose measurements were not used due to their poor validity. (2) Pregestational diabetes was classified as type 1 (ICD-10 codes: E10, O24.0; ATC code: A10A; ICD-8 code: 249) or type 2 (ICD-10 codes: E11, O24.1; ATC code: A10B; ICD8 code: 250).	ICD-10: F-20 - F-29 ICD-8: 295.x9, 296.89, 297.x9, 298.29–298.99, 299.04, 299.05, 299.09, 301.83	Maternal history of any psychiatric disorder, maternal age, parity, maternal educational level, maternal smoking during pregnancy, marital status, maternal residence, only-child status, offspring sex, birth year, and maternal body mass index.
An association between high birth weight and schizophrenia in a Finnish schizophrenia family study sample[13]	NR*	DSM-IV* 295,10, 295,20, 295,30, 295,60, 295,90; DSM-IV 295,40; DSM-IV 295,70; DSM-IV 297,1; DSM-IV 298,8; DSM-IV 296,24, 296,34; DSM-IV 296,04, 296,44, 296,54, 296,64; DSM-IV 298.9 .	Offspring gender, place of birth, and birth period.
Patterns of Fetal and Childhood Growth and the Development of Psychosis in Young Males: A Cohort Study[14]	NR	ICD-9* (schizophrenia: ICD-9 code 295); ICD-10 (schizophrenia: ICD-10 code F20)	Neonatal factors: head circumference, Apgar score, cesarean delivery, prolonged labor, congenital malformation at birth. Maternal factor: preeclampsia, maternal hypertension, maternal diabetes, antepartum hemorrhage, maternal age and parity. Demographic and socioeconomic factors: season of birth, urbanicity of area of residency at the time of birth, parental education.

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Legend: Summarizes the diagnostic codes and classifications used for maternal diabetes and schizophrenia, along with adjusted variables in each study.
*ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
*ICD-8: International Classification of Diseases, Eighth Revision
*ATC: Anatomical Therapeutic Chemical
*NR: not reported
*DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
*ICD-9: International Classification of Diseases, Ninth Revision

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Publication bias

Formal assessment of publication bias was not performed, as three studies were included in the meta-analysis. In accordance with the Cochrane Handbook[17], funnel plot inspection and statistical test for asymmetry are not recommended when fewer than 10 studies are available, as the number of studies does not provide sufficient statistical power to distinguish true asymmetry from chance findings and small-study effects.

Maternal diabetes and the risk of Schizophrenia in the offspring

Statistical analyses were performed separately according to the effect measure reported by the included studies. Three studies were eligible for quantitative synthesis: Gunnell et al. (2003)[19], Nogueira Avelar e Silva et al. (2021)[1], and Wegelius et al. (2011)[18].

Among studies reporting HRs, two studies were included in the meta-analysis. The pooled estimate demonstrated that maternal DM during pregnancy was associated with a significantly increased risk of schizophrenia in the offspring (HR = 1.58, 95% CI: 1.22–2.03; P = 0.0004) (Figure 2). No evidence of heterogeneity was observed between studies (I^2 = 0%, χ^2 = 0.05, P = 0.82), indicating high consistency across the included cohorts.

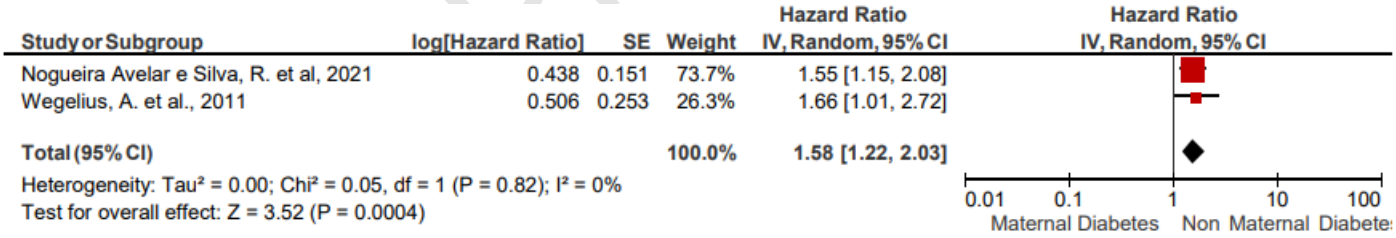


Figure 2 - Forest plot of the association between maternal diabetes during pregnancy and schizophrenia risk in offspring based on hazard ratios (generic inverse variance model). Shows individual hazard ratio (HR) and 95% confidence intervals (CIs) for each included study.

Among studies reporting ORs, only one study was available for analysis. This study reported an increased, although non-significant, risk of incidence of schizophrenia among the offspring exposed to maternal DM during pregnancy

(OR = 2.15, 95% CI: 0.13–34.69; P = 0.59) (Figure 3). The wide CI reflects the limited precision of the estimate.

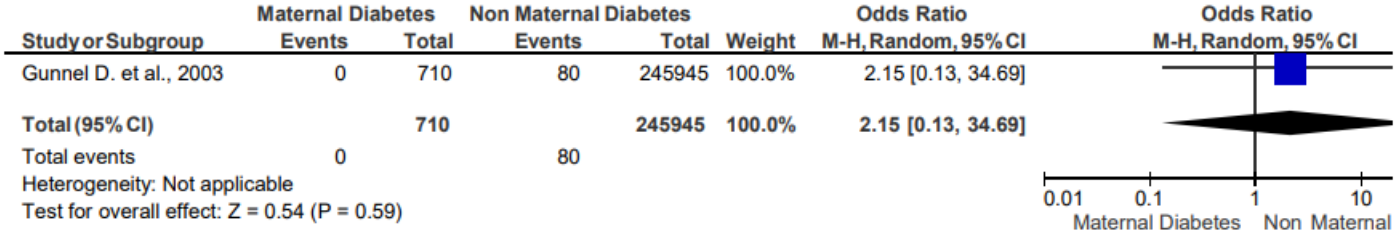


Figure 3 - Forest plot of the association between maternal diabetes during pregnancy and schizophrenia risk in offspring based on odds ratios (Mantel–Haenszel method). Shows individual odds ratios (ORs) and 95% confidence intervals (CIs) for the included study

The risk of incidence of schizophrenia among the offspring born to mothers with DM during pregnancy ranged from 0.00% to 22.47% across studies, whereas among the offspring of mothers without DM, the risk ranged from 0.03% to 14.11%. Specifically, Gunnell et al. (2003)[19] reported risks of 0.00% and 0.03% in the exposed and unexposed groups, respectively. Nogueira Avelar e Silva et al. (2021)[1] reported corresponding risks of 1.53% and 0.99%, while Wegelius et al. (2011)[18] reported risks of 22.47% and 14.11%, respectively.

Diabetes Prevalence in Pregnant Women

In the cohort reported by Nogueira Avelar et al (2021)[1], the prevalence of maternal DM during pregnancy was 2.3% among live births, corresponding to 56,206 cases out of 2,413,335 deliveries. Regarding DM subtypes, the distribution was as follows: pre-gestational type 1 DM accounted for 22,614 cases (1.0%), pre-gestational type 2 DM for 6,713 cases (0.3%), and GDM for 26,879 cases (1.1%). These data indicate that approximately 2.3% of pregnant women in the cohort had a diagnosis of DM either before or during pregnancy.

In the cohort studied by Wegelius et al. (2013)[18], the prevalence of DM among mothers, used as a proxy for GDM, was 10.3% at the time of data collection.

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In the cohort studied by Gunnell et al. (2003)[19], the recorded prevalence of maternal DM was approximately 0.29% This low prevalence suggests probable underreporting of maternal DM in the birth registry, particularly of milder forms of gestational glucose intolerance.

Sensitivity analysis

A sensitivity analysis was planned using a leave-one-out approach, in which each study would be sequentially excluded and the pooled effect estimate recalculated. However, the HR-based meta-analysis included only two studies, limiting the interpretability of this procedure because exclusion of either study left only a single study available for analysis. Nevertheless, both studies independently reported an increased risk of incidence of schizophrenia among the offspring exposed to maternal DM during pregnancy, supporting the consistency of the observed relationship.

For the OR-based analysis, sensitivity analysis was not feasible because only one study was available for quantitative synthesis. Consequently, the robustness of the OR estimate could not be formally assessed.

Overall, the limited number of studies included in both analyses should be considered when interpreting the stability of the pooled estimates.

Certainty assessment

The certainty of the evidence was assessed using the GRADE system approach, which is widely applied in systematic reviews. The results of this assessment are presented in Table 3. According to the GRADE framework, the certainty of the evidence was initially rated as low because all included studies were observational. Although low risk of bias according to the NOS (scores ranging from 8 to 9) and low statistical heterogeneity ($I^2 = 0\%$) were found in all the analyzed studies, no criteria for upgrading the certainty of the evidence were met. Therefore, the overall certainty remained low.

DISCUSSION

This meta-analysis included data from three retrospective cohort studies, evaluating a sample of approximately 2,603,889 individuals. A significant association between intrauterine exposure to maternal DM and an increased

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risk of schizophrenia in the offspring was found. The pooled estimate from studies reporting HRs indicated that individuals exposed to maternal DM during pregnancy had a 58% higher risk of developing schizophrenia compared with those unexposed (HR = 1.58; 95% CI: 1.22–2.03). The analysis based on ORs showed a similar direction of association, although not statistically significant (OR = 2.15; 95% CI: 0.13–34.69), likely due to the limited number of available studies and the resulting wide CIs.

Intrauterine exposure to maternal hyperglycemia triggers a series of changes that can compromise key stages of fetal neurodevelopment, including neurogenesis, neuronal migration, and synaptic maturation[1]. High blood glucose levels trigger systemic inflammation, characterized by an increase in cytokines (such as IL-6 and TNF-α) and adipokines, which cross the placenta[20-21]. Fetal exposure to this inflammatory environment leads to inappropriate activation of microglia, which results in alterations in neuronal differentiation and synapse formation, which are involved in schizophrenia pathogenesis[3].

Studies performed with animal models have shown that DM during pregnancy can reduce the expression of the microglial receptor CX3CR1, thereby impacting the CX3CL1-CX3CR1 pathway, which plays a crucial role in synaptic homeostasis and immune cell regulation in the central nervous system. Failure in this signaling can lead to a neuroinflammatory condition, which can result in changes in brain connectivity and structure[22-24]. Some studies have found modifications in paramount areas such as the prefrontal cortex and thalamus, which are closely related to emotional regulation and cognition, and also with the neural circuits linked to schizophrenia[25-26].

A Japanese epidemiological study observed an increase in the frequency of subclinical psychotic experiences in adolescents exposed to maternal DM in early pregnancy, highlighting the importance of intrauterine hyperglycemia as a risk factor for psychopathologies. Among the symptoms reported, auditory and visual hallucinations stood out, suggesting a greater vulnerability to psychotic manifestations starting in childhood. Although this study used a questionnaire-based approach to identify subclinical psychotic experiences, its results reinforce the link between maternal DM during pregnancy and alterations in neurodevelopment that may predispose to schizophrenia, since early stages of life[24].

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The study conducted by Nogueira Avelar et al. (2021)[1] found that exposure to any type of maternal DM increased the risk of schizophrenia in the offspring by 55%, even after controlling for sociodemographic factors, parental psychiatric history and obstetric conditions. In general, this risk was more pronounced from the age of 20, coincidentally a period with the highest incidence of the first psychotic episodes, suggesting a biologically plausible temporal association. Notably, this study showed that the link between maternal DM during pregnancy and schizophrenia was not restricted to a specific subtype of maternal DM, but was present in cases of both PGDM (types 1 and 2) and GDM. This finding indicates that the preponderant etiological factor lies in fetal exposure to intrauterine hyperglycemia, regardless of the underlying etiology of the maternal metabolic disorder.

The association between maternal DM during pregnancy and the risk of schizophrenia in the offspring requires careful consideration regarding potential confounding factors beyond hyperglycemia, such as elevated maternal pregestational body mass index[27], obstetric complications (preeclampsia, intrauterine growth restriction, perinatal hypoxia, and preterm birth)[19] and genetic susceptibility to schizophrenia[28]. Furthermore, prior or gestational use of second-generation antipsychotics (such as olanzapine, quetiapine, and clozapine) has been correlated with a substantial increase in the risk of GDM, potentially acting as mediators or confounders in this association[29]. Pregnant women with DM also exhibit greater vulnerability to bacterial and viral infections, which are also considered risk factors for the development of psychosis in the offspring[30]. Lastly, unfavorable socioeconomic conditions, lower educational attainment, and behaviors such as smoking can influence the incidence of schizophrenia in the offspring[31]. Although the pooled hazard ratios were derived from adjusted estimates, the adjustment strategies differed across the included studies, and several potentially important confounders were not consistently measured or included in the adjustment models. Therefore, residual confounding cannot be excluded and should be considered when interpreting the observed relationship.

The primary objective of Wegelius et al. (2011)[18] was to evaluate whether maternal DM during pregnancy and birth weight were associated with an increased risk of schizophrenia in the offspring, using a sample of Finnish

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families with a history of this psychiatric disorder. The authors found that children born to mothers with DM during pregnancy had a significantly higher risk of developing schizophrenia (adjusted HR = 1.66; 95% [CI]: 1.01–2.72). Notably, this association persisted even after adjusting for birth weight, suggesting that maternal DM exerts an independent effect on schizophrenia risk, beyond the influence of fetal growth. In this context, the authors suggest that this increased risk may stems from metabolic and epigenetic changes that occur during the intrauterine life. These mechanisms include metabolic imprinting, defined as fetal metabolic programming resulting from excessive exposure to glucose and insulin, which leads to long-lasting metabolic and organic functional changes. On the other hand, it is possible that gene reprogramming could occur, which involves epigenetic alterations that modulate gene expression during brain development, which may increase vulnerability to psychiatric disorders. Thus, the increased risk of schizophrenia is primarily associated with the adverse metabolic environment and its molecular consequences during pregnancy, and not exactly with birth weight.

In the sample studied by Gunnell et al. (2003)[19], none of the 710 individuals born to mothers with DM during pregnancy were diagnosed with schizophrenia or other non-affective psychoses. However, the authors recognized important methodological limitations in their study, such as the underreporting of mild cases of DM due to the diversity of diagnostic criteria used for DM, and also added that maternal DM during pregnancy may play an important role in the risk of schizophrenia.

Maternal diabetes, neurodevelopment, and cognitive vulnerability

Cognitive impairment constitutes a core feature of schizophrenia, encompassing deficits in working memory, executive functions, processing speed, social cognition, and attention[32]. These deficits precede the onset of psychotic symptoms and are present from prodromal stages, being classified as endophenotypes of the disorder and defined as early neurodevelopmental alterations[33]. Cognitive endophenotypes tend to remain relatively stable over time, are less influenced by acute clinical fluctuations[34], and function as intermediate markers between environmental risk factors and the clinical

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expression of schizophrenia, thereby reinforcing the neurodevelopmental model of the disease[9].

In addition, epidemiological studies have identified associations between GDM and neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), which share cognitive and behavioral domains with the endophenotypes observed in schizophrenia[35-37]. A meta-analysis involving more than 56 million pregnancies demonstrated that the presence of GDM and PGDM was correlated with an increased risk of multiple neurodevelopmental disorders, including impairments in communication skills, learning abilities, and overall cognitive performance in the offspring[35]. Conversely, a large study including data from more than 200,000 mother–child pairs did not find a significant link to alterations in nonverbal intelligence or motor function in children across any age group. However, children aged 4 to 10 years born to mothers with GDM exhibited significantly higher levels of externalizing problems [38].

Some longitudinal studies have indicated that certain schizophrenia-related endophenotypes are more frequently observed in the offspring exposed to GDM, particularly when exposure occurs early in gestation[24,39]. These include early psychotic experiences, auditory and visual hallucinations during childhood, executive function deficits, and increased externalizing behaviors. Specifically, higher rates of auditory and visual hallucinations were observed in 10-year-old children exposed to maternal DM early in pregnancy, independently of depressive symptoms or other covariates[24].

From a physiological perspective, maternal hyperglycemia interferes with fundamental processes of fetal neurodevelopment through mechanisms such as oxidative stress, fetal hypoxia, inflammation, and epigenetic alterations[20]. Recent reviews have indicated that GDM is related to persistent changes in DNA methylation in umbilical cord blood and placental tissue, as well as elevated levels of inflammatory cytokines and metabolic markers, such as C-peptide, which have been linked to early impairments in communication and cognition. These biomarkers suggest plausible biological pathways connecting intrauterine exposure to hyperglycemia with long-lasting alterations in brain development[35,39-40].

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Limitations of the study

Despite the strength of the evidence, this analysis has some limitations that must be mentioned. Firstly, all the included studies were observational, precluding the establishment of a causal relationship between maternal DM during pregnancy and schizophrenia in the offspring. Differences in the diagnostic criteria and definitions of maternal DM across studies, particularly regarding the classification of type 1 DM, type 2 DM, and GDM, may also have introduced variability in exposure assessment. Shared genetic and environmental factors may contribute to the risk of schizophrenia and should be considered when interpreting the findings. Although statistical heterogeneity was low (I^2 = 0%), methodological differences existed among the included studies, particularly regarding sample size, diagnostic criteria, and adjustment strategies. However, the effect estimates were in the same direction across studies. Additionally, all studies included in the meta-analysis were conducted in Scandinavian countries. Therefore, the generalizability of the findings to populations from other geographic regions, ethnic backgrounds, and healthcare systems should be interpreted with caution. Residual confounding cannot be excluded, as the included studies adjusted for different sets of covariates and did not consistently account for important confounders, such as maternal BMI, glycemic control, socioeconomic status, psychiatric family history, antipsychotic exposure, and obstetric complications

Strengths of the study

The main strengths of this study lie in the rigorous methodological approach, which included a systematized search in multiple databases, allowing for a comprehensive selection of studies focused on the association between DM during pregnancy and the risk of schizophrenia in the offspring. The assessment of the methodological quality and risk of bias of the included studies corroborates the reliability of the results. In addition, the analysis of other relevant clinical variables, such as maternal obesity, birth weight, and coverage of all types of maternal DM, enabled a more comprehensive interpretation of the mechanisms underlying the increased risk of schizophrenia in the offspring. Thus, this study contributes significantly to understanding the

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impact of the adverse intrauterine metabolic environment on neuropsychiatric development.

CONCLUSION

The findings of this meta-analysis suggest that maternal DM during pregnancy may be associated with an increased risk of schizophrenia in the offspring. The pooled analysis of studies reporting HRs demonstrated a statistically significant increase in the risk with consistent findings across cohorts, whereas the analysis based on ORs yielded a similar direction of effect, however the estimate was not statistically significant due to the limited number of available studies and the wide CI. Given that the evidence is based on a small number of observational cohort studies, these findings should be interpreted with caution. Overall, the available evidence suggests a potential relationship between maternal DM during pregnancy and schizophrenia in the offspring and underscores the need for further well-designed prospective studies to confirm these findings and clarify the underlying biological mechanisms.

Conflict of Interest: There is no conflict of interest to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and privacy considerations, the dataset is not publicly available. All relevant aggregated data are included within the article. Additional details may be provided by the authors upon reasonable request, in accordance with institutional and ethical committee regulations.

Authors' Contributions:

Conceptualization: Marianna Zanette Molha (MZM), Beatriz Yukie Filosi Hasegawa (BYFH); Data curation: MZM, BYFH, Ana Julia de Magalhães Pina (AJMP), Beatriz Fernandes Lima (BFL); Formal analysis: MZM, AJMP; Investigation: MZM, BYFH, AJMP, BFL; Methodology: MZM, BYFH, AJMP, BFL; Validation: MZM, AJMP; Visualization: MZM; Software: AJMP; Project

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administration: MZM; Resources: Carlos Antonio Negrato (CAN); Supervision: CAN; Writing – original draft: MZM, BYFH, AJMP, BFL; Writing – review and editing: MZM, CAN.

All authors have read and approved the final version submitted and take public responsibility for all aspects of the work."

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