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Maternal obesity and neurodevelopmental and psychiatric disorders in offspring

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Abstract

There is a growing body of evidence from both human epidemiologic and animal studies that prenatal and lactational exposure to maternal obesity and high-fat diet are associated with neurodevelopmental and psychiatric disorders in offspring. These disorders include cognitive impairment, autism spectrum disorders, attention deficit hyperactivity disorder, cerebral palsy, anxiety and depression, schizophrenia, and eating disorders. This review synthesizes human and animal data linking maternal obesity and high-fat diet consumption to abnormal fetal brain development and neurodevelopmental and psychiatric morbidity in offspring. In addition, it highlights key mechanisms by which maternal obesity and maternal diet might impact fetal and offspring neurodevelopment, including neuroinflammation; increased oxidative stress, dysregulated insulin, glucose, and leptin signaling; dysregulated serotonergic and dopaminergic signaling; and perturbations in synaptic plasticity. Finally, the review summarizes available evidence regarding investigational therapeutic approaches to mitigate the harmful effects of maternal obesity on fetal and offspring neurodevelopment.

MATERNAL OBESITY: A GROWING PROBLEM

Maternal obesity is increasing to near epidemic proportions globally. In the United States, approximately 27% of reproductive age women are overweight (body mass index (BMI) ≥25 and <30 kg/m^2) and 37% are obese (BMI ≥30 kg/ m^2).[1–3] This represents a 70% rise in pre-pregnancy obesity in the United States over the course of a decade.[4] While over all rates are lower in Europe, the trends are similar, with the most recent data suggesting rates of maternal obesity above 25% in the UK and above 20% in five additional European countries.[5] Maternal overweight and obesity are also rising in the developing world, particularly in urban settings.[6] This suggests that in the United States currently and soon throughout the world, a majority of infants born will be exposed to maternal overweight or obesity during critical periods of perinatal development.

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As the prevalence of obesity has risen, so as the prevalence of neurodevelopmental and psychiatric disorders.[7,8] Understanding whether there is a causal relationship between maternal obesity and offspring neurodevelopmental and psychiatric morbidity is important, particularly because increased identification of these morbidities in offspring is certainly also mediated by increased awareness and improved diagnostic tools and procedures.[9] A mechanistic understanding of how the maternal intrauterine and lactational environment may be mediating offspring neurodevelopmental morbidity is critical, because pregnancy may represent an important window for targeted intervention to ameliorate fetal and offspring risk.

The goals of this review are fourfold:

1. To summarize the human data suggesting an association between maternal obesity and offspring neurodevelopmental and psychiatric morbidity.
2. To summarize the data from animal model systems linking maternal obesity to fetal and offspring neurodevelopmental and psychiatric morbidity.
3. To provide an overview of putative mechanisms by which maternal obesity could impact fetal and offspring neurodevelopment.
4. To summarize the data regarding maternal dietary and lifestyle interventions and prenatal therapies that could ameliorate the harmful effects of maternal obesity on fetal and offspring brain development.

MATERNAL OBESITY IS ASSOCIATED WITH NEURO-DEVELOPMENTAL AND PSYCHIATRIC MORBIDITY IN OFFSPRING

Human studies

Epidemiologic studies have demonstrated an association between maternal obesity and neurodevelopmental and psychiatric morbidities in offspring, including intellectual disability/cognitive deficits; autism spectrum disorders (ASDs); attention deficit hyperactivity disorder (ADHD); cerebral palsy (CP); anxiety and depression; schizophrenia; and eating disorders, including food addiction, anorexia, and bulimia (Table 1). What follows is a summary of the existing human data regarding offspring risk for each category of neurodevelopmental or psychiatric morbidity.

Intellectual disability, decreased IQ, and cognitive impairment—Maternal obesity is associated with a 1.3 to 3.6-fold increase in the risk for intellectual disability or cognitive impairment in offspring, depending on the study in question.[10–13] Maternal obesity has been linked to decrements in offspring IQ, ranging on average from 2 to 5 points lower in offspring of obese versus non-obese women.[10,14,15] High gestational weight gain (GWG) seems to augment this association.[10] Maternal pre-pregnancy obesity plus GWG of >40 lb was associated with a threefold increase in offspring IQ deficit (mean of 6.5 points lower).[10] Two studies, both using data from the Danish National Birth Cohort, suggested an inverse dose–response relationship between maternal pre-pregnancy BMI and offspring IQ, reporting that every increase of one unit in maternal pre-pregnancy BMI was associated with

a reduction in offspring IQ of 0.2–0.3 points (adjusted for maternal IQ).[16,17] In one of the studies, paternal BMI was also inversely associated with child IQ.[16] Of note, several studies have described U-shaped or J-shaped associations between maternal obesity and offspring IQ, with extremely low maternal pre-pregnancy BMI (<18.5 kg/m^2) also significantly associated with lower offspring IQ, but with more subtle decrements seen in underweight than in the setting of maternal obesity.[10,12,14]

While the majority of large epidemiologic studies support an association between maternal obesity and offspring cognitive deficits, at least two large studies have failed to find consistent associations between maternal overweight/obesity and offspring cognition,[13,18] asserting that the presumed association may reflect confounding by genetic, socioeconomic, or postnatal factors.[18] While human studies are inherently limited in their ability to control for this type of confounding, animal model studies have been able to isolate the variable of maternal obesity with greater precision, and data from animal model studies corroborate impairment in offspring cognition in the setting of maternal obesity (see section on Evidence from animal models).

Autism spectrum disorders—The majority of studies that have examined a link between high maternal BMI and childhood diagnosis of ASD have found a significant positive association [adjusted odds ratios (ORs) range from 1.5 to 1.7].[19–22] This risk may be further augmented by intrauterine growth restriction,[23] preterm birth,[21] high GWG,[22] gestational or pre-gestational diabetes,[19,20] and preeclampsia.[24] A recent large retrospective case–control study reported a J-shaped association between maternal BMI and ASD, with both maternal underweight {AOR 1.43 [95% confidence interval (CI) 1.01, 2.04]} and maternal obesity [AOR 1.54 (95% CI 1.26–1.89)] significantly associated with ASD in offspring.[25] However, two recent studies including matched sibling analyses failed to find a significant relationship between maternal pre-pregnancy BMI and ASD risk,[26,27] suggesting that maternal BMI might be a proxy marker for other familial risk factors conferring an increased risk of ASD in offspring. High GWG was independently associated with offspring ASD risk, even in those studies that failed to find an association with maternal pre-pregnancy obesity.[26,27] Paternal obesity has also been demonstrated to be independently associated with increased ASD risk in offspring.[28]

Attention deficit hyperactivity disorder—Three large Nordic pregnancy cohorts noted a dose-dependent increase in ADHD symptoms in children as maternal pre-pregnancy BMI increased from overweight to obese.[29] Several later studies provided additional support for this association, reporting a 1.6 to 2.8-fold increased risk of offspring ADHD in obese women.[30–32] However, not all studies have reported a robust association between maternal obesity and increased risk of ADHD in offspring. A recent study found that children of White obese women had an increased risk for ADHD, but the association did not hold true for children of Black obese women.[33] Another recent study reported a significant association between maternal pre-pregnancy obesity and offspring ADHD [hazard ratio 1.64 (95% CI 1.57–1.73)], but this association was no longer significant in full sibling comparisons [hazard ratio 1.15 (95% CI 0.85–1.56)], leading the authors to conclude that the association

identified between maternal obesity and ADHD risk might be due to unmeasured familial confounding.[31]

Cerebral palsy—Maternal overweight and obese BMI has been reported to increase odds of offspring CP in a dose-dependent fashion.[34–37] In one study, each one-unit increase in maternal BMI increased the risk of offspring CP by 7%, and each kilogram of additional weight at 34 weeks increased the risk of offspring CP by 2%.[34] Given that other maternal inflammatory conditions associated with placental inflammation (such as chorioamnionitis) are known to confer an increased risk for CP,[35,38] one possible underlying mechanism may be the chronic systemic and placental inflammation induced by maternal obesity.[39]

Anxiety and depression—The impact of maternal obesity on offspring risk of anxiety and depression remains understudied, in part due to the inherent difficulty of linking maternal obesity to these morbidities typically diagnosed in adolescence or adulthood.[40] Maternal pre-pregnancy obesity was associated with a twofold increased risk of difficulty regulating emotions including sadness and fear, as reported by kindergarten teachers in a large Swedish cohort.[32] Another large Australian cohort demonstrated higher maternal pre-pregnancy BMI was associated with an increased risk of internalizing problems (including withdrawal and depression) after adjusting for confounders.[41] The increased risk of internalizing behaviors was first detected at age 8 years and persisted through the end of the study (age 17 years).[41]

Links between maternal obesity and increased offspring risk of anxiety and depression can at best be indirect, given the multiple confounders that often emerge between fetal exposure to an obese intrauterine environment and offspring diagnosis of anxiety and depression in adolescence or adulthood. These confounders include, but are not limited to (1) being born large or small for gestational age, both of which are linked to maternal obesity[40,42,43] and also to future risk of anxiety and depression[44,45]; (2) childhood obesity, which is linked to both maternal obesity/diabetes and to anxiety and depression[46–48]; and (3) adult obesity, which is linked to both maternal obesity and increased risk of anxiety and depressive disorders.[49,50] Anxiety and depression are more common in women than men,[51,52] and in adults, obesity is more strongly associated with anxiety and depression in women compared with men.[51,53] There are few human data regarding sex differences in the impact of maternal obesity on risk of anxiety and depression in offspring.[54,55] Because of the potential for confounding, a direct effect of maternal obesity on offspring anxiety-like and depressive behaviors may be more easily evaluated using animal models (see later).

Schizophrenia/Psychosis—Three human epidemiologic studies support a link between maternal obesity and schizophrenia.[56–58] The initial studies linking maternal nutrition to offspring risk of schizophrenia were from historic periods of famine. Offspring exposed to maternal malnutrition during the Dutch Hunger Winter of 1944–1945 had a twofold increased risk of developing schizophrenia.[59] Given the modern prevalence of maternal obesity and the rising prevalence of schizophrenia,[60] more recent studies have investigated a link between the two conditions.

Two large birth cohorts, including 19 000 US and 12 000 Finnish births, reported a twofold to threefold increase in schizophrenia in adult offspring of obese women.[56,57] In the US cohort, the association remained significant even after adjusting for maternal age, ethnicity, education, smoking status, and offspring sex, among other factors. In the Finnish cohort, however, the association between maternal obesity and increased schizophrenia risk in offspring was no longer significant after adjusting for maternal age at conception, socioeconomic status, and offspring sex.[56] A Japanese case– control study reported a 24% increase in offspring schizophrenia risk for every one-unit increase in maternal BMI in early pregnancy and a lesser (19%) increase in offspring risk for every one unit BMI increase in late pregnancy.[58] These findings suggest that early gestation and/or pre-pregnancy obesity may have a greater impact on offspring schizophrenia risk than late pregnancy obesity or GWG. These results conflict, however, with those of another study including over 7000 children born in Helsinki, Finland between 1924 and 1933. This study reported a threefold increased risk of schizophrenia in adult offspring of women with low BMI in late pregnancy (late pregnancy BMI <24 compared with BMI >30).[61] Additional studies investigating the link between maternal obesity/BMI and offspring schizophrenia risk in more racially and ethnically diverse populations are needed.

Eating disorders and food addiction—A limited number of studies have examined the relationship between maternal obesity, eating disorders, and addictive patterns of food consumption in offspring. Eating disorders are a significant concern given their high associated mortality compared with other neuropsychiatric disorders.[62] A 5-year prospective study found that maternal obesity was associated with inhibited and secretive eating behaviors over the first 5 years of life, possibly presaging an increased risk for anorexia and/or bulimia later in life.[63] This study was unable to distinguish developmental programming effects from effects of modeled maternal eating patterns observed by children. A cohort study including more than 1500 Australian adolescents reported each one-unit increase in maternal early pregnancy BMI increased the odds of eating disorders (anorexia, bulimia, and binge eating) in offspring by 11% [OR 1.10 (1.05–1.15)].[64] A German cross-sectional study found that young children (ages 6–7 years) whose mothers suffered from binge eating disorder had a sixfold increased risk of binge eating [OR 6.1 (2.7–13.5)] and a nearly eightfold increased risk of night eating [OR 7.8 (2.1–29.4)].[65] Maternal pre-pregnancy obesity/BMI were not explicitly reported in this study.

Human epidemiologic data have also examined maternal obesity as a risk factor for food addiction in offspring. Five-month-old infants of obese mothers were demonstrated to have greater overall energy intake and increased drive to consume high-carbohydrate foods compared with infants of normal-weight mothers.[66] A study that more directly examined the effect of maternal diet during pregnancy on offspring food intake and choice found an increased drive to overeat sweets in 1-year-old children of mothers who overconsumed sweet foods in pregnancy.[67]

Evidence from animal models

Animal models of maternal diet-induced obesity (DIO) have provided key mechanistic insights to complement human epidemiologic data linking maternal obesity to adverse

neurodevelopmental and psychiatric outcomes in offspring. Given the inherent issues with bias/confounding in epidemiologic studies, animal model studies have been able to more definitively support causation. DIO animal models have not only provided evidence of persistent changes in offspring cognition and behavior but also have provided insight into mechanism by describing alterations in fetal and offspring brain structure, gene expression, and inflammation, among other changes. Data from DIO animal models may be grouped into four broad categories:

Changes in brain structure and brain gene expression—Significant differences in brain structure and gene expression have been noted in fetuses and offspring of diet-induced obese rodents, including

1. Diminished proliferation and neuronal maturation of stem-like cells lining the third ventricle, hypothalamic region, and the cerebral cortex in fetal brains exposed to maternal obesity and high-carbohydrate diet *in utero*.[68,69]
2. Impaired hippocampal progenitor cell division and neuronal production in pups of high-fat diet (HFD)-fed dams.[70]
3. Decreased hippocampal apoptosis and decreased neuronal differentiation in the dentate gyrus of fetuses of HFD-fed dams.[71]
4. Increased hippocampal lipid peroxidation, and impaired hippocampal brain-derived neurotrophic factor (BDNF) production and neuronal arborization.[72]
5. Distinctive and sex-specific fetal brain gene expression signatures in the setting of maternal obesity with and without HFD consumption in pregnancy.[73,74] These studies point to increased inflammation and oxidative stress in fetal brains of obese dams and dysregulation of monoamine neurotransmitter signaling and hypothalamic orexigenic signaling.[69]

Cognitive/learning impairment—In rodent studies, maternal obesity and maternal HFD consumption resulted in impaired hippocampal learning, as measured by performance on the Morris Water Maze,[75–77] Barnes Maze,[72] operant conditioning,[78] and novel object recognition.[79] These learning impairments were accompanied by increased hippocampal lipid peroxidation and microglial activation in pups at birth and increased proinflammatory cytokine expression in the post-weaning and adult hippocampus,[72,75,77] suggesting that neuroinflammation and oxidative stress may be mediating cognitive impairment. Offspring exposed to maternal obesity also demonstrated impaired learning as measured by operant conditioning for sucrose reinforcement, with elevated maternal corticosterone levels proposed as a mechanistic link.[78] Exposure to maternal HFD during either pregnancy or lactation was sufficient to induce impairment in novel object recognition and the Barnes maze in adult offspring.[79]

Behavioral abnormalities—Rodent and nonhuman primate models have evaluated offspring performance on neurobehavioral tests that correlate with some of the behavioral abnormalities noted in human offspring of obese women. Decreased sociability (correlate for ASD) has been noted in female but not male offspring of diet-induced obese dams using the

three-chamber social interaction test.[55] This sociability alteration in females was normalized by maternal dietary intervention (low-fat control diet) in lactation. Hyperactivity has been evaluated via the open field test, with maternal obesity and HFD during gestation associated with increased hyperactivity in males but not females.[55] The male hyperactive behavioral phenotype was not altered by maternal dietary change in lactation.

Offspring anxiety has also been evaluated using the open field test, with increased anxiety noted in both male and female offspring of obese dams on a HFD in pregnancy and lactation.[55] Lactational switch to control diet in these dams improved both neuroinflammation and anxiety behaviors in female but not male offspring.[55] Adult offspring exposed to maternal obesity and HFD during gestation and lactation also displayed increased anxiety on the elevated plus maze.[75,80,81] These changes were accompanied by increased hippocampal expression of BDNF, GABA(A) alpha2 receptor subunit, and 5-hydroxytryptamine 1A, suggesting that maternal HFD may increase anxiety behaviors in offspring via alterations in GABAergic and neurotrophin systems in early life.[80] Studies have also utilized the Morris water maze,[75] novel object test,[82] and Porsolt swim test[83,84] to demonstrate associations between maternal obesity/HFD consumption and anxiety-like and depressive behavior in offspring.

Disordered eating/food addiction—There are no data from animal models investigating the relationship between maternal obesity and anorexia or bulimia of offspring; such studies would be useful in elucidating underlying mechanisms. Three rodent studies support a link between maternal obesity and an increased risk of food addiction-type behaviors in offspring. Rat dams who consumed a ‘junk food’ diet of high-fat, high-salt, and high-sugar foods (e.g. potato chips and marshmallows) had offspring who were more likely than controls to overeat the same junk food diet when offered and more likely to become obese.[85] Another rat model of maternal ‘junk food’ diet demonstrated higher fat intake of offspring from weaning until 3 months of age and altered development of the central mesolimbic reward pathway.[86] Offspring of mouse dams fed a HFD during gestation and lactation were more likely to overeat high-fat, high-sugar foods compared with controls. These behavioral-related changes related to food consumption were associated with epigenetic changes that resulted in long-term alteration in expression of genes related to dopamine and opioid (reward-based) signaling.[87] A rat model of maternal HFD during pregnancy and lactation found that offspring demonstrated enhanced operant responses to fat, but not to sucrose. These altered reward properties of food in offspring were associated with abnormalities in presynaptic dopamine regulation in the nucleus accumbens.[88] Animal models have also provided important data about dysregulated dopaminergic and serotonergic signaling in offspring in the setting of maternal obesity, which is described in greater detail as follows.

POSSIBLE UNDERLYING MECHANISMS

The primary mechanisms that have been proposed to underlie the risk of neurodevelopmental morbidity in offspring of obese women are often interrelated (Figure 1) and include

1. Oxidative stress and inflammation-induced malprogramming.
2. Dysregulation of insulin, glucose, and leptin signaling in the developing brain.
3. Dysregulation of dopaminergic and serotonergic signaling and impaired reward circuitry.
4. Perturbations in brain-derived neurotrophic factor-mediated synaptic plasticity.

Oxidative stress and inflammation-induced malprogramming

Circulating free fatty acids (FFAs) are increased in obese women, because of dietary intake and increased adipose tissue lipolysis, and these FFAs are known to cross the placenta.[9,36,89] FFAs are known to increase oxidative stress burden and inflammation, both of which may negatively affect offspring cognition.[90] RNA-Seq analysis found gene expression patterns consistent with lipotoxicity and increased oxidative stress in placentas from obese compared with lean women at term.[91] Global gene expression profiling of amniotic fluid from obese and lean women in the second trimester suggested upregulation of genes related to oxidative stress response, in particular *Apolipoprotein D* (*APOD*), which is highly expressed in the central nervous system and was ninefold upregulated in fetuses of obese compared with lean women.[92] These findings were later corroborated in a mouse model of maternal DIO, where both male and female brains exposed to maternal obesity *in utero* demonstrated gene expression patterns consistent with dysregulated reactive oxygen species metabolism.[93] Increased hippocampal lipid peroxidation has been noted in pups of obese dams on a HFD,[70] and evidence of increased brain oxidative stress persists in adult offspring of obese, HFD-fed dams.[77]

Chronic systemic inflammation is a feature of both maternal obesity and pregnancy itself.[94] Obese pregnant women are known to have higher levels of circulating pro-inflammatory cytokines than their normal-weight counterparts.[39,95,96] Maternal BMI is directly correlated with maternal pro-inflammatory cytokine concentrations and activation of pro-inflammatory placental pathways.[39,97] Elevated maternal systemic pro-inflammatory cytokine levels during gestation are associated with an increased risk for cognitive delay and ASDs in children.[98] Placental and intrauterine inflammation are associated with altered fetal cytokine expression, fetal neuronal damage, and changes in neonatal brain gene expression.[96,99]

Animal studies have corroborated associations between maternal obesity, maternal and placental inflammation, fetal brain inflammation, and abnormal neurodevelopment in offspring.[36,96] In rat models of maternal obesity and HFD consumption, offspring demonstrated significantly increased neuronal and systemic inflammation, cognitive deficits, and striking differences in anxiety-like behavior and spatial reasoning performance.[75,77] Increased fetal and offspring brain inflammation and neurobehavioral deficits including decreased sociability, impaired hippocampal learning, and increased hyperactivity have also been noted in murine and nonhuman primate models of maternal obesity and HFD consumption in pregnancy.[55,100] Placental and fetal brain inflammation in the setting of maternal obesity may also contribute to abnormal serotonin and dopamine signaling in offspring and resultant neuropathology (see the section on Dysregulation of serotonergic and dopaminergic signaling).[101–103]

Dysregulation of insulin, glucose, and leptin signaling in the developing brain

Even in the absence of overt gestational or pre-gestational diabetes, fetuses of obese women are likely chronically exposed to insulin resistance and a glucose-rich environment.[40] Inflammatory changes in fetal adipose tissue and skeletal muscle increase peripheral fetal insulin resistance, and the fetal pancreas overproduce insulin.[104,105] Peripheral insulin resistance may have significant effects on the central nervous system.[79] The insulin receptor is highly expressed in the hippocampus and cortex, and growing evidence suggests that synaptic insulin signaling plays a key role in learning and memory.[79,106,107] In a rat model, maternal HFD was associated with decreased hippocampal gene expression of insulin receptor (*Insr*) and glucose transporter 1 (*Slc2a1*) in juvenile offspring, with persistently decreased expression of *Insr* in adulthood.[79] Maternal hyperinsulinemia has been implicated in increased offspring risk of ASD and neurodevelopmental delay.[101]

Leptin resistance and elevated leptin levels are also prominent in obese mothers.[101,108] The leptin receptor is highly expressed in the hippocampus and other brain regions involved in behavioral regulation (cortex, amygdala, thalamus, and hypothalamus).[109,110] Maternal HFD was found to decrease hippocampal gene expression of leptin receptor (*Lepr*) in juvenile and adult offspring.[79] Leptin signaling is thought to play a critical role in hippocampal dependent learning through regulation of synaptic plasticity and neurotransmitter receptor trafficking.[79] Leptin is also a critical neurotrophic factor, and leptin signaling abnormalities during fetal development have been associated with decreased neuronal stem cell differentiation and growth.[111] Thus, deranged leptin signaling during key developmental periods is another potential mechanism underlying abnormal neurodevelopment in fetuses of obese women.[22]

Dysregulation of serotonergic and dopaminergic signaling and impaired reward circuitry

Maternal obesity is also associated with abnormal development of the serotonergic (5-HT) and dopaminergic systems. Impaired serotonergic and dopaminergic signaling may contribute to offspring risk for a wide variety of neurodevelopmental and neuropsychiatric morbidity, including anxiety and depression, schizophrenia, eating disorders, and food addiction, ASD, and ADHD. 5-HT signaling plays a significant role in neuronal migration, cortical neurogenesis and synaptogenesis during fetal brain development.[82,101] Animal models of maternal HFD consumption have demonstrated decreased offspring serotonin synthesis and associated neurobehavioral deficits including increased hyperactivity and anxiety-like behavior.[9,40] In rodent models, high levels of pro-inflammatory cytokines were associated with reduced serotonin axon density and reduced embryonic neuronal survival in brain regions critical for behavioral regulation.[102,112] Increased breakdown of the serotonin precursor trypophan in the setting of subclinical inflammation is another possible mechanism by which maternal obesity may decrease serotonin production in offspring.[101] Reduced serotonin synthesis in humans has associated with increased incidence of ADHD, ASD, anxiety and depression.[9,40]

Maternal obesity also affects the developing dopaminergic system, which mediates eating and addictive behaviors and reward neural circuitry, among other functions. A rat model of maternal HFD reported impaired mesolimbic dopaminergic signaling in offspring,

associated with impairments in reward response to food.[88,113] Mice exposed to HFD *in utero* demonstrated epigenetic changes leading to dysregulation of the dopamine reuptake transporter and increased preference for high-sugar, high-fat foods.[87] Similar to serotonin, abnormal dopamine signaling in offspring of obese females may be mediated through increased maternal inflammation; abnormal offspring dopamine signaling was noted in a rat model of maternal inflammation.[103] Impaired dopaminergic signaling in humans is known to be associated with schizophrenia, disordered eating, ASD, and ADHD.[40]

Alteration of brain-derived neurotrophic factor-mediated synaptic plasticity

Umbilical cord gene expression profiling has identified patterns consistent with neurodegeneration/premature brain aging in fetuses of obese women compared with lean.[115] Direct examination of fetal brain gene expression in a mouse model of maternal DIO demonstrated dysregulation of pathways related to synaptic plasticity and long-term potentiation in females exposed to maternal obesity and HFD *in utero*, and neurodegeneration in males with the same exposure.[73] The role of BDNF in regulating synaptic repair may provide insight into mechanisms underlying these abnormalities.[115] BDNF is a member of the neurotrophin family and promotes neuronal survival. It is a key regulator of synaptic transmission, plasticity, growth, and repair.[115] Multiple studies in rodents have demonstrated that obesity and HFD consumption are associated with decreased expression of BDNF in the cortex and hippocampus.[79,116,117] Impaired hippocampal BDNF production in the setting of maternal obesity and HFD has been linked to deficits in spatial learning and memory in juvenile and adult offspring.[72,76] Thus, the deleterious effects of maternal obesity on offspring learning and memory may be mediated by alteration of BDNF-mediated synaptic plasticity.[79] Lending further support to this concept, calorie restriction[118] and exercise[119] have been demonstrated to ameliorate the harmful effects of HFD on synaptic plasticity and cognitive function, in part via upregulation of BDNF.[118,119]

PRENATAL DIAGNOSIS AND EXPLORATORY PRENATAL THERAPIES

Given that many of the neurodevelopmental and psychiatric morbidities associated with maternal obesity are difficult to diagnose before school age or adolescence, prenatal diagnosis of neurodevelopmental and psychiatric disorders in the setting of maternal obesity remains difficult. There are no data in the literature at this time regarding prenatal diagnosis of offspring neurodevelopmental or psychiatric abnormalities in the setting of maternal obesity.

Both animal and human data suggest that the impact of maternal obesity on fetal and offspring neurodevelopment may be modifiable by maternal dietary and lifestyle changes, maternal metformin treatment, and maternal antioxidant and polyunsaturated fatty acid supplementation in pregnancy. All of these interventions have been explored as candidates to improve offspring neurodevelopment in maternal obesity.[120–125]

Maternal dietary and lifestyle change

In animal studies, pre-pregnancy and lactational change from HFD to a low-fat control diet reduced offspring adiposity, circulating leptin, and anxiety behaviors.[120] When obese, HFD-

fed dams were changed to a low-fat control diet in lactation and female offspring demonstrated reduced neuroinflammation and improvement in social behavioral deficits.[55] In addition to dietary changes, maternal exercise has also been demonstrated to improve juvenile and adult offspring cognition, hippocampal cell survival, and synaptic plasticity in animal models.[119,126] There is an ongoing randomized controlled trial of maternal exercise in obese pregnant women to examine the impact on offspring metabolic programming.[127] The impact of maternal exercise on offspring neurodevelopmental programming has not yet been investigated in humans.

Prenatal medical therapies and nutritional supplements

Maternal metformin therapy in obese pregnancy has been evaluated in both human and animal studies. There have been two randomized controlled trials of metformin therapy for obese pregnant women who do not have diabetes.[128,129] One of these studies showed no impact of maternal metformin on any maternal or neonatal outcomes examined,[128] the other showed that maternal metformin therapy significantly reduced maternal weight gain and the incidence of preeclampsia, but had no significant impact on any neonatal parameters examined, including birthweight.[129] Neither study has yet reported on longer-term effects of maternal metformin therapy on metabolic or neurodevelopmental outcomes in offspring. In a rat model of DIO, maternal metformin treatment reduced fetal and placental inflammation, although neuroinflammation and neurobehavioral outcomes of offspring were not specifically interrogated.[121]

Given that oxidative stress is increased in obese pregnancy, a variety of antioxidant therapies to ameliorate maternal and fetal morbidity have been investigated.[130] An ongoing clinical trial in obese pregnant women employs BMI-based prenatal micronutrient supplementation, with the goal of decreasing maternal and fetal oxidative stress and inflammation.[125] The antioxidants resveratrol and luteolin have been demonstrated to have neuroprotective effects in the setting of obesity and HFD, reducing markers of oxidative stress and neuroinflammation in rodents and nonhuman primates on a HFD.[131,132] Luteolin supplementation of obese, HFD-fed adult mice was also found to be associated with improved cognitive performance.[132] However, while resveratrol therapy in obese pregnant macaques and rodents was reported to have beneficial effects on placental long-chain polyunsaturated fatty acid uptake and offspring oxidative stress and metabolic dysfunction,[133,134] we are not aware of studies that have investigated the effects of resveratrol or luteolin on offspring neurodevelopment.

Observational data has pointed to polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6 fatty acids, as possible candidate therapeutics in maternal obesity. Omega-3 PUFAs protect against brain inflammation and enhance serotonin signaling.[9] Maternal omega-3 fatty acid deficiency has been associated with increased risk of offspring ASD and ADHD.[122] Human pilot studies of supplementation of obese pregnant women with omega-3 fatty acids demonstrated reduction in maternal and placental inflammation.[123] Studies in the fat-1 transgenic mouse demonstrated that an increase in the maternal omega-3: omega-6 fatty acid ratio was associated with a reduction in obesity-related maternal and placental inflammation and a reduction in deleterious metabolic programming effects in offspring of

obese dams.[135] Data are conflicting regarding the effect of maternal omega-6 supplementation on offspring neurodevelopmental outcome. 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 offspring ASD risk.[124] However, data from murine models suggest the opposite, reporting that maternal diet rich in omega-6 PUFAs during gestation and lactation produced autism-like changes in offspring sociability on the three-chamber social interaction test, increased anxiety in the elevated plus maze, hyperactivity in the open field test, and increased offspring aggression.[136,137] Given the lack of definitive safety and efficacy data and some conflicting data from human versus animal model studies, there is insufficient evidence at this time to support omega-3 or omega-6 PUFA supplementation in obese pregnancy to improve offspring neurobehavioral outcomes.

SUMMARY

Maternal obesity and consumption of the 'Western diet' high in saturated fat are increasing worldwide, creating the potential for a parallel increase in neurodevelopmental and psychiatric morbidity in the next generation. Human epidemiologic studies have provided ample evidence of an association between maternal obesity and adverse neurodevelopmental and psychiatric outcomes in offspring. While there is mounting evidence from both human and animal studies that this association may be causal (temporal relationship between exposure and outcome; dose–response relationship noted between maternal obesity class and offspring risk of cognitive delay, ADHD, CP, and schizophrenia; biologic plausibility), the data still must be interpreted with caution, given the relatively low strength of the reported associations as measured in odds ratios or relative risks; the failure of some human studies to identify these associations after controlling for confounders; and the inability to isolate maternal obesity as the sole causal variable, particularly in human studies. While data from animal model studies do support causation and have helped elucidate potential underlying mechanisms, more work remains to be performed in this area. While there are some promising investigational therapies that may ameliorate neurodevelopmental malprogramming in the setting of maternal obesity, there are currently insufficient data on efficacy and safety to recommend any maternal medical or nutritional supplemental therapy to improve offspring neurodevelopmental and psychiatric outcomes. The best evidence at this time still suggests that minimizing GWG and encouraging pre-pregnancy weight loss are the safest and most effective methods for mitigating offspring neurodevelopmental and psychiatric risk.

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Maternal obesity is associated with an increased risk for neurodevelopmental disorders in offspring, including cognitive impairment, autism spectrum disorders, attention deficit hyperactivity disorder, and cerebral palsy.
- Maternal obesity is associated with an increased risk for psychiatric disorders in offspring, including anxiety and depression, schizophrenia and psychosis, eating disorders, and food addiction.

WHAT DOES THIS STUDY ADDS?

- This comprehensive review integrates both human epidemiologic and animal data linking maternal obesity and high-fat diet consumption with increased risk of neurodevelopmental and psychiatric morbidity in offspring.
- Synthesizes existing data regarding possible underlying *in utero* mechanisms and investigational therapeutics.

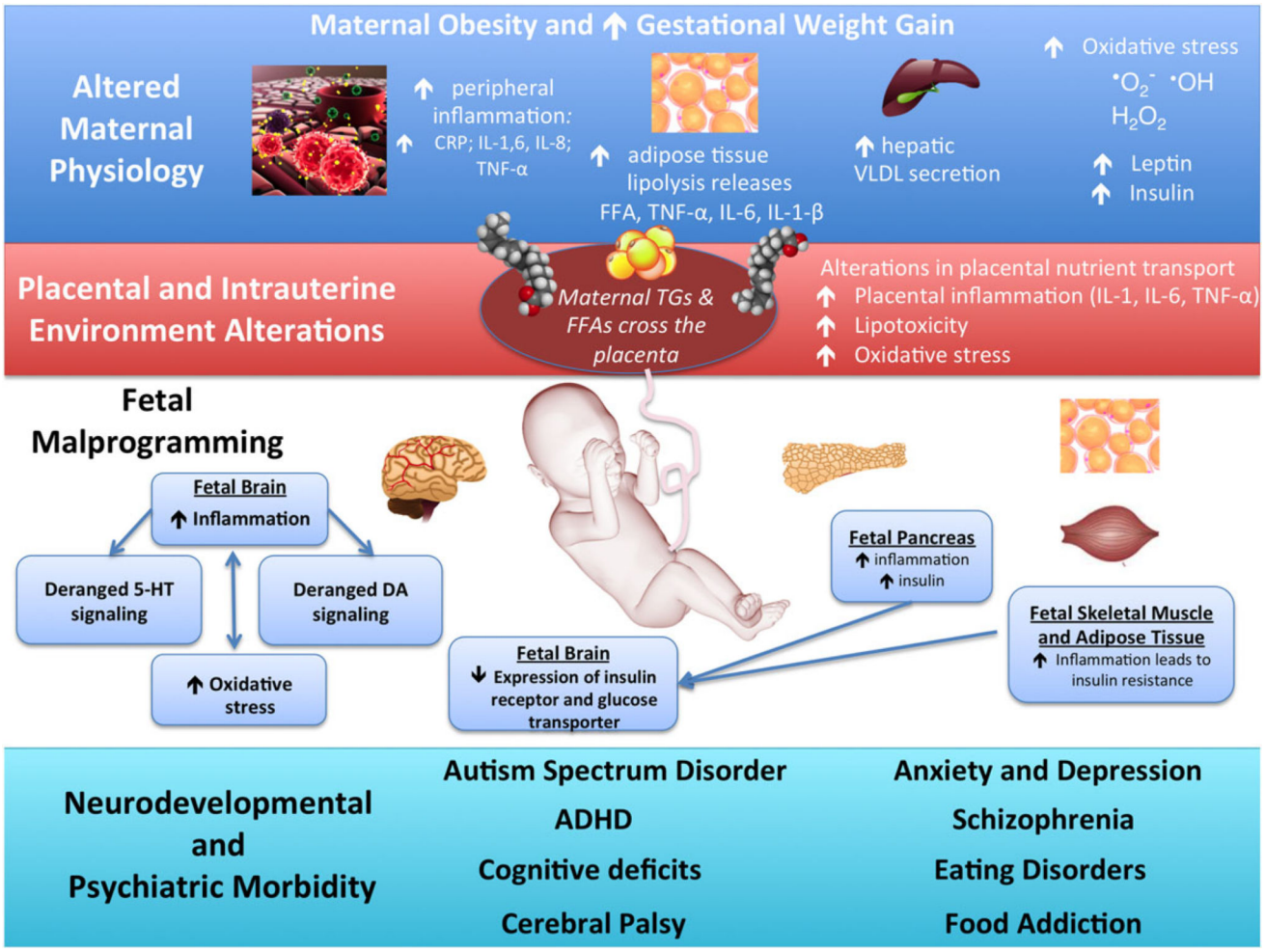

Figure 1.

Mechanisms by which maternal obesity may result in offspring neurodevelopmental and psychiatric morbidity. Altered maternal physiology results in increased inflammation, lipotoxicity, and oxidative stress in the fetoplacental unit. These changes in the *in utero* environment contribute to malprogramming of the fetal brain, pancreas, skeletal muscle, and adipose tissue, among other organs. Peripheral inflammation and insulin resistance contribute to central insulin resistance and aberrant central glucose metabolism and transport. Only organ malprogramming known to influence fetal and offspring neurodevelopment is depicted here. *In utero* malprogramming results in an increased risk for offspring neurodevelopmental and psychiatric morbidity. CRP, C-reactive protein; DA, dopamine; FFA, free fatty acid; IL, interleukin; TG, triglyceride; TNF, tumor necrosis factor; VLDL, very low-density lipoprotein; 5-HT, serotonin

Table 1

Human epidemiologic studies examining effects of maternal obesity on offspring neurodevelopmental and psychiatric outcomes

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
Intellectual disability/ decreased IQ/ cognitive impairment	Cognitive performance (IQ) and motor development age 5	Pre-pregnancy BMI (BMI >29 considered obese)	No	355 children born to US mothers 1985–1989	Cohort (USA)	MATOB significantly associated with ~5-point decrement in IQ. No significant gross motor differences.	Neggers *et al.*, 2003
	Intellectual disability (IQ <70) age 11.5	Pre-pregnancy BMI	Yes	Two Finnish birth cohorts: **1** 1966, *N* = 12 058 **2** 1986, *N* = 9032	Cohort (Finland)	MATOB significantly associated with offspring IQ <70 in the 1986 birth cohort [OR 3.6, (95% CI 2.0–6.6)], but not in the 1966 cohort [OR 1.3, (95% CI 0.5–3.1)]	Heikura *et al.*, 2008
	Cognitive performance and behavioral problems ages 30 months to 8 years	Pre-pregnancy BMI	Not specified	Two birth cohorts: **1** *N* = 5000, born 1991–1992, children assessed 38–47 months and 8 years for cognitive performance and behavioral problems (British) **2** *N* = 2500, born 2002–2006, children assessed 30–36 months for behavioral	Cohort (UK, The Netherlands)	MATOB significantly associated with lower IQ age 8 in 1 of 2 cohorts; significantly associated with greater child total behavioral problems in 1 of 2 cohorts; no associations persisted in both cohorts after adjusting for confounders	Brion *et al.*, 2011

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
				problems (Dutch)			
	Cognitive and motor performance age 2	Pre-pregnancy BMI	Not specified	Early Childhood Longitudinal Study Birth Cohort (sample of US children born 2001), *N* = 6850	Cohort (USA)	Maternal pre-pregnancy BMI <18.5 kg/m^2 or ≥35 kg/m^2 associated with mental but not motor delay at age 2	Hinkle *et al.*, 2012
	Cognitive performance, ages 5 and 7	Pre-pregnancy BMI	Not specified	UK population-based cohort, sample of all infant births 2000– 2002 *N* = 15 043 age 5; *N* = 13 681 age 7	Cohort (UK)	MATOB significantly associated with lower cognitive performance at ages 5 and 7.	Basematur *et al.*, 2013
	Standardized reading and math scores, ages 5–7	Pre-pregnancy BMI	Yes	3412 children born to US mothers 1986–2008	Observational/ Survey (USA)	MATOB associated with significantly lower reading (3 points or 0.23 SD units) and math scores (2 points, 0.16 SD units) ages 5–7	Tanda *et al.*, 2013
	Cognitive performance age 5	Pre-pregnancy BMI	Yes	1782 children, born 1998–2003. Sample from the Danish National Birth Cohort	Cohort (Denmark)	Significant inverse association between maternal pre-pregnancy BMI and child IQ age 5, effect size small	Eriksen *et al.*, 2013
	Cognitive performance age 7	Pre-pregnancy BMI	No	30 212 children born to US mothers 1959– 1965	Cohort (USA)	Both low and obese maternal pre-pregnancy BMI significantly associated with decreased child IQ at age 7 (2–2.5 points lower for MATOB); GWG >40 lb increased IQ decrement threefold, to 6.5 points lower	Huang *et al.*, 2014

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
	Cognitive performance age 5	Pre-pregnancy BMI	Yes	1783 children from Danish National Birth Cohort, born 1996– 2002	Cohort (Denmark)	Significant inverse association between maternal pre-pregnancy BMI and child IQ at age 5; however, similar association with paternal BMI	Bliddal *et al.*, 2014
	Intellectual disability (IQ <70), age of follow-up variable (median age 6)	Pre-pregnancy BMI	Yes	2734 children born to US mothers, 1998– 2014	Cohort (USA)	MATOB significantly associated with intellectual disability in offspring, effect augmented by gestational or PGDM	Li *et al.*, 2016
Neonatal neurobehavior	NNNS (NICU Network Neurobehavioral Scale) performance at 2 and 32 days of life	Pre-pregnancy BMI, GWG (IOM criteria by pre-pregnancy BMI)	No	261 mother-infant pairs (infant assessed at 2 and 32 days)	Cohort (USA)	MATOB with high GWG significantly associated with lower arousal, increased lethargy in early neonatal period; increased difficulty self-soothing in late neonatal period. MATOB or GWG alone had a significant impact on early or late NNNS scores	Aubuchon-Endsley *et al.*, 2016
ASD	ASD diagnosis (ICD-9, ICD-10 codes) in children aged 1–17. At least 1 diagnosis code after age 2 required	Pre-pregnancy weight ≥90 kg, GWG >18 kg	Yes	Birth cohort: all live births >20 weeks in Nova Scotia, 1990–2002 (N = 129 733. 924 with ASD)	Cohort (Canada)	Pre-pregnancy weight ≥90 kg and GWG >18 kg both significantly associated with increased risk for ASD in children	Dodd *et al.*, 2011
	ASD diagnosis by clinicians (ADOS, ADI-R) children aged 2–5	Pre-pregnancy BMI	Not specified	N = 1004, 517 with ASD; children enrolled 2003–2010	Case–control (USA)	MATOB significantly associated with increased odds of ASD in children	Krakowiak *et al.*, 2012

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
	ASD diagnosis, identified by: **1** Cohort 1: ICD-9 coding and school records review. Children age 8 **2** Cohort 2: ASD diagnosis by clinicians (ADOS, ADI-R). Child age not specified	Pre-pregnancy BMI, GWG	Not specified	2 cohorts: **1** *N* = 194 cases identified through autism monitoring networks and registries, confirmed by review of medical/ school records. *N* = 10 920 zipcode-matched controls. Children born 1994, diagnosed 2002. **2** *N* = 288 ASD cases, *N* = 493 unaffected sibling controls, identified through Utah Genetics Study. Children born after 1988	Case–control (USA)	GWG 2 SD above the mean, but not MATOB, was significantly associated with increased risk of ASD in children	Bilder *et al.*, 2013
	Positive ASD screen age 2 (MCHAT)	First trimester BMI	Yes	62 mother-child pairs. Children born ≤30 weeks gestation, 2007–2010.	Cohort (USA)	MATOB was significantly associated with increased odds of positive autism screen in children at age 2	Reynolds *et al.*, 2014
	ASD diagnosis, identified by medical records diagnostic	Pre-pregnancy BMI	Yes	N = 889 cases of ASD and 3530 controls identified from the UK General Practice Research	Case–control (UK)	J-shaped association between maternal pre-pregnancy	Getz *et al.*, 2016

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
	codes. Children diagnosed ages 2– 17			Database. Children born 1993– 2008		BMI and child ASD risk. Both maternal underweight and MATOB significantly associated with increased odds of offspring ASD	
	ASD diagnosis, identified by medical records diagnostic codes. Children assessed age 6	Pre-pregnancy BMI	Yes	*N* = 2734 mother-child pairs, including 102 ASD cases. Children born 1998–2014	Cohort (USA)	MATOB alone not significantly associated with increased odds of offspring ASD, but MATOB with GDM and MATOB with PGDM were both significantly associated with increased offspring ASD risk	Li *et al.*, 2016
	ASD diagnosis, identified by ICD-9, ICD-10, and DSM-IV codes	First trimester BMI, GWG	Not specified	*N* = 33 057 individuals, 6420 with ASD. Born 1984–2007 in Stockholm County	Cohort (Sweden)	MATOB and excess GWG significantly associated with increased risk of ASD in children at the population level; in matched sibling analyses, no significant association between MATOB and offspring ASD risk. Nearly significant relationship between excess GWG and offspring ASD [OR 1.48 (0.93–2.38)].	Gardner *et al.*, 2015
ADHD	ADHD symptoms, rated by teachers using 2 standardized/ validated instruments. Children assessed ages 7–12	Pre-pregnancy BMI, GWG (IOM criteria by pre-pregnancy BMI)	No	3 pregnancy cohorts, *N* = 12 566 children. Evaluation ages 7–8 (Sweden, Finland); 10– 12 (Denmark)	Cohort (Sweden, Denmark, Finland)	MATOB associated with increased odds of teacher-rated ADHD symptoms in	Rodriguez *et al.*, 2008

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
						school-aged children. Excess GWG further augments the risk	
	ADHD symptoms, rated by teachers and mothers. Children assessed age 5	Pre-pregnancy BMI	No	Follow-up study of a Swedish birth cohort (*N* = 2634) at age 5. Final *N* = 1714	Cohort (Swedish)	MATOB associated with increased risk of ADHD symptoms by teachers' ratings, but not by mothers' ratings	Rodriguez, 2010
	ADHD symptoms rated by mothers (CBCL). Children assessed age 7	Pre-pregnancy BMI, GWG	Yes (preterm 34–37 weeks included)	Pregnancy cohort, *N* = 174	Cohort (USA)	MATOB associated with increased risk of ADHD symptoms, association mediated by impaired executive function	Buss *et al.*, 2012
	ADHD diagnosis, identified by medical records diagnostic codes	Pre-pregnancy BMI	Not specified	Population-based cohort, *N* = 673 632 born from 1992–2000, including 272 790 full biological siblings. Children followed through ages 9–17	Cohort (Swedish)	MATOB associated with increased risk of offspring ADHD, but associations did not persist in full sibling comparisons	Chen *et al.*, 2014
	ADHD symptoms rated by mothers (BPI). Children assessed ages 8–10	Pre-pregnancy BMI	No	*N* = 3395 (2127 White and 1268 African-American). Mothers surveyed 1986–2008.	Observational (USA)	MATOB associated with increased risk of offspring ADHD among the White sample only	Tanda and Salsberry, 2014
CP	CP diagnosis at ≥age 4, identified by national registry	Pre-pregnancy BMI, maternal weight at 34 weeks	No	Children with CP born at term, 1983–94 (N = 309), matched with controls (N = 618)	Case–control (Sweden)	MATOB and weight at 34 weeks both associated with increased risk of CP in univariate analysis, only weight at 34 weeks significantly associated in	Ahlin *et al.*, 2013

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
						multivariate analysis	
	Children receiving services for CP, diagnosis ≥age 5	ICD-9 codes for obesity/ morbid obesity at time of delivery	Yes	All California hospital births 1991–2001 (N = 6.2 million, 67 200 with MATOB and 7878 with morbid MATOB) linked to records of children receiving services	Population-based (USA)	MATOB associated with increased risk of child CP, morbid MATOB (BMI ≥40) further augments	Crisham Janik, *et al.* 2013
	CP identified by ICD-9 codes, public school records, Medicaid billing records	Pre-pregnancy BMI, GWG	Not specified	All South Carolina Medicaid-insured live births 2003–2007. N = 83 901 maternal-child pairs, 100 cases CP	Cohort (USA)	MATOB associated with increased risk of child CP, morbid MATOB (BMI ≥40) further augments. For every one-unit increase in BMI, odds of CP increase 4%	Pan, *et al.* 2014
Anxiety and Depression	Child negative emotionality and regulation of emotions by mother and teacher report	Pre-pregnancy BMI	No	Pregnancy cohort, N = 1714. Children evaluated at age 5	Cohort (Swedish)	MATOB associated with increased risk of negative emotions and difficulty with negative emotion regulation (evaluated by teachers)	Rodriguez, 2010
	Child internalizing problems (including withdrawal and depression) rated by mothers using CBCL	Pre-pregnancy BMI	Not specified	N = 2785 children of mothers in the West Australian Pregnancy Cohort. Children evaluated at ages 5, 8, 10, 14, and 17	Cohort (Australian)	Maternal pre-pregnancy BMI associated with increased risk of child internalizing problems at age 8, increasing through age 17	Van Lieshout *et al.*, 2013
Schizophrenia/ psychosis	Adult diagnosis of schizophrenia (determined by diagnostic interview and medical records review)	Pre-pregnancy BMI	Not specified	N = 6633, 63 cases schizophrenia Births to all women enrolled in a health plan 1959– 1967. Adult offspring still in health plan followed up 1981–1997	Cohort (USA)	MATOB associated with increased risk of schizophrenia in adult offspring. Maternal underweight (BMI <18 kg/m^2)	Schaefer *et al.*, 2000

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
						not significantly associated	
	Diagnosis of schizophrenia ages 16–28 (identified by individual record review for DSM-III-R criteria)	Pre-pregnancy BMI (BMI ≥29 considered obese)	Yes	1966 general population birth cohort. *N* = 11 017 subjects alive age 16, followed to age 28. 76 cases schizophrenia	Cohort (Finland)	Women with BMI ≥29 had twice the odds of having a child with schizophrenia, but this finding did not achieve statistical significance [OR 2.1, (0.9–4.6)]	Jones *et al.*, 1998
	Diagnosis of schizophrenia (DSM-IV criteria), receiving care sthrough a city hospital	First-trimester and third-trimester BMI	No	*N* = 52 patients with schizophrenia, 284 healthy controls (sex-balanced) Patients recruited from hospitals in Hamamatsu City	Case–control (Japan)	Higher maternal BMI was associated with increased offspring schizophrenia risk. 24% increase in risk for every one-unit BMI increase in early pregnancy, and 19% increase for every one-unit BMI increase in late pregnancy	Kawai *et al.*, 2004
Disordered eating	Diagnosis of eating disorder (anorexia, bulimia, binge-eating disorder) by DSM-IV or DSM-V criteria	First-trimester BMI	Not specified	*N* = 1383; population-based sample of male and female adolescents followed from ages 14– 20	Cohort (Australia)	Each one-unit increase in maternal early pregnancy BMI increased odds of eating disorders in offspring by 11% [OR 1.10 (1.05–1.15)]	Allen *et al.*, 2013
	Child inhibited eating, secretive eating, overeating, and vomiting as reported by parents	Maternal BMI at 6-month postpartum	No	*N* = 216 newborn-parent triads (100 female, 116 male children), followed birth to age 5	Cross-sectional (USA)	MATOB, neonatal body mass, and feeding behaviors in first month of life were significantly predictive of emergence of disordered eating in childhood.	Stice *et al.*, 1999

Offspring morbidity	Specific outcome(s) examined	Maternal obesity risk factor[a]	Preterm offspring included?	Sample	Study design	Finding	Reference
						Risk increased annually through age 5	
	Infant energy consumption and food composition, mother and infant body composition, directly measured over a 24-h observation period	Maternal BMI and body composition at ~5-month postpartum	Not specified	*N* = 7 mother-infant dyads (4 obese and 3 normal weight mothers). Infant feeding behavior directly observed over 24 h	Subanalysis of a larger cohort (USA)	Infants of obese mothers consumed significantly more calories and over-consumed high-carbohydrate calories, compared with infants of normal weight mothers	Rising and Lifshitz, 2005
	Infant diet at 1 year (maternal report)	Maternal diet in pregnancy (maternal obesity not specifically evaluated). Obesity defined as BMI >25	Not specified	Population-based cohort, *N* = 10 762 mother-infant pairs. Infants born 1977–1979. Eating behaviors evaluated 9– 18 months (mean 12 months)	Cohort study (Sweden)	Overconsumption of sweets in pregnancy significantly associated with increased drive to overeat sweets in children at age 1. Maternal overweight and MATOB (BMI >25) also significantly associated with earlier introduction of sweet foods and beverages	Brekke *et al.*, 2007

ADHD, attention deficit hyperactivity disorder; ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview, Revised; ASD, autism spectrum disorder; BMI, body mass index; BPI, Behavior Problem Index; CBCL, Child Behavior Checklist; CI, confidence interval; CP, cerebral palsy; GDM, gestational diabetes; GWG, gestational weight gain; MATOB, maternal obesity; MCHAT, Modified Checklist for Autism in Toddlers; OR, odds ratio; PGDM, pre-gestational diabetes; SDQ, Strengths and Differences Questionnaire.

[a]Unless otherwise specified, BMI ≥30 kg/m^2 was used to define obesity, and excess/high GWG was defined as greater than the Institute of Medicine Criteria for pre-pregnancy BMI.