

GESTATIONAL WEIGHT GAIN AND RISK OF AUTISM SPECTRUM DISORDERS IN OFFSPRING : A SYSTEMATIC REVIEW

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Abstract

Autism, also known as Autism Spectrum Disorder (ASD), is a neurodevelopmental disorder characterized by abnormalities in social behavior, language skills, and communication abilities. A correlation was found between ASD patients and their mothers' excessive weight gain during pregnancy. However, the relationship between BMI before pregnancy and ASD incidence is inconclusive. In addition, research investigates the potential role that preventative factors, such as folate and fatty acid consumption, play in the development of the disease. There is growing evidence that certain factors, including advanced maternal and paternal age, valproate consumption, exposure to toxic chemicals, maternal diabetes, enhanced steroidogenic activity, immune activation, and possibly altered zinc-copper cycles and treatment with selective serotonin reuptake inhibitors, are associated with an increased risk of autism spectrum disorder in offspring. The large, multisite case-control study discovered that severe maternal obesity (obesity Class 2/3) was associated with approximately double the risk of ASD (with or without ID) and increased odds of DD. In the United States, an investigation was conducted. ASD was also associated with GWG when gestational age was considered, and this association was particularly strong in male offspring. Still, no connection between GWG and DD could be established. No correlations were found between the GWG rate and ASD or DD when the data was evaluated based on how well it matched clinical recommendations. Patients with autism spectrum disorder whose mothers gained an unhealthy quantity of weight during pregnancy were found to have a correlation. However, there is little correlation between BMI before pregnancy and the risk of having a child with autism spectrum disorder (ASD).

Keyword: Autism Spectrum Disorders; Body Mass Index (BMI); Gestational Weight; Offspring

INTRODUCTION

Autism Spectrum Disorder (ASD) or known as autism is a complex neurodevelopmental disorder in which people with this disorder show characteristics in the form of abnormalities in social behavior, language skills and communication skills.¹ This disorder is usually seen in children of preschool age. Autism spectrum disorder is a developmental disorder in children that is quite severe because it interferes with children's social, language skills and cognitive abilities.² Today's cases of autism in children tend to increase, generally complaints that parents convey are speech delays, strange and indifferent behavior.³

The World Health Organization (WHO) estimates the world prevalence for ASD is 0.76%; however, this figure accounts for only 16% of the global child population. The Centers for Disease Control (CDC) estimates that around 1.68% of children in the United States aged 8 years (1 in 59 children) are diagnosed with ASD. In the US alone, ASD diagnoses reported by parents in 2016 had a higher average of 2.5%. The prevalence of ASD in US more than doubled between 2000-2002 and 2010-2012, according to Autism and Developmental Disabilities Monitoring Network (ADDM) estimates. In the US, ASD prevalence was stable without a statistically significant increase from 2014 to 2016.³

Most people with ASD and related conditions have been identified as experiencing adverse events in the prenatal, antenatal and postnatal periods. It's not clear whether pregnancy complications cause ASD or whether ASD and pregnancy complications result from environmental or other problems. During the perinatal period, risk factors associated with ASD are maternal hypertension or diabetes, risk of abortion, antepartum bleeding, caesarean delivery, gestational age ≤ 36 weeks, parity ≥ 4 , spontaneous delivery, induced labour, obstructed labour, breech presentation, preeclampsia, and fetal distress.^{4,5}

These studies provide evidence in support of a connection between maternal obesity and ASD; however, significant confounding factors that could be shared by obesity and ASD (such as obstetrical difficulties, parity, advanced mother age, and socioeconomic level) were not taken into account in the analyses of obesity and weight gain. Krakowiak et al. (2012) conducted a study in which they evaluated the body mass index (BMI) and other metabolic parameters in children with ASD, children with developmental disabilities (DD) exclusively, and children with usual development. They did this by using a number of well-established ASD risk variables as covariates.⁶

This lends credence to the theory that postprandial hyperglycemia, and not diabetes, is to blame for autism spectrum disorder (ASD). Obesity during pregnancy and gestational diabetes both contribute to an increased risk of ASD. People who are obese tend to be sedentary, despite the fact that aerobic activity can bring glucose levels down. Children are at a greater chance of being diagnosed with ASD if their mothers were obese before becoming pregnant or gained more than 18 kilograms during their pregnancies. Inactivity and a diet heavy in carbohydrates both contribute to the development of postprandial hyperglycemia and hyperinsulinemia.⁴

Weight gain and obesity are both caused by hyperinsulinemia, which is a lipogenic hormone.⁴ According to the findings of the most current meta-analysis, maternal obesity before to pregnancy is associated with an increased likelihood that the kid would have ASD. A number of previous studies point to the possibility that obesity in the mother before pregnancy may have an effect on the development of the nervous system of the offspring through the intestinal flora, oxidative stress and inflammation-induced mal-programming, and the leptin resistance mechanism in offspring, which ultimately leads to an increased risk of autism spectrum disorder in the offspring.^{7,8}

Moreover, changes in intestinal flora, elevated inflammatory levels, and an active leptin resistance mechanism are all associated with gestational weight gain (GWG). Using this framework, epidemiological research has been conducted to assess the potential connections between GWG and ASD.^{9,10} Yet, their findings do not all point to the same conclusion. For instance, the research conducted by Bilder et al. (2013)¹¹ and Xiang et al. (2015)¹² found a positive correlation between GWG and the risk of ASD. In contrast, the research conducted by Jo et al. (2015)⁸ and Hendrix et al. (2012)¹³ did not show any results that were statistically significant.

The purpose of this research was to establish whether or not there is a correlation between a mother's higher weight during pregnancy and an increased likelihood that their child will have autism spectrum disorders.

METHODS

The author of this study made certain that it complied with the prerequisites by referring to the recommendations provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This is done in order to guarantee that the findings of the investigation are accurate. This review investigates the link between maternal weight gain during pregnancy and the risk of autism spectrum disorders in children. This is accomplished by evaluating or analyzing previous research on the topic. The purpose of this essay is to emphasize the significance of the issues discussed.

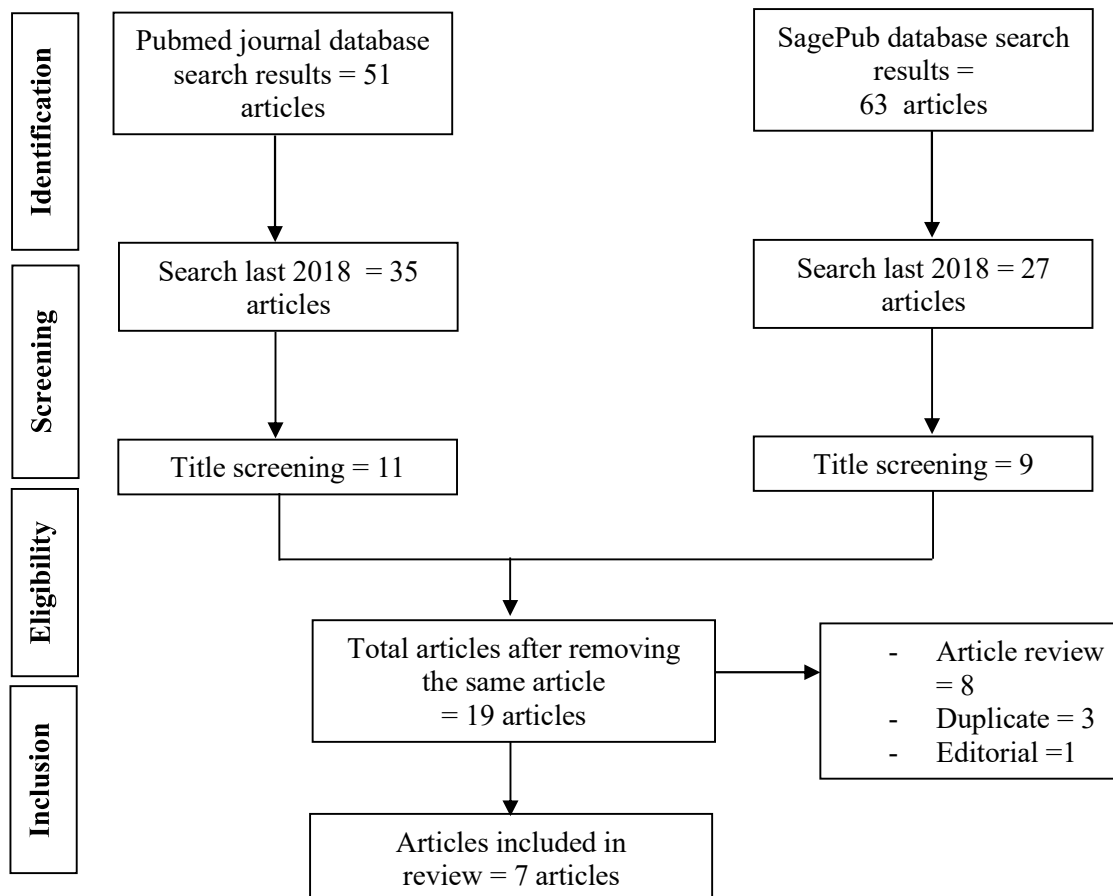


Figure 1. Article search flowchart

Researchers who participated in the investigation were required to meet the following criteria: 1) The manuscript must be written in English and concentrate on the association between fetal weight gain and the risk of autism spectrum disorders in order to be accepted for publication. 2) This evaluation encompasses works published after 2018, but prior to the considered time period. Editorials, submissions without a DOI, previously published review articles, and entries that are nearly identical to previously published journal articles are examples of inadmissible research.

We used "gestational weight gain" and "autism spectrum disorders" as keywords. The search for studies to be included in the systematic review was carried out from May, 24th 2023 using the PubMed and SagePub databases by inputting the words: ("gestational weight gain"[MeSH Terms] OR ("gestational"[All Fields] AND "weight"[All Fields] AND "gain"[All Fields]) OR "gestational weight gain"[All Fields]) AND ("autism spectrum disorder"[MeSH Terms] OR ("autism"[All Fields] AND "spectrum"[All Fields] AND "disorder"[All Fields]) OR "autism spectrum disorder"[All Fields] OR ("autism"[All Fields] AND "spectrum"[All Fields] AND "disorders"[All Fields]) OR "autism spectrum disorders"[All Fields]) used in searching the literature.

The authors assessed each study's eligibility based on its abstract and title. Then, they used historical books. Many investigations with the same pattern yielded this outcome. English-language contributions must be unpublished. Only eligible studies were considered in the systematic review. This filters search results. Unsatisfactory research findings are not examined. Analysis will follow. The study revealed names, authors, publication dates, location, study activities, and parameters. Duplicate articles were removed from the search results in Endnote. Two reviewers identified relevant publications by examining their titles and abstracts.

First, their full texts were looked at for eligibility and data extraction. Review articles, studies on animals, papers from conferences, and research on GWG and other health problems. During discussion, the reviewers came to an agreement. Before choosing which publications to dig deeper into, each author did their own analysis of the studies given in the title and abstract of each publication. Then, we will evaluate all papers that meet the review's criteria for inclusion and are, therefore, good enough to be included. Then, we'll decide which papers to include in the review based on what we've learned. This is how the papers to be evaluated are chosen and choose which papers to review.

RESULT

Chen, et al (2023)¹⁴ showed 1.9% children were diagnosed ASD. In the second trimester, lower RGWG (0.25 kg/week) was linked with a 9% increased chance of any NDD diagnosis (95% CI = 4-15%) compared to the median of 0.57 kg/week. Higher RGWG was not associated with NDD risk. In third trimester, higher RGWG (1 kg/week) was linked with a 28%

increased risk of NDD diagnosis (95% CI = 16-40%) compared to the median (0.51 kg/week). Lower RGWG was not associated with NDDs. In classified RGWG, delayed weight gain in the second trimester followed by rapid weight gain in the third trimester most substantially enhanced the risk of ADHD and ID in offspring.

Lee, et al. (2022) found that inadequate GWG elevated offspring IDD risk by 21% (95% CI = 1.11–1.31). However, using the LifeCycle category, kids of mothers with inadequate or excessive GWG had higher risks of IDD than those of mothers with optimal GWG (HR = 1.14, 95% CI = 1.05–1.24). Very low GWG (20th centile) and low GWG (20th–40th centile) enhanced IDD in children. A stratified study by maternal early-pregnancy BMI showed that overweight/obese mothers (BMI 25 kg/m²) with extremely excessive GWG (>25 kg) had a greater risk of IDD in their kids.¹⁵

Matias, et al (2021)¹⁰ showed class 2/3 maternal obesity was related to ASD (adjusted odds ratio [AOR] = 1.87, 95% confidence interval [CI] = 1.40-2.51) and DD (AOR = 1.61, 95% CI = 1.22-2.13). GWG z score was not linked with DD (AOR = 1.14, 95% CI: 0.95-1.36), while the highest tertile was associated with elevated chances of ASD, especially in male children (AOR = 1.47, 95%, 1.15-1.80). Severe maternal obesity before pregnancy raises the risk of ASD and DD in children, and high gestational-age-adjusted GWG is a risk factor for ASD in male children.

Table 1. The literature include in this study

Author	Origin	Method	Sample Size	Result
Chen, 2023 ¹⁴	United State of America (USA)	Retrospective cohort study	57,822 children born to 53,516 mothers	Slow second-trimester weight gain and quick third-trimester weight gain were related with the highest risk of NDDs in children.
Lee, 2022 ¹⁵	Sweden	Retrospective cohort study	467,485 patients	Our data suggest that low maternal GWG may raise children's risk of IDD, regardless of the mother's BMI at conception. However, only moms whose BMI was below 25 kg/m ² were pregnant with their first kid if the GWG was over 25 kg.
Matias, 2021 ¹⁰	United State (US)	Retrospective cohort study	ASD (n = 1,159) and DD (n = 1,617), versus control children (n = 1,633)	The data suggest that a high gestational-age-adjusted GWG is a risk factor for autism spectrum disorder in male offspring and that severe maternal obesity before pregnancy increases the risk of autism and developmental delay in children.
Kyoung, 2021 ¹⁶	USA	Retrospective cohort study	1,164 mother-child	Prepregnancy Pregnancy BMI and adiponectin may help monitor autism risk. Pregnant women's adiponectin levels may prevent autism spectrum diseases.
Windham, 2019 ⁹	USA	Case control	ASD: n = 540, Developmental delays: n = 720, Control: n = 776/Singleton births	Children with developmental abnormalities were more likely to have overweight or obese mothers before pregnancy, but not throughout pregnancy. Overweight and weight gain may indicate changeable circumstances.
Shen, 2018 ¹⁷	China	Case control	705 Han Chinese autism parents and 2,236 unrelated generally developing children	Prenatal BMI may not independently predict autism risk. However, high GWG levels may raise autism risk in children of overweight or obese mothers.
Qiu, 2018 ¹⁸	China	Case control	36 children who were diagnosed with ASD (ASD group) and 72 non-ASD	Before the mother becomes pregnant, the father must maintain a normal body mass index to reduce the risk of autism spectrum disorder in the child.

Kyoung, et al (2021)¹⁶ showed the higher second-trimester adiponectin levels were associated with a lower risk of ASD in offspring (AOR 0.49; 95% CI, 0.30-0.78; and OR 0.54; 95% CI, 0.32-0.91 after adjusting for maternal race/ethnicity, education, child sex, and BMI, gestational weight gain, gestational diabetes, and smoking status). ASDs were not associated with maternal leptin, cord blood leptin, or adiponectin levels. The use of body mass index (BMI) and adiponectin during pregnancy may be useful as an autism risk monitoring approach. Increasing adiponectin levels in pregnant women may help prevent autism spectrum disorders.

Windham, et al (2019)⁹ showed that relationships with higher GWG were stronger (Quintile5 vs. Quintile3 AOR = 1.58, 95%CI 1.08-2.31), and this was especially true for overweight/obese women (AOR = 1.90, 95%CI 0.98-3.40). DD was linked with maternal overweight and obesity (obesity AOR = 1.48, 95%CI 1.01-2.01) but not with total GWG or clinical recommendations. High maternal BMI and GWG are risk factors for other pregnancy and infant outcomes, and our data imply they may also reflect modifiable neurodevelopmental risk factors.

Qiu, et al (2018) showed the detection rate of overweight or obesity in the father was considerably greater in the ASD group (56% vs. 32%; $P=0.018$) in comparison to the control group when the mother became pregnant. The odds ratio for autism spectrum disorder (ASD) in offspring was calculated to be 2.66 and 2.58, respectively, when univariate and multivariate logistic regression analyses were performed. This indicated that a father's overweight or obesity before the mother became pregnant was a risk factor for autism spectrum disorder (ASD) in offspring.¹⁸

Shen, et al (2018)¹⁷ surveyed parents of 705 Han Chinese children with autism and 2,236 unrelated generally developing children. After controlling for children's gender, parental age, and family income, high GWG was associated with autism risk in the entire population (OR = 1.327, 95% CI = 1.021–1.771), whereas mother pre-pregnancy BMI was not. Stratification studies showed that high GWG increased autism risk in overweight/obese women (OR = 2.468, 95% CI = 1.102–5.50) but not in underweight or normal weight mothers.

DISCUSSION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, limited interests, and repetitive behavior. In 2013, the Diagnostic and Statistical Manual of Mental Disorders—5th edition (DSM-V) was published, updating the diagnostic criteria for ASD from the previous 4th edition (DSM-IV).^{19,20} In the DSM-V, the concept of a "spectrum" ASD diagnosis was established, in which case ASD incorporates the separate diagnoses of pervasive developmental disorder (PDD) in the DSM-IV: autistic disorder, asperger's disorder, childhood disintegration disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS).²¹

In addition, research investigates the potential role that preventative factors including dietary folate and fatty acid consumption have in the disease's development. There is more and more evidence suggesting that certain factors, such as advanced maternal and paternal age, consumption of valproate, exposure to toxic chemicals, maternal diabetes, enhanced steroidogenic activity, immune activation, and possibly altered zinc–copper cycles and treatment with selective serotonin reuptake inhibitors, are associated with an increased risk of autism spectrum disorder in offspring.^{9,13}

Because the other conditions that make up the maternal metabolic syndrome are significant factors that contribute to maternal gestational inflammation and the potential mechanisms associated with the risk of developing ASD, it is essential that further research be conducted into the association between those factors and the risk of developing ASD. For each of the variables that make up the maternal metabolic syndrome (pre-gestational DM, GDM, pre-pregnancy weight, and GWG), we include at least one study that supports a link with an increased risk of ASD in this review. However, this does not provide enough evidence to reach any conclusive conclusions.²²

The large, multisite case-control study found that severe maternal obesity (obesity Class 2/3) was linked to about double the chance of ASD (with or without ID) and higher odds of DD. In the United States, the probe was done. ASD was also linked to GWG when gestational age was taken into account, and this link was especially strong in male children. Still, there was no link between GWG and DD that could be found. When the data was looked at in terms of how well it fit clinical advice, there were no links found between GWG rate and either ASD or DD.¹⁰

Shen, et al (2018)¹⁷ showed that the maternal BMI before pregnancy is not independently related with the risk of autism. However, GWG levels that are too high may be linked to an increased risk of autism in children born to women who are overweight or obese. Only children born to moms who are overweight or obese, but not those whose mothers are underweight or of normal weight, could be at a greater risk of developing autism if their mothers had an excessively high GWG. Hence, there is a possibility that the interactions between BMI and GWG are related to the risk of autism.²³

The study conducted by Shen et al. was a case-controlled study, which means that it did not investigate the association between BMI and GWG with risk of autism among obese mothers separately, nor did it adjust for the confounding variables related to the risk of autism, such as gestational diabetes or gestational hypertension. Instead, it focused solely on the risk of autism in children born to mothers who were obese. Diabetes mellitus during pregnancy and obesity in the mother before pregnancy have both been shown to increase the risk of autism in offspring in a number of earlier studies.¹⁷

There is a correlation between obesity and systemic inflammation, which may be seen in the increased cytokine production that occurs as a result of an increase in the amount of adipose tissue.²⁴ Because they are able to pass the blood–placenta barrier, inflammatory mediators can have an effect on the neurodevelopment of the fetus.²⁵ As a result, the primary mechanisms through which maternal obesity might affect child neurodevelopment are related to maternal inflammation. These mechanisms include neuroinflammation; increased oxidative stress; dysregulated insulin, glucose, and leptin signaling; dysregulated serotonergic and dopaminergic signaling; and perturbations in synaptic plasticity.²⁶

In particular, a dysfunction in the control of serotonin production in the placenta, which is produced by inflammation in the mother, modifies neurogenesis and axonal growth in the fetal forebrain, which has the potential to alter the course that fetal brain development takes.²⁷ Also, there is a possibility that epigenetic modulation of inflammatory pathways is linked to changes that occur in the brain as a consequence of the prenatal environment.²⁴ In comparison to women of normal weight, obese women's fetuses' umbilical cord gene expression profiles showed patterns that are associated with neurodegeneration, lower survival of sensory neurons, and decreased neurogenesis. These findings were seen in the fetuses' umbilical cords.²⁸

The discovery that pre-pregnancy obesity paired with gestational diabetes more than doubles the risk of autism spectrum disorder (ASD) lends credence to the concept that postprandial hyperglycemia, and not diabetes, is the culprit in the pathogenesis of autism spectrum disorder (ASD). Aerobic exercises are known to be quite beneficial in regulating glucose levels; however, people who are fat typically do not engage in physical activity. Before to pregnancy obesity and a weight gain of less than 18 kilograms during pregnancy are two factors that raise the likelihood of having a kid who has autism spectrum disorder (ASD).^{4,23}

Postprandial hyperglycemia may be both a cause and a consequence of these factors. Postmeal hyperglycemia and hyperinsulinemia are the results of insufficient time spent being physically active paired with a diet that is high in carbohydrates. Hyperinsulinemia is associated with weight growth and, in the long run, obesity because insulin is a hormone that promotes fat storage. Adipose tissue-derived cytokines are responsible for the impairment of insulin signaling that leads to postprandial hyperglycemia in obese patients.^{4,23}

CONCLUSION

Autism spectrum disorder patients whose moms gained an unhealthy amount of weight during pregnancy were found to have a consistent connection. However, there isn't much of a correlation between your BMI before pregnancy and the risk of having a child with ASD.

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