Maternal High Fat Diet Consumption during the Perinatal Period Programs Offspring Behavior

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Abstract

The environment that developing offspring experience during the perinatal period is markedly influenced by maternal health and diet composition. Evidence from both epidemiological studies and animal models indicates that maternal diet and metabolic status play a critical role in programming the neural circuitry that regulates behavior, resulting in long-term consequences for offspring behavior. Maternal diet and metabolic state influence the behavior of offspring directly by impacting the intrauterine environment and indirectly by modulating maternal behavior. The mechanisms by which maternal diet and metabolic profile shape the perinatal environment remain largely unknown, but recent research has found that increases in inflammatory cytokines, nutrients (glucose and fatty acids), and hormones (insulin and leptin) affect the environment of the developing offspring. Offspring exposed to maternal obesity and high fat diet consumption during development are more susceptible to developing mental health and behavioral disorders such as anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Recent evidence suggests that this increased risk for behavioral disorders is driven by modifications in the development of neural pathways involved in behavioral regulation. In particular, research indicates that the development of the serotonergic system is impacted by exposure to maternal obesity and high fat diet consumption, and this disruption may underlie many of the behavioral disturbances observed in these offspring. Given the high rates of obesity and high fat diet consumption in pregnant women, it is vital to examine the influence that maternal nutrition and metabolic profile have on the developing offspring.

1.0 Introduction

The majority of infants born in the United States and other western countries are exposed to maternal obese or overweight metabolic status and high fat diet (HFD) consumption during perinatal development. In the U.S., data from latest National Health and Nutrition

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Examination Survey (compiled from 1999–2010) indicates that 69% of adults are overweight or obese [1]. This increased risk of obesity is thought to be due to hyperphagia [2] and decreased physical activity [3]. At this time, about one third of pregnant women in the U.S. are obese [4], and this metabolic state has persistent implications for both the women and their children. Mammals encounter two environments during neural development: the intrauterine and early postnatal environments. Both of these are highly influenced by maternal diet and metabolic status. Animal models provide strong evidence that perinatal nutrition has an enduring impact on numerous aspects of offspring physiology and behavior, including a higher likelihood of developing mental health disorders [5, 6], impairments in social behaviors [7], decreased cognitive abilities [6, 8, 9], enhanced response to stress [10, 11], and altered reward-based behaviors [12]. The metabolic profile of the mother has an additional impact on the developing offspring. Factors associated with maternal obesity, such as inflammation [13], hyperlipidemia, lipotoxicity, hyperglycemia, and insulin resistance, have each been demonstrated to have a long-term effect on the developing offspring and are associated with increased risk of mental health disorders including anxiety and depression [5, 6, 14], attention deficit hyperactivity disorder (ADHD) [15], and autism spectrum disorders (ASD) [16–18].

With the current prevalence of obesity in western nations, it is vital to examine the impact that this may have on the behavior and physiology of future generations. In animal models, a HFD is commonly used to promote maternal obesity. In the majority of these studies, most of the females consuming the HFD become obese, and so it is difficult to determine which outcomes are due to factors associated with maternal obesity (i.e. hyperlipidemia, hyperglycemia, hyperinsulinemia) versus the consumption of a HFD. Furthermore, maternal HFD consumption and obesity often co-occur in humans, making it difficult to discriminate the effects of the HFD itself from the maternal metabolic profile. Our group has developed a nonhuman primate (NHP) model of maternal obesity, and an important advantage of this model is that approximately one third of the females consuming the HFD are resistant to weight gain in response to the diet. These animals have body weights similar to control animals, and this allows us to distinguish the effects of HFD intake from maternal obesity. As the majority of studies examine maternal obesity induced by HFD consumption, this review will therefore discuss the effects of both factors and will assume that consumption of a diet high in fat results in obesity. In addition, we will highlight studies that are able to distinguish between the effects of maternal HFD consumption and maternal obesity on offspring.

2.0 Co-morbidity Between Obesity and Mental Health Disorders

In humans, the obese state itself is associated with increased risk of developing mental health disorders, including anxiety [19], depression [19], and ADHD [20]. Obesity also increases susceptibility to neurodegenerative disorders such as Alzheimer's [21–23] and Parkinson's disease [24, 25]. When combined with obesity, factors like socioeconomic status, ethnicity, and maternal attitudes further increase the propensity for children to develop problems with internalization and social interaction [26]. Conversely, anxiety and depression are known to influence human obesity risk by impacting ingestive behavior, food preference, and physical activity level. Mood disorders like anxiety and depression are associated with enhanced desire for palatable energy-dense foods [27] and decreased levels of physical activity [28]. Reward-based eating has been shown to decrease feelings of stress in human patients [29], and has been described as an addiction or a type of self-medication with comfort food [30].This effect is supported by animal studies that show that consumption of a palatable diet decreases anxiety in the short-term [31] and decreases anxiety and depression-like symptoms in rats exposed to perinatal stress [32]. Evidence from rodent studies indicates that the observed reduction in anxiety-like behaviors is linked to an

increase in glucocorticoid receptor mRNA expression in the hippocampus, providing support to the idea that palatable diet consumption influences the endocrine system to alleviate anxiety [32]. Perinatal exposure to a HFD has been demonstrated to alter the development of key pathways implicated in regulating mood and behavior such as the serotonergic [33] and dopaminergic [2, 34] systems.

3.0 HFD Consumption Impacts Offspring Behavior by Modifying Maternal Behavior

When diet affects the behavior of mothers, it indirectly results in changes in the behavior of the offspring. In rodent models, naturally occurring individual differences in maternal care during early postnatal life are associated with the programming of differences in offspring behavior and stress response [35–37]. Mothers that display decreased grooming and a lack of attentive behavior towards their offspring have offspring with increased anxiety-like behavior, and mothers who are attentive have offspring who are less anxious and better suited to handle stressful situations [38, 39]. Offspring from attentive mothers have improved hippocampal plasticity during stress and enhanced contextual fear conditioning [37]. In addition, male offspring of rat dams that exhibited a high frequency of licking and grooming behavior towards their pups display decreased aggression towards their peers [35]. All of these measures indicate that the nature of the interaction between mother and offspring influences the behavior of the offspring.

There is also evidence that experiencing maternal rejection or separation has a long-term impact on offspring behavior. NHP offspring experiencing maternal rejection are reported to be more prone to anxiety-like behaviors [40]. Female rodent offspring exposed to maternal separation displayed increased anxiety-like behavior in social situations [41]. However, other studies find that early maternal rejection increases offspring independence and decreases infant stress behaviors [42]. Therefore, the behavioral outcome appears to be influenced by the time period when the offspring experiences the maternal separation or rejection. For example, monkeys separated from their mother at one week of age showed increased self-comforting behaviors (such as thumb sucking), whereas those separated from their mother at one month sought more social comfort [43]. These studies provide strong evidence that maternal behavior (or lack thereof) has an important effect on the behavior of offspring.

Several human studies further support the impact that maternal behavior and stress have on offspring behavior. For example, postpartum depression (PPD) is known to influence the behavior of both mother and child [44]. Children of mothers who experienced PPD exhibit an increase in both violent and internalizing behaviors (seen in withdrawal or depression) [44]. Adolescent daughters of mothers with major depression are also more likely to develop psychiatric disorders: 30 months after recruitment, 45% of these daughters had a psychiatric disorder while none of the daughters of control mothers exhibited any type of psychopathology [45]. Human and animal offspring exposed to maternal stress display elevated anxiety and an increase in negative interactions with peers [46–48]. In addition, the quality of parental emotional care is inversely associated with the offspring's risk of developing coronary heart disease [49]. It is hypothesized that these effects of maternal stress seen in the infant may be due to changes in the placental environment or epigenetics of the offspring [46]. However, the factors that affect this maternal environment remain largely unknown, and knowledge about the mechanisms by which maternal behavior influences the behavior of the next generation is limited.

Data from several studies indicates that maternal diet impacts maternal behavior and parenting style and therefore indirectly affects offspring behavior. Research from rodent

models reveals that consumption of a HFD increases nursing [50, 51] and grooming [50]. Higher grooming rates have been documented in rodent models to have a beneficial effect on offspring behavior [38, 52], yet the consequences of increased nursing have not been well characterized. Furthermore, evidence from overfeeding studies suggests that higher rates of nursing will lead to hyperphagia, increased body weight, and reprogramming of the hypothalamic pathways that regulate energy balance [53]. Another way that diet may affect maternal behavior is demonstrated in a rodent model in which consumption of a high energy diet disrupted maternal hippocampal function and, consequently, learning and memory [54]. This was hypothesized to be due to the observed decrease in mRNA expression of tight junction proteins in the choroid plexus and blood-brain barrier. Human studies also provide preliminary evidence that diet influences maternal behavior. Consumption of a healthy diet has been found to reduce risk for PPD and improve symptoms while reduced access to healthy food increases PPD symptomology [55]. These relationships exemplify the interconnectivity of maternal diet and behavior as well as demonstrating pathways in humans through which maternal diet affects maternal behavior and therefore indirectly influences the behavior of the next generation.

4.0 Evidence from Animal Studies that Maternal HFD Impacts Offspring Behavior

4.1 Maternal HFD Programming of Anxiety

Intake of a HFD during gestation has been well documented in animal studies to alter offspring behavior. Maternal HFD consumption is associated with heightened anxiety in NHP [5] and rodent offspring [6]. These studies find that maternal HFD consumption exposes offspring to increased inflammatory cytokines that impact neural development [6]. In the rat model, mothers consuming a diet high in saturated or trans fat during pregnancy and lactation produced male pups that were more anxious as adults. The male rats on a trans fat diet swam faster in a swim test, indicating a higher level of anxiety and a desire to escape. The female rats did not exhibit this increase in anxiety, but this may have been because their baseline anxiety level was already elevated. In contrast, our NHP model found that exposure to a perinatal HFD resulted in increased anxiety in female offspring, which was associated with a reduction in neural serotonin [5]. Greater occurrence of anxiety in these female NHP offspring corresponds with human studies, which report that females have an increased susceptibility to anxiety and have a stronger association between obesity and anxiety [56].

It is clear that the timing of introduction to a diet high in fat during the perinatal period is critical. Offspring from mothers fed a HFD during gestation display increased anxiety [6], but exposure to a similar diet during lactation shows contradictory results. A cafeteria diet, which consists of chow supplemented with highly palatable food items such as cakes, meat pies, and cookies, resulted in reduced levels of anxiety when provided during lactation [57]. Additional support for this idea comes from findings that the anxiety and depression-like behaviors seen in offspring who experienced gestational stress are reduced by cafeteria diet consumption during the early postnatal period [32]. This data indicates that the behavioral outcome of offspring is differentially dependent on the timing of exposure to the HFD.

4.2 Maternal HFD Programming of Social Behaviors

The capacity to interact with conspecifics is essential for establishing stable social networks, for reproduction, and for survival, and these communicative behaviors are influenced by maternal diet. Several studies indicate that exposure to maternal HFD during the perinatal period impacts the social behavior of offspring. For example, maternal consumption of a diet high in polyunsaturated fatty acids (PUFA) led to offspring that displayed increased

aggressiveness to intruders, hyperlocomotion, and decreased immobility in a swim test [7]. This study examined several different strains of mice, and females in all three strains showed elevated rates of aggression. The increases in aggressiveness and locomotion and the decrease in immobility in the swim test were hypothesized to be due to an observed elevation in hypothalamic protein kinase C (PKC) activity. PKC was permanently down-regulated in most of the brain except for the hypothalamus, and it was proposed that PKC could serve as a biological mediator of the effect of maternal HFD diet on offspring behavior. PKC is also involved in the regulation of memory, manic-depressive illnesses, and alcohol-related behaviors [58,59], so the altered levels of PKC from a high PUFA maternal diet suggest a relationship between human mental health disorders and diet.

4.3 Maternal HFD Consumption Impacts Cognition

Evidence also demonstrates that maternal HFD is linked with differences in the cognitive abilities of offspring. Adult male rats from mothers exposed to a diet high in saturated or trans fat during gestation and lactation displayed deficits in spatial cognitive function [6]. Offspring of obese mothers had decreased hippocampal brain-derived neurotrophic factor (BDNF) production that resulted in decreased neurogenesis in this area [9]. These deficits in BDNF were linked to a delay in spatial learning in mouse offspring, but this cognitive impairment did not persist into adulthood, which indicates that the effects of maternal HFD diet on exploratory behavior may be most prominent in early life stages [9]. However, another study reported that maternal consumption of a diet high in lard impacted the spatial memory and learning ability of adult offspring [60]. HFD offspring also exhibited increased hippocampal microglial activation at birth that continued into adulthood [6], revealing the presence of inflammation in areas of the brain responsible for cognitive function. Thus, there is preliminary evidence that maternal diet and metabolic profile may negatively affect offspring cognitive abilities, and it will be important for future studies to clarify the role that maternal diet and obesity play in offspring cognition.

4.4 Maternal HFD Consumption Impacts Reward Pathways

Reward-based behaviors are also altered in the offspring of mothers consuming a HFD [61–64]. Preliminary findings from our NHP model indicate that the offspring exposed to maternal HFD consumption have heightened preference for diets with a high sugar and fat content (Sullivan and Grove, unpublished observation). Increased desire for fat, sugar, and salt was also documented in adult rat offspring exposed to junk food during either gestation or lactation [61–63]. These preferences create a positive feedback cycle where maternal HFD consumption programs cravings for palatable food in the offspring, which further increases HFD consumption. These results are supported by evidence that maternal HFD intake causes perturbations in the dopaminergic system of adult rodents in areas associated with the rewarding value of food, such as the nucleus accumbens and ventral tegmental area [12]. This alteration of the dopaminergic system in the nucleus accumbens also leads to decreased behavioral sensitization to amphetamine due to a reduction in negative feedback [65]. Thus, perinatal nutrition appears to have a persistent impact on reward-seeking behaviors like palatable food consumption and desensitization to illicit substances.

5.0 Maternal Obesity is Linked to Elevated Risk of Mental Health Disorders

Evidence from animal models indicates that maternal obesity increases the risk for offspring to develop neurological and psychological dysfunction. Results from human studies provide further support that maternal obesity or overnutrition is linked to mental health disorders in children. Pre-pregnancy maternal obesity predicted a two-fold increase in the likelihood of the child having difficulties with emotional intensity and the regulation of sadness, fear, and anger [66]. It is also twice as likely for the mother of a child with ADHD to be obese

compared to the mother of a child without ADHD [15]. Obesity prior to pregnancy also doubles the risk of the child developing ADHD symptoms compared to the children of women with a healthy weight status during pregnancy [67]. Genetic predispositions for being overweight and having ADHD did not explain this relationship because it remained after adjusting for ADHD symptoms in the parent [66]. A proposed mechanism behind this correlation is dysfunction in dopaminergic and serotonergic systems that leads to ADHD symptoms [67]. These serotonergic disruptions, as previously mentioned, have been found in a primate model in response to maternal HFD exposure, and future studies are examining ADHD symptomology in these animals.

Diabetes is another condition associated with maternal obesity and HFD consumption, and correlational studies in humans have found associations between maternal diabetes and psychological dysfunction in children. Children of diabetic mothers have higher rates of ADHD symptoms and hyperactivity, similar to the offspring of overweight or obese mothers [68]. Children of diabetic mothers are also at increased risk for disturbances like anxiety, depression, and trouble with social situations [26]. The children of diabetic mothers display deficits in fine and gross motor function, but their IQ score does not differ from control children [68] despite deficits in expressive verbal skills [69]. These findings further support the presence of a link between maternal metabolic state and the mental and social functioning of offspring.

Recent evidence indicates that exposure to maternal obesity and HFD consumption during fetal development may also increase the risk of developing ASD. Rising rates of ASD are matched with the high frequency of adult obesity in North America [70]. Moreover, maternal metabolic states such as obesity, diabetes, and hypertension have been recently shown to be associated with greater risk of ASD in offspring [69]. A proposed mechanism is the role of leptin: leptin is released in proportion to body fat, and high levels of leptin observed in obesity are associated with placental dysfunction that disrupts normal neurological development [71, 72]. When compared with controls, children with ASD have higher plasma levels of leptin [18]. Further research will need to examine the strength of the relationship between these factors.

The role that placental dysfunction plays in the development of ASD is relevant because of the physiological similarity between maternal HFD consumption and infections or illness, all of which have been found to increase ASD risk when they occur during pregnancy [73]. Infections or illness during pregnancy provoke an inflammatory response and cause the transfer of elevated inflammatory cytokines to the developing fetus, similar to the effects of HFD consumption and gestational obesity [74]. This increased exposure to cytokines causes an inflammatory reaction in the fetal brain during crucial developmental periods [16]. The placental dysfunction that is seen with hyperleptinemia has also been documented with high levels of inflammatory cytokines [75, 76], making offspring of obese mothers particularly susceptible to placental dysfunction. Numerous studies have demonstrated that environmental factors that increase exposure of the developing offspring to inflammatory cytokines result in behavioral abnormalities consistent with ASD [73, 77, 78] and ADHD [78]. Obesity is considered an inflammatory and immune disease, and it also results in an increase in a host of inflammatory cytokines circulating through the body and numerous organs, including the brain [13]. Maternal obesity and gestational diabetes have been associated with the activation of inflammatory responses in the placenta [79–82], and NHP [74] and ovine [83] models show a link between HFD consumption and placental dysfunction. Importantly, gestational consumption of a HFD stimulates inflammatory cytokines such as interleukin (IL)-4, IL-5, monocyte chemotactic protein-1, RANTES, and granulocytemacrophage colony-stimulating factor, and these cytokines have been associated with ASD in humans [84–86]. Furthermore, these HFD offspring have a suppression of the

adaptive immune response, which is also a marker of the ASD profile in humans [73]. The inflammatory cytokines passed from an obese or diabetic mother to the fetus could therefore initiate the physiological and behavioral responses observed in children with ASD whose mothers experienced infections during pregnancy. Additionally, inflammation from poor maternal metabolic health and diet differs from infection-induced inflammation in that it results in prolonged exposure to inflammatory cytokines, and therefore it has a long-term impact on fetal development.

6.0 Mechanisms for HFD Programming of Behavior

The field is at an early stage of defining the mechanisms by which maternal HFD consumption and obesity influence the development of the complex neural circuitry that regulates behavior. There is evidence that neurotransmitter signaling pathways such as the serotonergic [5] and dopaminergic [34] systems are modified by maternal HFD consumption. The development of these pathways is influenced by exposure to increased levels of circulating inflammatory cytokines, hormones (leptin, insulin), and nutrients (fatty acids, triglycerides, and glucose). It is also possible (as discussed in sub section 3.0) that maternal HFD consumption impacts offspring neural development indirectly by modifying maternal behavior toward the infant, which has also been shown to induce changes in neural pathways critical in regulating behavior: the serotonergic [5], dopaminergic [2], and melanocortinergic [87] systems.

6.1 Inflammation-Induced Programming

Enduring inflammation occurs in the obese state because greater adiposity results in an elevation in many circulating markers of inflammation, including c reactive protein, IL- 6, IL-1β, and tumor necrosis factor-α [13]. Risk for a number of metabolic diseases such as cardiovascular disease, heart disease, insulin resistance, type II diabetes mellitus, and hypertension increases with the exposure to elevated levels of these inflammatory markers [13]. The relationship between obesity and higher levels of inflammatory cytokines has been observed in pregnant women; obese pregnant women have increased levels of inflammatory cytokines, which leads to endothelial [75] and placental dysfunction [88, 89]. There is strong evidence that exposure to higher levels of circulating cytokines during the neonatal period impacts neural development and thus may be a potential mechanism by which maternal HFD consumption programs the brain. The development of neurotransmitter systems that are important for behavioral regulation, such as the serotonergic system, dopaminergic system, and melanocortinergic system, have all been shown to be sensitive to circulating cytokine levels [13]. Fetal NHP offspring from mothers consuming a HFD exhibited elevated systemic and hypothalamic cytokines early in the third trimester [87], which may have led to the observed disruptions in the melanocortinergic [87] and serotonergic systems [5].

Further evidence for this hypothesis is supported by human studies, which find that emotional and behavioral disorders including anxiety [90, 91], depression [90, 92], ASD [84–86], and ADHD [93, 94] are associated with increased inflammatory cytokines. As exposure to inflammation during development causes a nonspecific response that impacts many neurotransmitter systems, it is important for future research to directly examine the influence of maternal obesity and HFD consumption-induced inflammation on each neural pathway important in behavioral regulation. A step in this direction is seen in the research on ursolic acid, which improved cognitive function when given to mice consuming a HFD [60]. As ursolic acid inhibits inflammatory signaling, the observed improvements suggest that anti-inflammatory compounds may be therapeutic for treating cognitive deficits due to HFD consumption [60]. An animal model has recently demonstrated that anti-inflammatory

compounds may be beneficial for treating Parkinson's disease as they block the neurodegenerative pathways stimulated by pro-inflammatory cytokines [24].

6.2 Programming by Excess Hormones and Nutrients

Maternal obesity has clear associations with gestational diabetes, maternal hyperglycemia, and hyperinsulinemia [95]. Glucose, but not insulin, can pass through the blood-placenta barrier and enter the fetal environment [96], and consequently the fetal pancreas must compensate for the resultant hyperglycemia by enhancing insulin release. Insulin is an important neural growth factor [97], and exposure to high levels of insulin during critical periods of brain development causes perturbations in the neural circuitry critical in regulating energy balance. For example, insulin administration during the last trimester of gestation results in offspring obesity [98, 99], and direct administration of insulin to the hypothalamus when the projections between the arcuate nucleus and the paraventricular nucleus are forming results in rodent offspring that have elevated body weight, hyperinsulinemia, impaired glucose tolerance, and elevated diabetes risk [100].

The exposure of offspring of obese mothers to high levels of leptin during development is also postulated to influence circuitry in the brain that regulates behavior and physiology. The concentration of leptin experienced during fetal development is critical in regulating the wiring of brain areas such as the hypothalamus [97], thus an elevation in fetal leptin concentration may be a critical factor in programming behavior and physiology. Rodent models indicate that postnatal leptin plays an important role in the development of hypothalamic neural circuitry [101, 102]. A role for leptin is further confirmed by studies in humans that demonstrated increased leptin levels in obese and diabetic mothers [103, 104] and lower leptin in infants that experienced intrauterine growth restriction at term [105]. It is important to note that circulating leptin levels do not rise until after completion of the development of the majority of neural circuitry in the hypothalamus in human and NHP gestation [105, 106]. Though leptin has been shown to be critical in rodent brain development, its role in primate brain development is uncertain [107]. However, high levels of leptin are associated with dysfunction of the placenta [81, 108], and so it is possible that leptin impacts primate brain development indirectly by acting on the placenta. Leptin's influence on the development of brain regions and pathways that regulate behavior has been largely unexplored. Given recent studies which indicate an important role of maternal metabolic state on offspring behavior, it is imperative that the role that leptin plays in programming behavior is further explored.

6.3 The Serotonin System is Suppressed by Maternal HFD Consumption

Numerous aspects of brain development including neuronal migration, neurogenesis, and synaptogenesis are regulated by the serotonin (5-HT) system [109, 110]. In addition, metabolism of 5-HT's precursor tryptophan (TRP) by the kynurenine (KYN) pathway plays an important role in modulating immune function during pregnancy by preventing allogeneic rejection of the fetus [111] and regulating blood flow between the fetus and placenta. The induction of maternal inflammation in animal models produces an increase in KYN metabolites [112]. As the KYN pathway competes with 5-HT for TRP, an up-regulation of this pathway decreases TRP availability for 5-HT synthesis. This reduction in 5-HT synthesis may therefore impact immune function and placental blood flow, which matches the results seen in our NHP model. As described earlier in this review, chronic consumption of a HFD during pregnancy in NHPs reduces placental blood flow, and this effect is amplified if the animals are obese and insulin resistant. Reduction in neural 5-HT synthesis is associated with mental health and behavioral disorders in humans, including anxiety [33], depression [113], ADHD [114], and ASD [81, 115], and so this suppression of

the serotonergic system increases the risk of offspring developing a number of behavioral disorders.

7.0 Conclusion

The mechanisms by which maternal obesity and HFD consumption may impact neural development and the regulation of offspring behavior include increased exposure to inflammatory cytokines, nutrients, and hormones in offspring of obese mothers in addition to the consequences of placental dysfunction. A primary potential mediator of maternal HFD-induced behavioral dysregulation is the serotonergic system because suppression of this system in response to maternal HFD consumption has been documented in a number of animal models. Furthermore, this suppression of the serotonin system results in the increased occurrence of behavioral abnormalities that are documented across animal models of maternal HFD-induced obesity. These behavioral irregularities are consistent with psychopathologies linked to maternal obesity in humans. This body of research shows that the current frequency of maternal obesity and HFD consumption will put future generations at greater risk of developing behavioral and mental health disorders. In response to the present staggering rates of maternal obesity, future studies need to investigate therapies that prevent and reduce the impact that maternal HFD consumption has on offspring behavioral regulation.

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Highlights

- Maternal diet and metabolic status have a long-term impact on offspring behavior.

- Obesity is associated with increased inflammatory cytokines, nutrients, and hormones.

- Increases in circulating factors impact the environment of the developing offspring.

- Offspring exposed to maternal obesity during development are at increased risk for mental health disorders.