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Maternal Obesity and ADHD: An Original Review of Evidence and Potential Mechanisms

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Abstract

This review explores the potential link between maternal obesity [body mass index (BMI) >30 during pregnancy] and the development of attention-deficit/hyperactivity disorder (ADHD) in offspring. This study assesses the strength of this association by examining epidemiological studies and investigating possible biological mechanisms, including inflammation, oxidative stress, hormonal changes, prenatal programing, and epigenetic modifications. In addition, the review considers moderating variables and discusses the public health implications, with the objective of providing valuable insights into addressing this complex relationship for future clinical approaches and public health policies. This original review conducted a comprehensive literature search in August 2023 using various databases and keywords related to maternal obesity and ADHD. English articles published from 2005 to 2023, including case-control studies, cross-sectional studies, cohort studies, and reviews were considered. Multiple authors independently conducted searches, screened titles/abstracts, and extracted data to ensure rigorous methodology. Initially, 414 articles were retrieved from various databases and managed using Zotero. After eliminating 96 duplicates, 318 articles remained for screening on Rayyan. Of these, 47 papers met the eligibility criteria and underwent full-text review for inclusion in the study. Multiple studies suggest a positive correlation between maternal obesity and ADHD symptoms in children. Additionally, maternal obesity is associated with other neurodevelopmental disorders and behaviors in offspring, including heightened motor and anxiety behaviors. The complex relationship between maternal obesity and ADHD necessitates further investigation. Although existing research indicates associations, causality remains unconfirmed. Genome-wide association studies reveal shared genetic pathways, supported by rodent models. Human studies must address confounding factors. Promising interventions exist but require validation. Comprehensive research encompassing genetic, environmental, and metabolic factors is crucial for understanding the full impact of maternal obesity on neurodevelopmental outcomes.

Keywords: Maternal obesity, attention deficit hyperactivity disorder, neurodevelopmental disorders, overweight

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Introduction

Maternal obesity, defined as having an excessive body weight with a BMI >30 during pregnancy, has emerged as a significant global public health concern. In recent years, the prevalence of maternal obesity has surged, raising concerns about its potential impact on infant neurodevelopment. Among various neurodevelopmental disorders, attention-deficit/hyperactivity disorder (ADHD) has gained particular attention because of its widespread prevalence and enduring effects.[1] Understanding the possible link between maternal obesity and ADHD is essential for identifying modifiable risk factors and developing targeted interventions to improve the neurodevelopmental outcomes of children.

Investigation into the potential connection between these two conditions holds significant importance, considering the escalating rates of maternal obesity and the high prevalence of ADHD among children.[2] Uncovering a substantial association could have profound implications for public health strategies aimed at reducing the prevalence and impact of ADHD. Identifying maternal obesity as a potential risk factor for ADHD would underscore the significance of early interventions during pregnancy and postnatally, thereby mitigating the risk of neurodevelopmental challenges. Moreover, unraveling the mechanisms underlying this connection could provide insights into the pathophysiology of ADHD and open new avenues for therapeutic interventions.

The primary objective of this review is to provide a comprehensive overview of existing research on the potential links between maternal obesity and ADHD in offspring. By systematically examining epidemiological studies, animal research, and mechanistic investigations, we ascertain the strength of this association and uncover plausible biological mechanisms. This review seeks to clarify how maternal obesity might influence offspring neurodevelopment and its potential relevance to ADHD risk. Through meticulous analysis and synthesis of current evidence, we contribute to the understanding of how maternal obesity during pregnancy may contribute to the emergence of ADHD in children.

The specific aims of this review are as follows: (1) summarize findings from epidemiological studies that have investigated the association between maternal obesity and ADHD; (2) explore potential biological mechanisms, such as inflammation, oxidative stress, and hormonal changes during pregnancy, that could elucidate the maternal obesity- ADHD link; (3) investigate studies on prenatal programming and epigenetic modifications as potential explanatory factors; (4) identify potential moderating variables that could influence the strength of the maternal obesity-ADHD association; and (5) discuss the public health implications of this association and consider potential preventive measures. By achieving these goals, this review intends to offer valuable insights into the complex interplay between maternal obesity and ADHD, guiding future clinical approaches and public health policies.

Material and Method

Search Strategy and Inclusion Criteria

This original review was conducted in August 2023 to investigate the potential link between maternal obesity and the development of ADHD in offspring. The authors performed a search through PubMed, Scopus, Scielo, Cinahl, Web of Science, and ScienceDirect using the following keywords: “Maternal Obesity”, “Maternal Overweight”, “Attention Deficit Disorders with Hyperactivity”, “ADHD”, “Attention Deficit Hyperactivity Disorder”, “Attention Deficit-Hyperactivity Disorder”, “Attention Deficit-Hyperactivity Disorders”, “Deficit-Hyperactivity Disorder Attention”.

The inclusion criteria for articles considered in this review were as follows:

Publication Language: Articles published in the English language were included.

Publication Date: Articles published from 2005 to 2023 were considered to ensure coverage of recent research and developments.

Study Design: Various types of studies were included, such as case-control studies, cross-sectional studies, cohort studies, and review articles. These diverse study designs were chosen to capture a wide range of evidence on the topic.

Selection Process

Two authors independently conducted the literature searches, ensuring a comprehensive search across the specified databases. Duplicate articles were automatically detected and removed using Zotero. After eliminating duplicates, the remaining 318 articles underwent further screening on Rayyan. During this screening process, three authors independently evaluated the titles and abstracts of these articles, excluding any literature that did not meet the inclusion criteria. The reasons for exclusion at this stage included studies not related to maternal obesity and ADHD, non-English articles, and those published before 2005.

Following the title and abstract screening, the full text of 47 papers was reviewed to determine their eligibility for inclusion in the study. These full-text reviews were conducted to ensure that the selected articles contained detailed and relevant information regarding the potential link between maternal obesity and ADHD. The screening process is visually depicted in **Figure 1**.

Data Analysis

Three authors independently extracted data from the 47 included studies. Data extraction encompassed key information such as study design, sample size, participant characteristics, methodologies, main findings, and any information pertinent to the review’s objectives. This approach ensured that a comprehensive and thorough assessment of the literature was performed.

By following this methodological process, we aimed to identify and select articles that were most relevant to the objectives of this review, thereby providing a robust foundation for our analysis of the association

between maternal obesity and ADHD and the potential mechanisms underlying this relationship.

Results

A comprehensive search and screening process were conducted to identify relevant articles for this review. A total of 414 articles were initially retrieved from various databases, which were then managed using Zotero. After eliminating 96 duplicate articles, 318 articles remained for screening on Rayyan. Following a rigorous screening process, 47 papers were identified as meeting the eligibility criteria and underwent full-text review for inclusion in the study. A summary of the results is visually depicted in **Table 1**.

Highlights

- Maternal obesity is a global public health concern with rising prevalence, raising concerns about its potential impact on attention-deficit/hyperactivity disorder (ADHD).
- This review examines the potential link between maternal obesity and ADHD, exploring biological mechanisms and epidemiological evidence.
- Findings suggest a potential association between maternal obesity and ADHD but lack causality confirmation.
- Shared genetic pathways and biological mechanisms may contribute to this association.
- Future research should prioritize randomized controlled trials and comprehensive investigation of confounding factors.

Few studies have examined the relationship between maternal obesity and ADHD risk in offspring. In a systematic review published by Sullivan et al.,[3] an association between maternal obesity and several mental health disorders, mainly ADHD, has been found. Similarly, a cohort study of 331 women who were enlisted from antenatal hospital facilities and clinics in Durham-North Carolina between April 2005 and June 2011 reported their offspring's ADHD symptoms at a mean age of 3 years. In this cohort, Fuemmeler et al.[4] found a positive correlation between pre-pregnancy BMI (especially a BMI ≥35) and total ADHD symptoms (B=0.17, p=0.001), attention deficit behavior (B=0.08, p<0.001), hyperactive-impulsive behavior (B=0.09, p=0.02), and executive functioning concern (B=0.38, p=0.02). Additionally, the authors revealed that, when compared to mothers with adequate gestational weight gain (GWG), mothers with less than adequate weight gain noted increased impulsivity and hyperactivity (B=2.04, p=0.02). However, greater than adequate GWG was statistically significantly associated with challenging behaviors related to working memory (B=0.08, p=0.046), and planning and organizing (B=0.07, p=0.01).[4] In an integrated analysis, van der Burg et al.[5] demonstrated that, via an inflammatory state, maternal obesity increased the risk of neurodevelopmental disorders in children mostly ADHD, autism, psychosis, and intellectual disability. Moreover, in a prospective cohort study, Buss et al.[6] evaluated 174 children [mean age =7.3±0.9 (standard deviation) yrs, 55% girls] for symptoms of ADHD with maternal pre-pregnancy BMI being a possible predictor. In this study, it was shown that while maternal GWG was not significantly associated with ADHD symptoms, pre-pregnancy BMI was significantly associated with ADHD symptoms after controlling for potential confounding variables [F (1,158)=4.80, p=0.03]. They also assessed the severity of ADHD symptoms in children of obese, overweight, and normal weight with the former showing increased symptom severity (p=0.02).[6]

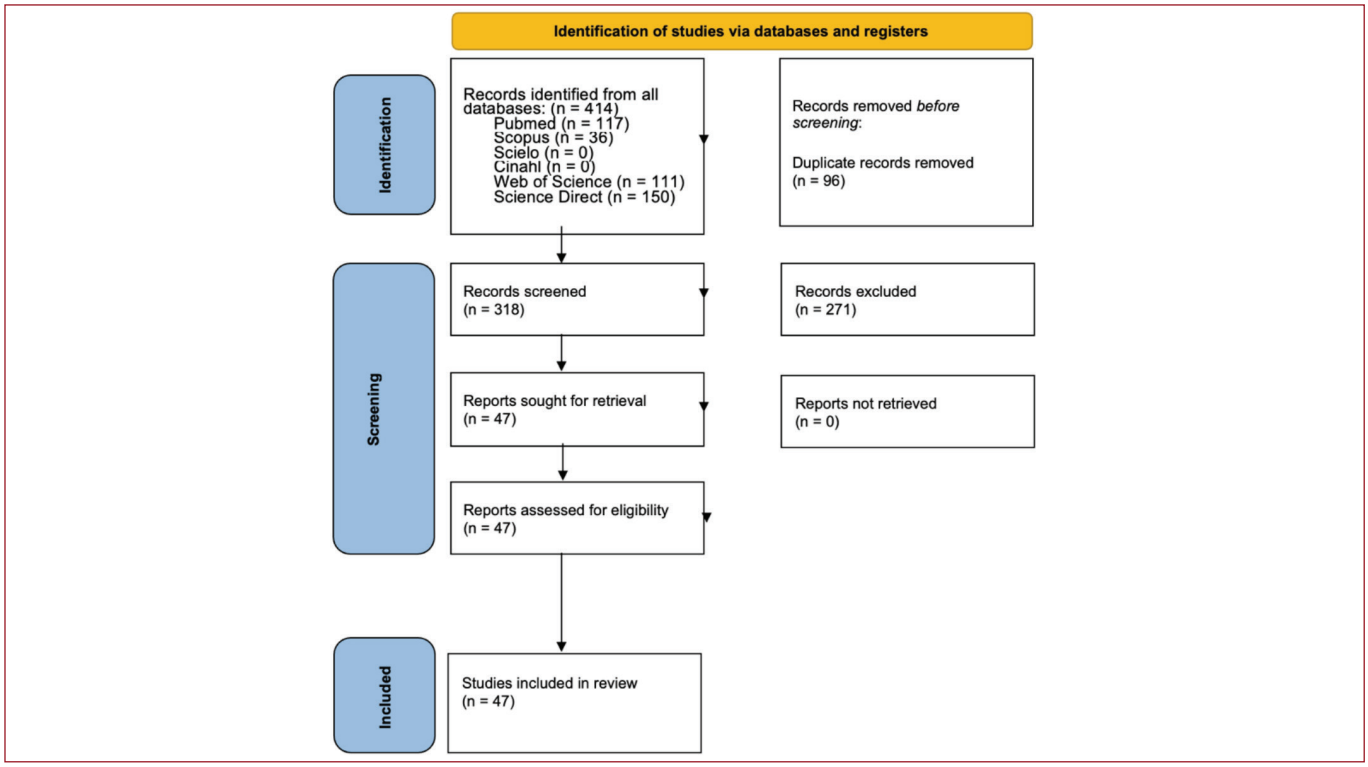

Figure 1. PRISMA flow diagram of literature screening for maternal obesity and ADHD

ADHD; Attention-deficit/hyperactivity disorder

In another prospective study by Casas et al.[7] it was found that both maternal and paternal underweight and obesity were linked to an increase in ADHD-related symptoms in pre-school children, but the associations were not statistically significant. The type of diet itself has been assessed in an experiment by Raygada et al.[8] In this experiment, three strains of mice were fed either control of high n-6 Polyunsaturated fatty acid (PUFA) diets throughout gestation. It was determined that in utero exposure to a high (n-6) PUFA diet increases locomotor activity [among female (t=4.6, df=17, p<0.0003) and males (t=3.1, df=18, p<0.006) mice] and aggression [(among females χ^2=5.3, df=1, p<0.025) and males (t=5.4, df=16, p<0.0001)] in offspring.[8] Similarly, many studies revealed an association between maternal obesity and various neurodevelopmental disorders, other than ADHD per say. In fact, in an animal-model systematic review, authors revealed that maternal obesity was positively correlated with heightened motor [with a standardized mean difference (SMD) of 0.34 (0.10; 0.58)] and anxiety [SMD 0.47 (0.16; 0.79)] behaviors in offspring.[9] Similarly, a study conducted by Peleg-Raibstein et al.,[10] demonstrated that mice born to high fat diet mothers stayed in the maze for an average of time of 24.84% (±3.86) compared to the control group who spent 41.19% (±6.26) of time in the maze.

Discussion

Prevalence and Trends in Maternal Obesity and ADHD

Recent years have witnessed increased attention from researchers and medical professionals toward the prevalence and trends of maternal obesity and ADHD. The link between maternal obesity and adverse outcomes for both mothers and fetuses has propelled it into a prominent public health concern. Studies have demonstrated associations between maternal obesity and heightened risks of gestational diabetes, hypertension, and delivery complications.[11] Furthermore, maternal obesity could contribute to the emergence of juvenile obesity and long-term health issues in offspring. In addition, the prevalence of ADHD, characterized by symptoms of impulsivity, hyperactivity, and inattention, has surged. While the intricate relationship between maternal obesity and ADHD in offspring involves multifaceted factors, recent evidence suggests the plausibility of such a connection.[9]

Association Between Maternal Obesity and ADHD

According to Karhunen et al.[12], children born to obese mothers might face an elevated risk of developing ADHD later in life. While precise causal mechanisms remain elusive, theories suggest that metabolic disturbances, hormonal imbalances, and inflammation induced by maternal obesity during pregnancy could influence fetal brain development, thereby contributing to neurodevelopmental disorders such as ADHD.[1] Prenatal exposure to an obesogenic environment could also trigger enduring epigenetic changes in the child's DNA.[13] This highlights the importance of recognizing maternal obesity as a modifiable risk factor that could impact neurodevelopmental outcomes in the next generation. Comprehensive interventions targeting maternal health, diet, and lifestyle throughout pregnancy could play a pivotal role in minimizing ADHD risk among offspring.

Table 1.
Table showing the main findings concerning maternal obesity and its correlation to ADHD

Authors	Models used	Study design	Maternal factor	Child outcome
Sullivan et al.[3] (2012)	Human and animal	Systematic review	Obesity in pregnancy	Increased risk of developing several behavioral disorders, mainly ADHD
Fuemmeler et al.[4] (2019)	Human	Cohort study	Pre-pregnancy BMI >35 and GWG	Pre-pregnancy BMI >35 was associated with higher ADHD symptoms and worse behavior. Greater than adequate GWG was associated with worse working memory and planning behavior
Menting et al.[9] (2019)	Animal	Systematic review	Maternal obesity	Increased offspring locomotor activity and anxiety, but not memory performance
van der Burg et al.[5] (2016)	Human and animal	Systematic review	Maternal obesity and inflammation	Increased neurodevelopmental disorders, mainly ADHD
Peleg-Raibstein et al.[10] (2012)	Animal	Prospective cohort	High-fat diet	Increased anxiety-like behavior
Field[34] (2014)	Human	Case control	Omega-3 fatty acids deficient diet	An n3FA deficient diet may be an important factor in the rising incidence of ADHD and partial prevention through diet and supplements may be possible.
Raygada et al.[8] (1998)	Animal	Prospective cohort	(n-6) PUFA rich diet	In utero exposure to a high (n-6) PUFA diet subsequently increases locomotor activity and aggression
Buss et al.[6] (2012)	Human	Prospective cohort	Pre-pregnancy BMI	2.8-fold increase in the prevalence of ADHD among children of obese compared to those of non-obese mothers
Casas et al.[7] (2017)	Human	Prospective cohort	Pre-pregnancy obesity	Both maternal and paternal obesity were associated with an increase in ADHD-related symptoms

ADHD; Attention-deficit/hyperactivity disorder

Biological Mechanisms Underlying the Maternal Obesity and ADHD Link

Several biological mechanisms contribute to the potential association between maternal obesity and ADHD risk in offspring. Inflammation emerges as a crucial player in programing brain development,[14] as obesity triggers chronic inflammation through cytokine release, including C-reactive protein (CRP) and interleukin-6.[15,16] Similarly, maternal obesity is associated with heightened inflammatory markers, especially CRP.[17] These markers, notably cytokines, mediate communication between the immune and central nervous systems.[18] In addition, obese women's placentas have more CD68+ and CD14+ cells and pro-inflammatory cytokines than non-obese women.[19] These markers disrupt the integrity of the placenta and endothelium, damaging the serotoninergic (5-HT), dopaminergic (DA), and melanocortinergic neural circuits.[3,14]

The serotonergic pathway, which is pivotal for neural development, particularly serotonin's role in synaptogenesis and neurogenesis, is disrupted.[20,21] Newborns of obese mothers display reduced serotonin levels,[3] and diminished serotonin synthesis correlates with ADHD symptoms, particularly impulsivity and hyperactivity.[22,23]

Inflammatory interference with the serotonergic system, as indicated by studies on the impact of cytokines on serotonin neuronal fibers, contributes to this disruption.[24] A similar inflammatory mechanism disrupts the DA and melanocortinergic pathways, impairing the central reward system and eating behaviors.[14]

Metabolic hormone-induced programming, driven by maternal obesity, exposes offspring to elevated nutrient (fatty acid, glucose) and metabolic hormone levels (leptin mainly).[14] Brain regions governing behavior house leptin receptors, which are linked to metabolic hormone-induced brain development disruption.[25]

Epigenetics also contributes, as evidenced by maternal obesity-induced epigenetic changes in gametes and fetuses[26], alongside mitochondrial dysfunction.[27] The gut- brain axis, via altered gut microflora and short-chain fatty acids, also influences neurodevelopment.[27] Genetic and metabolic pathway[28,29] overlap between obesity and neurodevelopmental disorders emphasize shared pathways.[1] Environmental exposure during early pregnancy, alongside postnatal factors, affects brain development.[30,31]

Despite robust animal support.[14] Human research on the maternal obesity- ADHD link requires addressing confounders such as genetics and the postnatal environment.[1] Variables such as socioeconomic status, micronutrient deficiencies, and emotional distress should also be considered.[5] More research is necessary to clarify the mechanisms underlying the association between maternal obesity and ADHD.[4]

Role of Animal Studies in Determining the Pathophysiology Underlying the Maternal Obesity and ADHD Link

Animal studies have proven pivotal in understanding the mechanisms linking maternal obesity to offspring ADHD risk.[1] Inflammation induced by maternal obesity disrupts vital brain circuits that govern behavior.[14] Impaired serotonergic pathways are evidenced by elevated inhibitory auto-receptor levels in rodent high-fat diet progeny.[10] Placental dysfunction due to high-fat diets correlates with inflammation and impaired blood flow,[3] mirroring findings in sheep and rodents.[32] Neural inflammation in rodents that consume high-fat diets disrupts neurogenesis.[3,33]

Clinical and Public Health Recommendations

PUFAs, encompassing omega-3 and omega-6, present potential treatments for maternal obesity-associated neurodevelopmental issues. Omega-3 PUFAs alleviate brain inflammation and enhance serotonin signaling.[14] Insufficient omega-3 fatty acids during pregnancy are linked to higher ASD and ADHD risks.[34] Preliminary human studies suggest that omega-3 supplementation reduces inflammation in maternal bodies and placentas.[35] A retrospective analysis of data from the Nurses' Health Study II suggested that maternal intake of high levels of omega-6 PUFAs was associated with a 34% reduction in the risk of ASD,[36] which goes against what has been shown in animal studies: that maternal diet rich in omega-6 PUFAs during gestation and lactation produced autism-like traits in offspring sociability.[8] Metformin's effects on maternal obesity's impact on offspring neurodevelopment require further exploration. Two randomized controlled trials have been conducted involving metformin therapy for pregnant women with obesity and no existing diabetes. In one of these trials, there was no observed influence of maternal metformin on the outcomes examined in relation to both maternal and neonatal aspects.[37] However, another trial demonstrated that the use of maternal metformin notably decreased the extent of maternal weight gain and the occurrence of preeclampsia.[38] Neither study has yet reported any long-term effects on neurodevelopment in offspring.

Grasping the connections between prenatal influences and developmental aspects associated with ADHD and deficient self-regulation is crucial. This understanding is vital because childhood problems in these areas, regardless of an official diagnosis, can increase the chances of engaging in harmful behaviors in adulthood[39,40] and lead to substantial economic burdens.[41-43]

Guidance for healthcare providers and policymakers involves recognizing the link between prenatal influences and ADHD/self-regulation issues, which necessitates targeted interventions. Adequate prenatal care and lifestyle adjustments can reduce the risk of neurodevelopmental disorders. Adequate GWG is crucial, with deviations linked to ADHD symptoms.[39]

Intergenerational Effects and Translational Implications

The influence of both maternal and paternal BMI on offspring cognitive development deserves consideration.[6,44,45] For instance, a Danish national birth cohort study with 1783 mothers revealed that higher pre-pregnancy BMI in both parents correlated with lower IQ in their offspring. These associations remained significant even after adjusting for potential influencing factors, suggesting an impact beyond

the intrauterine environment.[41] However, in contrast, research from two birth cohort studies in Spain and Greece indicated that the effect of maternal BMI on infant cognitive development was more pronounced than that of paternal BMI.[42] This observation aligns with the idea of maternal-specific or intrauterine effects. Additionally, a study involving two cohorts-one British (N=5,000) and the other Dutch (N=2,500)-indicated inconsistent associations between pre-pregnancy overweight in parents and their child's cognitive abilities.[7] Hence, while interpreting these findings, it is important to consider potential hidden genetic and familial factors that might confound the results, as well as the ongoing brain maturation process that extends into early adulthood. Recent genome-wide association studies (GWAS) have revealed over 200 genetic regions linked to traits related to type 2 diabetes and obesity.[46-48] Similarly, neurodevelopmental and psychiatric conditions, ranging from moderately heritable ones such as depressive and anxiety disorders, as well as eating and sleeping disorders, to highly heritable ones including ASD, ADHD, bipolar, and psychotic disorders, have been identified.[49] Notably, an elevated susceptibility to obesity has been observed in children with ADHD or ASD.[50,51] One plausible explanation is the existence of shared genetic or metabolic pathways between obesity and neurodevelopmental disorders. The genetic locations identified in GWAS linked to obesity are found in proximity to genes implicated in appetite control, energy balance, and mood management.[52-54] Moreover, the gene encoding the β2-Adrenoceptor, a G protein-coupled receptor, is not only associated with circulatory, muscle, and digestive systems but is also connected to insulin resistance[55] obesity/diabetes,[56] and psychiatric conditions such as autism.

Future Directions for Research

Future studies should address gaps in understanding the maternal obesity- ADHD relationship. An emphasis on randomized controlled trials is needed to determine whether early dietary interventions can prevent mental health disorders in offspring.

Conclusion

The intricate relationship between maternal obesity and ADHD necessitates further investigation. In this review, we conducted a comprehensive examination of existing research to understand the potential links between maternal obesity and ADHD in offspring. While our analysis of the existing literature indicates associations between maternal obesity and ADHD, it is essential to acknowledge that causality remains unconfirmed. GWAS have shed light on shared genetic pathways between maternal obesity and neurodevelopmental disorders, and rodent models have provided valuable insights into the potential mechanisms underlying this association. However, human studies must address various confounding factors, including genetics and the postnatal environment. Socio-economic status, micronutrient deficiencies, and emotional distress are factors that should be considered in future research. Promising interventions have been identified, such as the use of PUFAs and omega-3 supplementation. These interventions show potential in mitigating the effects of maternal obesity on neurodevelopment. However, their effectiveness and safety need further validation through rigorous studies. In conclusion, the effects of maternal obesity on brain development have received significant attention, but it is recommended that future research be shaped to provide a more comprehensive understanding of the ADHD-maternal obesity relationship. Addressing the complex interplay between maternal obesity and ADHD requires multifaceted research that encompasses genetic, environmental, and metabolic factors. By doing so, we can better clarify the mechanisms underlying this association and identify effective interventions that can improve neurodevelopmental outcomes in the next generation. This ongoing research will be essential for developing targeted approaches to mitigate the risk of ADHD in offspring and improve public health strategies.

Ethical Approval: Not necessary.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Author Contributions: Boueri M: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Matar M: Analysis or Interpretation; Fakhoury M: Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Aoun C: Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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