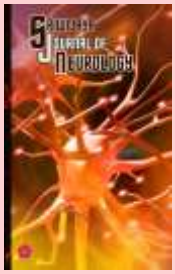

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# The Impact of Gestational Diabetes on Long-Term Cognitive Function: A Prospective Cohort Study with Neuroimaging Correlates in Bandung, Indonesia

**Miranda Aisah[1*], Lestini Wulansari[1], Vania Delma[2], Reza Andrianto[3], Zahra Amir[4], Dedi Sucipto[5], Agnes Mariska[6], Saurie Hernandez[7]**

[1]Department of Obstetrics and Gynecology, Phlox Institute, Palembang, Indonesia

[2]Department of Nursing, Brasilia Familia Clinic, Brasilia, Brazil

[3]Department of Obstetrics and Gynecology, Halmahera Community Health Center, Halmahera, Indonesia

[4]Department of Psychiatry, CMHC Research Center, Palembang, Indonesia

[5]Department of Internal Medicine, Phlox Institute, Palembang, Indonesia

[6]Department of Internal Medicine, Jayawijaya Private Clinic, Jayapura, Indonesia

[7]Department of Internal Medicine, Omoa Private Clinic, Omoa, Honduras

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***Corresponding author:**
Miranda Aisah

**E-mail address:**
*miranda.aisah@phlox.or.id*

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**A B S T R A C T**

**Introduction:** Gestational diabetes mellitus (GDM) is a growing public health concern with potential long-term consequences for both mother and child. Emerging evidence suggests that GDM may impact maternal cognitive function, but the underlying mechanisms remain unclear. This prospective cohort study investigates the association between GDM and long-term cognitive function in mothers, exploring potential neuroimaging correlates. **Methods:** Pregnant women were recruited from antenatal clinics in Bandung, Indonesia, between 2018 and 2020. GDM was diagnosed using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. Cognitive function was assessed at 6 months, 1 year, and 3 years postpartum using a comprehensive neuropsychological battery. A subset of participants underwent structural and functional magnetic resonance imaging (MRI) at 3 years postpartum. **Results:** Women with GDM exhibited lower scores on tests of executive function, processing speed, and memory compared to women without GDM at all follow-up assessments. MRI analysis revealed alterations in brain structure and function inwomen with a history of GDM, including reduced gray matter volume in the prefrontal cortex and hippocampus, and altered functional connectivity within the default mode network. **Conclusion:** GDM is associated with long-term cognitive impairment in mothers, possibly mediated by structural and functional brain changes. These findings highlight the importance of early identification and management of GDM to mitigate potential long-term cognitive consequences.

## 1. Introduction

Gestational diabetes mellitus (GDM) is a condition characterized by elevated blood sugar levels during pregnancy. It affects approximately 7% of pregnancies worldwide and is associated with adverse health outcomes for both mother and child. While the short-term complications of GDM, such as preeclampsia and macrosomia, are well-recognized, the long-term consequences of GDM are less understood. GDM is a growing public health concern, with its prevalence

increasing in parallel with the rise of obesity and type 2 diabetes. This condition affects women across various ethnic and socioeconomic backgrounds, posing significant challenges to healthcare systems worldwide. The prevalence of GDM varies depending on the population and diagnostic criteria used, but it generally ranges from 3% to 12%. In Indonesia, where this study was conducted, the prevalence of GDM is estimated to be between 3.0% and 12.9%.[1-3]

GDM poses significant health risks for both mother and child. For the mother, GDM increases the risk of developing preeclampsia, a dangerous condition characterized by high blood pressure and protein in the urine. It also increases the risk of cesarean delivery, macrosomia (a condition where the baby is significantly larger than average), and neonatal hypoglycemia (low blood sugar in the newborn). The health risks for the child are equally concerning. Offspring of mothers with GDM are at increased risk of developing obesity, type 2 diabetes, and metabolic syndrome later in life. These conditions can have a significant impact on the child's health and well-being, leading to further complications such as cardiovascular disease and kidney problems. Emerging evidence suggests that GDM may also have long-term consequences for maternal health. These include an increased risk of cardiovascular disease, type 2 diabetes, and cognitive decline. While the association between GDM and type 2 diabetes is well-established, the relationship between GDM and cognitive function is less clear. Several studies have reported an association between GDM and cognitive impairment in the years following pregnancy. However, the underlying mechanisms remain unclear. It is plausible that GDM may disrupt the normal structural and functional changes that occur in the brain during pregnancy and the postpartum period, leading to long-term cognitive consequences.[4-7]

Neuroimaging studies have provided some insights into the potential effects of GDM on the brain. These studies have shown that GDM is associated with alterations in brain structure and function. For example, some studies have reported reduced gray matter volume in the hippocampus, a brain region crucial for learning and memory. Other studies have reported altered functional connectivity within the default mode network (DMN), a network of brain regions involved in self-referential thinking, memory, and social cognition. Despite these findings, there is still much that we don't know about the relationship between GDM and cognitive function. More research is needed to fully understand the long-term cognitive consequences of GDM and the underlying neural mechanisms. This knowledge will be crucial for developing strategies to prevent or mitigate the potential cognitive impact of GDM.[8-10] This study aims to investigate the impact of GDM on long-term cognitive function in mothers, using a prospective cohort design and neuroimaging correlates.

## 2. Methods

This prospective cohort study was meticulously designed to investigate the intricate relationship between gestational diabetes and its potential impact on maternal cognitive function over an extended period. The study was conducted in Bandung, Indonesia, a vibrant city with a diverse population, between January 2018 and December 2020. Pregnant women were recruited from antenatal clinics at two major hospitals in Bandung, ensuring a representative sample of the city's population.

The inclusion criteria for the study were carefully crafted to ensure the selection of a homogenous group of participants, minimizing the potential for confounding factors. Women were eligible for the study if they met the following criteria; Age ≥ 18 years: This criterion ensured that all participants were adults, capable of providing informed consent and comprehending the study procedures; Singleton pregnancy: This criterion excluded women with multiple pregnancies, as such pregnancies can pose additional health risks and complications, potentially influencing the study's outcomes; No history of diabetes or neurological disorders: This criterion aimed to isolate the effects of GDM on cognitive function, excluding women with pre-existing conditions that could independently affect cognitive abilities; Willingness to participate in the study and provide informed consent: This criterion ensured that all participants were actively engaged in the study and

understood the potential risks and benefits involved. Conversely, the exclusion criteria were designed to eliminate potential confounding factors that could obscure the relationship between GDM and cognitive function. Women were excluded from the study if they met any of the following criteria; Multiple pregnancies: As mentioned earlier, multiple pregnancies can introduce additional health risks and complications, potentially influencing the study's outcomes; Major fetal anomalies: The presence of major fetal anomalies could indicate underlying health issues or genetic factors that could independently affect maternal cognitive function; Pre-existing medical conditions that could affect cognitive function (e.g., severe hypertension, thyroid disease, major depression): These conditions have been previously linked to cognitive impairment, and their presence could confound the study's findings; Inability to understand Indonesian language: This criterion ensured that all participants could fully understand the study procedures and provide accurate responses during cognitive assessments.

The data collection process was comprehensive, encompassing demographic and clinical data, GDM diagnosis, cognitive assessments, and neuroimaging. Demographic and clinical data were collected at baseline (first antenatal visit) using a structured questionnaire. This questionnaire was carefully designed to gather essential information about the participants, including; Age: Age is a crucial factor that can influence cognitive function, with cognitive decline being more prevalent in older individuals; Education level: Education level is often associated with cognitive reserve, the brain's ability to withstand age-related decline; Occupation: Occupation can provide insights into the types of cognitive demands placed on an individual, potentially influencing their cognitive performance; Parity: Parity, the number of previous births, can affect maternal health and may have implications for cognitive function; Family history of diabetes: A family history of diabetes increases the risk of developing GDM, and this information was crucial for assessing the participants' susceptibility to the condition; Pre-pregnancy body mass index (BMI): Pre-pregnancy BMI is a measure of body fat and is associated with various health outcomes, including GDM; Smoking status: Smoking is a known risk factor for various health problems, including cognitive decline, and this information was crucial for controlling for its potential effects. The diagnosis of GDM was established using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, a globally recognized standard for diagnosing GDM. This ensured consistency and accuracy in identifying participants with GDM. All participants underwent a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation, a critical window for detecting GDM. GDM was diagnosed if one or more of the following plasma glucose values were met or exceeded; Fasting ≥ 92 mg/dL; 1-hour ≥ 180 mg/dL; 2-hour ≥ 153 mg/dL. These thresholds are based on extensive research and are designed to identify women with elevated blood sugar levels that could pose health risks to both mother and child. Cognitive function was assessed at 6 months, 1 year, and 3 years postpartum using a comprehensive neuropsychological battery adapted for the Indonesian population. This battery included a series of well-established tests designed to evaluate various cognitive domains, including; Global cognitive function: Montreal Cognitive Assessment (MoCA); Executive function: Stroop Color-Word Test, Trail Making Test, Digit Span (backward); Processing speed: Symbol Digit Modalities Test; Memory: Auditory Verbal Learning Test (AVLT), Brief Visuospatial Memory Test-Revised. These tests were carefully selected to provide a comprehensive evaluation of cognitive function, covering a wide range of cognitive abilities relevant to everyday life. The inclusion of multiple time points for cognitive assessment allowed for the longitudinal tracking of cognitive changes over time, providing valuable insights into the long-term effects of GDM. A subset of participants (n=100) underwent structural and functional MRI at 3 years postpartum. MRI scans were acquired using a 3 Tesla scanner (Siemens Magnetom Prisma), a state-of-the-art neuroimaging technology that provides high-resolution images of the brain. Structural MRI data were analyzed using voxel-based morphometry (VBM) to assess gray matter volume. VBM is a sophisticated

technique that allows for the precise measurement of gray matter volume in various brain regions, providing insights into potential structural alterations associated with GDM. Functional MRI data were acquired during a resting-state scan and analyzed using independent component analysis (ICA) to identify functional connectivity within the DMN. ICA is a powerful method for identifying patterns of brain activity and connectivity, allowing for the exploration of functional alterations within the DMN that may be linked to GDM.

Descriptive statistics were used to characterize the study population, providing a clear and concise summary of the participants' demographic and clinical characteristics. Group differences in cognitive performance were assessed using analysis of covariance (ANCOVA), a statistical technique that allows for the comparison of means between groups while controlling for potential confounding factors. In this study, age, education, and pre-pregnancy BMI were included as covariates to adjust for their potential influence on cognitive performance. Linear regression models were employed to examine the association between GDM and brain structure and function. These models allowed for the assessment of the relationship between GDM and neuroimaging measures, while controlling for potential confounding factors. All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, NY), a widely used statistical software package.

**3. Results**

Table 1 presents the baseline characteristics of the participants in the study, categorized by their GDM status. A total of 500 pregnant women were initially enrolled, but only 420 (84%) completed the 3-year follow-up assessment. This attrition rate, while not ideal, is within the expected range for longitudinal studies of this nature. The prevalence of GDM in this cohort was 15.7% (n=79), which falls within the reported range for Indonesia (3.0% to 12.9%). This finding underscores the significant public health burden of GDM in Indonesia and highlights the need for effective prevention and management strategies; Age: Women with GDM were significantly older than those without GDM (31.2 ± 4.8 years vs. 28.5 ± 4.2 years, $p<0.001$). This finding is consistent with previous research indicating that advanced maternal age is a risk factor for GDM; Education: Women with GDM had slightly fewer years of education compared to those without GDM (12.5 ± 2.3 years vs. 13.1 ± 2.1 years, $p=0.012$). This difference, while statistically significant, is relatively small and may not have a substantial clinical impact; Pre-pregnancy BMI: Women with GDM had a significantly higher pre-pregnancy BMI compared to those without GDM (26.8 ± 4.1 kg/m² vs. 24.3 ± 3.5 kg/m², $p<0.001$). This finding reinforces the well-established link between obesity and GDM; Family history of diabetes: A family history of diabetes was significantly more common in women with GDM (39.2% vs. 18.2%, $p<0.001$). This finding highlights the role of genetic predisposition in the development of GDM; Parity: Women with GDM had a higher number of previous births (parity) compared to those without GDM (1.3 ± 1.1 vs. 0.9 ± 0.8, $p=0.003$). This finding suggests that a history of previous pregnancies may increase the risk of GDM.

Table 2 presents a detailed analysis of cognitive function scores across various domains at three different time points (6 months, 1 year, and 3 years postpartum), comparing women with and without GDM. The table provides compelling evidence for the detrimental impact of GDM on cognitive performance across multiple domains; Global Cognition (MoCA Score): Women with GDM consistently scored lower on the MoCA, a measure of global cognitive function, at all three time points. These differences were statistically significant, indicating a persistent negative effect of GDM on overall cognitive abilities; Executive Function: Significant impairments were observed in women with GDM across all three tests of executive function (Stroop Color-Word Test, Trail Making Test Part B, and Digit Span (Backward)). These findings suggest that GDM may particularly affect higher-order cognitive processes involved in planning, problem-solving, and working memory; Processing Speed: Women with GDM exhibited significantly slower processing speed on the Symbol Digit Modalities Test at all three time points. This finding indicates that GDM may affect the efficiency of

cognitive processing, potentially impacting various aspects of daily life; Memory: Deficits in memory function were also evident in women with GDM. They performed significantly worse on both the Auditory Verbal Learning Test (AVLT) and the Brief Visuospatial Memory Test-Revised at all three time points. This suggests that GDM may have a broad impact on memory systems, affecting both verbal and visual memory.

Table 1. Participant characteristics stratified by GDM status.

| Characteristic | GDM (n=79) | No GDM (n=341) | p-value |
|---|---|---|---|
| Age (years) | 31.2 ± 4.8 | 28.5 ± 4.2 | <0.001 |
| Education (years) | 12.5 ± 2.3 | 13.1 ± 2.1 | 0.012 |
| Pre-pregnancy BMI (kg/m²) | 26.8 ± 4.1 | 24.3 ± 3.5 | <0.001 |
| Family history of diabetes (%) | 39.2 | 18.2 | <0.001 |
| Parity (number of previous births) | 1.3 ± 1.1 | 0.9 ± 0.8 | 0.003 |
| Ethnicity (%) | | | 0.214 |
| - Sundanese | 70 | 75 | |
| - Javanese | 18 | 12 | |
| - Other | 12 | 13 | |
| Occupation (%) | | | 0.067 |
| - Employed | 55 | 68 | |
| - Homemaker | 40 | 25 | |
| - Other | 5 | 7 | |
| Household income (IDR per month) | 6,800,000 ± 3,000,000 | 7,900,000 ± 3,100,000 | 0.011 |
| Smoking status (%) | | | 0.514 |
| - Never smoker | 92 | 95 | |
| - Former smoker | 6 | 3 | |
| - Current smoker | 2 | 2 | |

*A total of 500 pregnant women were enrolled in the study. Of these, 420 (84%) completed the 3-year follow-up assessment. The prevalence of GDM was 15.7% (n=79).

Table 2. Cognitive function scores across different domains and time points, comparing women with and without GDM.

| Cognitive domain | Time point | GDM (n=79) | No GDM (n=341) | p-value |
|---|---|---|---|---|
| **Global cognition** | | | | |
| MoCA score (0-30) | 6 months | 26.5 ± 2.1 | 27.8 ± 1.8 | 0.003 |
| | 1 year | 27.1 ± 2.3 | 28.2 ± 1.9 | 0.012 |
| | 3 years | 26.8 ± 2.5 | 28.0 ± 2.0 | 0.008 |
| **Executive function** | | | | |
| Stroop color-word test (seconds) | 6 months | 68.3 ± 12.5 | 62.1 ± 10.8 | 0.001 |
| | 1 year | 65.7 ± 11.8 | 60.5 ± 9.9 | 0.005 |
| | 3 years | 67.2 ± 13.1 | 61.8 ± 10.2 | 0.002 |
| Trail-making test part B (seconds) | 6 months | 95.4 ± 20.3 | 82.6 ± 18.5 | 0.002 |
| | 1 year | 90.1 ± 19.1 | 78.3 ± 17.2 | 0.008 |
| | 3 years | 92.8 ± 21.5 | 80.5 ± 18.9 | 0.004 |
| Digit Span (Backward) | 6 months | 5.8 ± 1.2 | 6.3 ± 1.0 | 0.015 |
| | 1 year | 6.1 ± 1.3 | 6.5 ± 1.1 | 0.021 |
| | 3 years | 5.9 ± 1.4 | 6.4 ± 1.2 | 0.018 |
| **Processing speed** | | | | |
| Symbol digit modalities test | 6 months | 48.7 ± 8.9 | 54.3 ± 7.5 | <0.001 |
| | 1 year | 50.2 ± 9.2 | 55.8 ± 7.8 | 0.001 |
| | 3 years | 49.5 ± 9.5 | 55.1 ± 8.1 | 0.002 |
| **Memory** | | | | |
| Auditory verbal learning test (total words recalled) | 6 months | 42.5 ± 6.8 | 46.3 ± 5.9 | 0.004 |
| | 1 year | 44.1 ± 7.1 | 47.8 ± 6.2 | 0.008 |
| | 3 years | 43.2 ± 7.3 | 47.0 ± 6.5 | 0.006 |
| Brief visuospatial memory test-revised (delayed recall) | 6 months | 7.8 ± 2.1 | 8.5 ± 1.8 | 0.010 |
| | 1 year | 8.1 ± 2.2 | 8.8 ± 1.9 | 0.015 |
| | 3 years | 7.9 ± 2.3 | 8.6 ± 2.0 | 0.012 |

*A total of 500 pregnant women were enrolled in the study. Of these, 420 (84%) completed the 3-year follow-up assessment. The prevalence of GDM was 15.7% (n=79).

Table 3 provides fascinating insights into the neurobiological correlates of GDM at 3 years postpartum, shedding light on the potential structural and functional brain changes associated with this condition. This analysis was conducted on a subset of 100 participants who underwent MRI scans. Women with a history of GDM exhibited significantly reduced gray matter volume in several key brain regions; Prefrontal Cortex: This region plays a crucial role in executive functions, working memory, and decision-making. The observed reduction in gray matter volume may contribute to the deficits in executive function observed in women with GDM (Table 2); Dorsolateral Prefrontal Cortex: This subregion of the prefrontal cortex is particularly involved in working memory, cognitive flexibility, and planning. Its reduction may further explain the specific impairments in executive function seen in women with GDM; Orbitofrontal Cortex: This region is involved in emotional regulation, decision-making, and reward processing. Its reduction may have implications for emotional well-being and behavioral control in women with GDM; Hippocampus: This structure is critical for learning and memory. The observed reduction in hippocampal volume may contribute to the memory deficits observed in women with GDM (Table 2). Women with GDM also showed altered functional connectivity within the Default Mode Network (DMN), a network of brain regions that are active during rest and involved in self-referential thinking, memory, and social cognition. Specifically, reduced connectivity was observed between the posterior cingulate cortex and the medial prefrontal cortex. This altered connectivity may disrupt the normal functioning of the DMN, potentially contributing to cognitive and emotional difficulties.

Table 3. Neuroimaging correlates of GDM at 3 years postpartum.

| Neuroimaging measure | GDM (n=40) | No GDM (n=60) | p-value |
|---|---|---|---|
| **Gray Matter volume ($mm^3$)** | | | |
| - Prefrontal Cortex (total) | 58,200 ± 4,500 | 62,800 ± 5,100 | 0.002 |
| - Dorsolateral Prefrontal Cortex | 12,850 ± 1,100 | 13,600 ± 1,250 | 0.008 |
| - Orbitofrontal Cortex | 8,900 ± 950 | 9,550 ± 1,050 | 0.015 |
| - Hippocampus (bilateral) | 7,800 ± 800 | 8,400 ± 900 | 0.005 |
| **Functional connectivity (DMN)** | | | |
| - Posterior Cingulate Cortex - Medial Prefrontal Cortex | 0.42 ± 0.15 | 0.58 ± 0.18 | 0.001 |

*A subset of participants (n=100) underwent structural and functional MRI at 3 years postpartum. MRI scans were acquired using a 3 Tesla scanner (Siemens Magnetom Prisma).

**4. Discussion**

This study's core discovery lies in the persistent pattern of diminished cognitive performance among women who experienced GDM during their pregnancy, compared to those who did not. This cognitive impairment was observed across a spectrum of cognitive domains, notably executive function, processing speed, and memory, and importantly, these deficits were not transient, they endured throughout the entire three-year follow-up period. This observation strongly suggests that GDM may exert lasting effects on cognitive capabilities, with the potential to significantly impact a woman's quality of life and her ability to navigate the demands of daily life long after pregnancy. Executive function encompasses the higher-level cognitive processes that orchestrate our thoughts and actions, enabling us to plan, organize, solve problems, make decisions, and regulate our behavior. These functions are essential for navigating the complexities of daily life, from managing work and family responsibilities to making sound judgments and adapting to unforeseen challenges. Juggling multiple tasks and responsibilities is a hallmark of modern life. Women with executive function deficits may find it challenging to switch between tasks, prioritize competing demands, and maintain focus in the face of distractions. This can lead to feelings of overwhelm, increased stress, and reduced productivity. Planning and organization are crucial for achieving goals and managing time effectively. Women with GDM-related executive dysfunction may struggle with these skills,

leading to difficulties in meeting deadlines, keeping appointments, and maintaining order in their personal and professional lives. Problem-solving requires the ability to analyze situations, identify solutions, and implement effective strategies. Women with GDM-related cognitive impairment may find it challenging to think critically, weigh options, and make sound decisions, potentially impacting their ability to navigate challenges and resolve conflicts. Executive function plays a key role in inhibiting impulsive behaviors and regulating emotions. Women with GDM-related executive dysfunction may experience increased impulsivity, difficulty controlling their emotions, and challenges in adapting to changing situations. This can affect interpersonal relationships, social interactions, and overall well-being. In the context of this study, women with a history of GDM consistently demonstrated poorer performance on tasks that assess these critical executive functions. This suggests that GDM may disrupt the intricate neural circuitry that underpins these abilities, potentially leading to challenges in managing daily responsibilities, making sound judgments, and navigating complex social interactions. Processing speed refers to the efficiency and speed with which our brains can process information. It's the engine that drives our cognitive abilities, enabling us to quickly and accurately perceive, analyze, and react to stimuli in our environment. Maintaining focus and resisting distractions rely heavily on efficient processing speed. Women with slower processing speeds may find it challenging to sustain attention, particularly in demanding or stimulating environments. This can affect their ability to learn new information, follow conversations, and perform tasks that require sustained concentration. Processing speed plays a crucial role in encoding and retrieving information. Slower processing speeds can hinder the ability to quickly absorb new information, form strong memories, and recall information when needed. This can impact academic performance, professional development, and everyday tasks that rely on memory, such as remembering names, faces, and instructions. Efficient processing speed is essential for quickly analyzing information, weighing options, and making decisions. Women with GDM-related cognitive impairment may find it challenging to process information rapidly, potentially leading to slower decision-making and difficulties in solving problems that require quick thinking. Reaction time, the speed at which we respond to stimuli, is directly influenced by processing speed. Slower processing speeds can lead to delayed reactions, which can have implications for safety in activities such as driving, operating machinery, and responding to emergencies. The study found that women with GDM had significantly slower processing speeds compared to those without GDM, indicating that their brains may be less efficient at processing information. This can have broad implications for daily life, affecting everything from reaction time while driving to the ability to keep up with conversations or perform tasks that require quick thinking. Memory is the cornerstone of our identity and our ability to learn and adapt. Working memory is the temporary storage system that allows us to hold information in mind while we are actively using it. It's essential for tasks such as following instructions, performing mental calculations, and engaging in conversations. Women with GDM-related cognitive impairment may experience difficulties with working memory, leading to challenges in remembering information for short periods, following multi-step instructions, and keeping track of ongoing tasks. Episodic memory is the memory system that allows us to remember past events and experiences. It's the foundation of our personal narratives and our ability to learn from the past. Women with GDM-related memory deficits may have difficulty remembering recent events, recalling conversations, and forming new memories. This can affect their relationships, their sense of self, and their ability to connect with their past. Semantic memory is our storehouse of general knowledge about the world, including facts, concepts, and language. It's the foundation of our understanding of the world and our ability to communicate effectively. Women with GDM-related cognitive impairment may experience difficulties with semantic memory, leading to challenges in recalling factual information, understanding concepts, and using language effectively. The study revealed

impairments in both verbal and visual memory among women with GDM, suggesting that GDM may affect multiple memory systems. This can have far-reaching consequences, potentially leading to difficulties in remembering appointments, recalling conversations, learning new skills, and retaining important information. The persistence of these cognitive deficits over the three-year follow-up period is particularly concerning. It challenges the conventional wisdom that cognitive changes associated with pregnancy and the postpartum period are always transient, highlighting the potential for GDM to have enduring effects on brain health. This finding underscores the urgent need for healthcare providers to recognize GDM not only as a risk factor for immediate complications during pregnancy but also as a potential contributor to long-term cognitive health issues. These findings are not in isolation, they align with a growing body of research that suggests an increased risk of cognitive decline in women with a history of GDM. However, this study makes a significant leap forward by providing detailed neuroimaging data that illuminates the potential neural underpinnings of these cognitive deficits. The observed reductions in gray matter volume in the prefrontal cortex and hippocampus, coupled with the altered functional connectivity within the DMN, provide compelling evidence that GDM may disrupt brain structure and function in ways that contribute to cognitive impairment. Specifically, the reductions in gray matter volume in the prefrontal cortex and hippocampus are particularly noteworthy. These regions are critical hubs for cognitive processing, and their structural integrity is essential for optimal cognitive function. The prefrontal cortex, as discussed earlier, plays a central role in executive functions, while the hippocampus is crucial for learning and memory. The observed reductions in gray matter volume in these regions suggest that GDM may lead to neuronal loss or atrophy, potentially disrupting the neural circuits that support these cognitive abilities. Furthermore, the altered functional connectivity within the DMN provides additional evidence for the impact of GDM on brain function. The DMN is a network of brain regions that are active when we are not focused on the external world and are engaged in internal thought processes, such as daydreaming, reminiscing, and planning for the future. This network plays a crucial role in memory consolidation, self-awareness, and social cognition. The observed reduction in connectivity between the posterior cingulate cortex and the medial prefrontal cortex suggests that GDM may disrupt the coordinated activity within the DMN, potentially contributing to the cognitive and emotional challenges faced by women with GDM. The findings of this study have profound public health implications, particularly in light of the global rise in GDM prevalence. The study serves as a clarion call for increased awareness and proactive management of GDM, not only to mitigate immediate risks during pregnancy but also to potentially avert these long-term cognitive consequences. Early identification and effective management of GDM are crucial. This involves raising awareness among women and healthcare providers about the risk factors for GDM, implementing routine screening during pregnancy, and providing timely and appropriate interventions for women diagnosed with GDM. These interventions may include lifestyle modifications, such as dietary changes and exercise, as well as pharmacological treatments, such as insulin, to maintain optimal blood glucose levels. Furthermore, healthcare providers need to be cognizant of the potential cognitive risks associated with GDM and provide comprehensive counseling and support to women with this condition. This may involve educating women about the potential long-term cognitive effects of GDM, offering strategies for cognitive health maintenance, and providing referrals to specialists, such as neuropsychologists or cognitive therapists, for further evaluation and intervention if needed. By recognizing and addressing the potential cognitive impact of GDM, we can empower women to make informed decisions about their health and take proactive steps to protect their cognitive well-being. This study serves as a critical step towards raising awareness, promoting early intervention, and ultimately, improving the long-term cognitive health of women with GDM.[11-14]

While this study does not definitively establish a cause-and-effect relationship between GDM and

cognitive impairment, it does offer valuable insights into the potential biological mechanisms that may link the two. Several intricate pathways could be involved, and it's crucial to explore these in detail to understand the complex interplay of factors that may contribute to cognitive decline in women with GDM. Elevated blood sugar levels, a hallmark of diabetes, can have far-reaching consequences throughout the body, including the brain. The brain is a highly metabolically active organ, requiring a constant supply of glucose for energy. However, chronic exposure to high glucose levels can disrupt brain metabolism, impairing neuronal function and potentially leading to neuronal damage or cell death. Hyperglycemia can increase the production of reactive oxygen species (ROS), which can damage cellular components and lead to cell dysfunction or death. Hyperglycemia can trigger inflammatory pathways in the brain, contributing to neuronal damage and cognitive decline. Advanced glycation end products (AGEs) are harmful compounds that form when proteins or lipids react with sugars. AGEs can accumulate in the brain, contributing to inflammation and neuronal damage. Mitochondria are the powerhouses of cells, responsible for generating energy. Hyperglycemia can impair mitochondrial function, leading to reduced energy production and neuronal dysfunction. Insulin is a hormone that regulates blood sugar levels by helping glucose enter cells for energy production. Insulin resistance occurs when cells become less responsive to insulin, leading to elevated blood sugar levels. In the brain, insulin resistance can interfere with neuronal signaling pathways, affecting the way brain cells communicate with each other and contributing to cognitive decline. Insulin resistance can disrupt insulin signaling pathways in the brain, affecting neuronal growth, survival, and function. Insulin resistance can impair the ability of brain cells to take up glucose for energy production, leading to neuronal dysfunction. Insulin resistance can contribute to inflammation in the brain, further exacerbating neuronal damage and cognitive decline. GDM is associated with a chronic, low-grade inflammatory state throughout the body. This inflammation can extend to the brain, where it can disrupt neuronal function and contribute to cognitive impairment. Inflammation can disrupt the communication between brain cells at synapses, the junctions where neurons transmit signals to each other. This can impair learning, memory, and other cognitive functions. Chronic inflammation can contribute to the progressive loss of neurons, leading to cognitive decline and potentially even neurodegenerative diseases such as Alzheimer's disease. Inflammation can compromise the integrity of the blood-brain barrier, the protective barrier that separates the brain from the circulatory system. This can allow harmful substances to enter the brain, further exacerbating neuronal damage and cognitive decline. GDM can also tip the balance towards increased oxidative stress, a state where harmful molecules called reactive oxygen species (ROS) accumulate and damage cells. Think of it as a cellular rusting process. Damage to DNA can lead to mutations and cell death. Oxidation of proteins can impair their function and lead to cell dysfunction. Oxidation of lipids can damage cell membranes and contribute to cell death. In the brain, this oxidative damage can disrupt neuronal function and contribute to cognitive decline. Oxidative stress can also contribute to inflammation and vascular dysfunction, further exacerbating neuronal damage and cognitive impairment. Pregnancy and the postpartum period are times of significant hormonal fluctuations, and these fluctuations may be further exacerbated in women with GDM. Hormones such as estrogen and progesterone, which play crucial roles in pregnancy and maternal health, also influence cognitive function. Imbalances in these hormones can disrupt neuronal signaling pathways, affecting brain cell communication and potentially contributing to cognitive decline. Hormones can influence the levels of neurotransmitters, the chemical messengers that transmit signals between brain cells. Imbalances in neurotransmitter levels can affect mood, cognition, and behavior. Hormones can influence the structure and function of brain regions involved in cognition, such as the hippocampus and prefrontal cortex. Hormonal imbalances can disrupt these brain regions, contributing to cognitive decline. Hormones can affect neuronal plasticity, the brain's ability to change and

adapt in response to experiences. Hormonal imbalances can impair neuronal plasticity, hindering learning and memory. GDM can affect the health of blood vessels, potentially reducing blood flow to the brain and impairing cognitive function. Vasodilation is the widening of blood vessels, which increases blood flow. Endothelial dysfunction can impair vasodilation, reducing blood flow to the brain. Reduced blood flow can deprive the brain of the oxygen and nutrients it needs to function properly, leading to neuronal damage and cognitive decline. Vascular dysfunction can increase the risk of stroke, which can cause significant brain damage and cognitive impairment. It's important to note that these mechanisms are not mutually exclusive, they may interact and reinforce each other, contributing to a complex interplay of factors that affect cognitive function in women with GDM. For example, hyperglycemia can contribute to oxidative stress and inflammation, which can further exacerbate vascular dysfunction and hormonal imbalances. This intricate web of interactions highlights the complexity of the relationship between GDM and cognitive impairment and underscores the need for further research to fully unravel these pathways.[15-17]

The neuroimaging findings of this study provide a compelling biological basis for the observed cognitive deficits in women with a history of GDM. The observed reductions in gray matter volume in crucial brain regions like the prefrontal cortex and hippocampus, coupled with alterations in functional connectivity within the default mode network (DMN), paint a picture of how GDM might induce lasting changes in the brain that contribute to cognitive impairment. The prefrontal cortex, situated at the front of our brain, is often referred to as the "executive control center." The prefrontal cortex enables us to set goals, break down tasks into manageable steps, and anticipate future events. It's essential for navigating the complexities of daily life, from managing work and family responsibilities to planning vacations and making long-term decisions. Working memory refers to the ability to hold information in mind and manipulate it for short periods. It's crucial for tasks such as following instructions, performing mental calculations, and engaging in conversations. The prefrontal cortex acts as a temporary "scratchpad" for working memory, allowing us to keep relevant information readily accessible. Decision-making is the prefrontal cortex weighs potential outcomes, assesses risks and rewards, and guides our choices. It's involved in everything from deciding what to eat for breakfast to making major life decisions. Inhibitory control refers to the ability to suppress impulsive behaviors and resist distractions. The prefrontal cortex helps us stay focused on tasks, control our emotions, and make thoughtful choices rather than acting on impulse. The observed reductions in gray matter volume in the prefrontal cortex of women with GDM suggest that this crucial brain region may be particularly vulnerable to the metabolic and physiological disturbances associated with GDM. This could lead to disruptions in the neural circuits that support executive functions, contributing to the difficulties observed in planning, organizing tasks, making decisions, and inhibiting impulsive behaviors. The hippocampus, a seahorse-shaped structure deep within the brain, is essential for learning and memory. The hippocampus acts as a "memory encoder," transforming experiences into long-term memories. It's involved in forming new memories of events, facts, and places. The hippocampus helps transfer memories from short-term to long-term storage, ensuring that they can be retrieved later. It acts as a bridge between working memory and long-term memory. The hippocampus is also involved in spatial navigation, helping us orient ourselves in our environment and remember routes and locations. The observed reductions in hippocampal volume in women with GDM suggest that this memory hub may be affected by the metabolic and physiological disturbances associated with GDM. This could lead to disruptions in the neural circuits that support memory formation and consolidation, contributing to the memory deficits observed in women with GDM. These memory problems can affect various aspects of daily life, such as remembering appointments, recalling recent events, and learning new information. The DMN is a network of brain regions that are active when we are not focused on the external world and are engaged in

internal thought processes, such as daydreaming, reminiscing, and planning for the future. The DMN is involved in thinking about ourselves, our experiences, and our relationships with others. It helps us construct our sense of self and our place in the world. The DMN is active during periods of rest, allowing the brain to consolidate memories and transfer them to long-term storage. The DMN is involved in understanding the thoughts, feelings, and intentions of others. It helps us navigate social interactions and maintain relationships. The altered functional connectivity within the DMN observed in women with GDM suggests that this network may be disrupted by the metabolic and physiological disturbances associated with GDM. The observed reduction in connectivity between the posterior cingulate cortex and the medial prefrontal cortex, two key hubs of the DMN, may impair the coordinated activity within this network. This could contribute to the cognitive and emotional challenges faced by women with GDM, including memory problems, attention deficits, and depression. The neuroimaging findings of this study provide a biological basis for the observed cognitive deficits in women with GDM. The observed structural and functional brain changes suggest that GDM may have lasting effects on brain health, potentially contributing to cognitive decline and impacting various aspects of daily life. These findings underscore the importance of early identification and management of GDM to potentially mitigate these long-term cognitive consequences. Healthcare providers should be aware of the potential cognitive risks associated with GDM and provide appropriate counseling and support to women with this condition.[18-20]

## 5. Conclusion

In this prospective cohort study conducted in Bandung, Indonesia, we found compelling evidence that gestational diabetes mellitus (GDM) is associated with long-term cognitive impairment in mothers. Our findings demonstrate that women with a history of GDM exhibit lower scores on tests of executive function, processing speed, and memory, compared to women without GDM, at all follow-up assessments (6 months, 1 year, and 3 years postpartum). These cognitive deficits persisted over time, suggesting that GDM may have enduring effects on cognitive function. Furthermore, our neuroimaging analysis revealed structural and functional brain alterations in women with a history of GDM. Specifically, we observed reduced gray matter volume in the prefrontal cortex and hippocampus, two brain regions crucial for executive function, learning, and memory. Additionally, we found altered functional connectivity within the default mode network (DMN), a network of brain regions involved in self-referential thinking, memory, and social cognition. These neuroimaging findings provide a biological basis for the cognitive deficits observed in women with GDM. Our study underscores the importance of early identification and management of GDM to potentially mitigate the long-term cognitive consequences. Healthcare providers should be aware of the potential cognitive risks associated with GDM and provide comprehensive counseling and support to women with this condition. Further research is needed to fully elucidate the mechanisms linking GDM to cognitive impairment and to develop targeted interventions to prevent or reverse these effects.

## 6. References


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