Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Published in final edited form as:

Front Neuroendocrinol. 2020 April ; 57: 100834. doi:10.1016/j.yfrne.2020.100834.

Maternal stressors and the developmental origins of neuropsychiatric risk

Seva G. Khambadkone[a,b], **Zachary A. Cordner**[a], **Kellie L.K. Tamashiro**[a,b,*]

[a]Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

[b]Cellular & Molecular Medicine Graduate Program, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

Abstract

The maternal environment during pregnancy is critical for fetal development and perinatal perturbations can prime offspring disease risk. Here, we briefly review evidence linking two well-characterized maternal stressors – psychosocial stress and infection – to increased neuropsychiatric risk in offspring. In the current climate of increasing obesity and globalization of the Western-style diet, maternal overnutrition emerges as a pressing public health concern. We focus our attention on recent epidemiological and animal model evidence showing that, like psychosocial stress and infection, maternal overnutrition can also increase offspring neuropsychiatric risk. Using lessons learned from the psychosocial stress and infection literature, we discuss how altered maternal and placental physiology in the setting of overnutrition may contribute to abnormal fetal development and resulting neuropsychiatric outcomes. A better understanding of converging pathophysiological pathways shared between stressors may enable development of interventions against neuropsychiatric illnesses that may be beneficial across stressors.

Keywords

Developmental origins of health and disease; Maternal stress; Maternal diet; Maternal obesity; Maternal immune activation; Inflammation; Allostatic load; Neuropsychiatric risk; Autism spectrum disorders; Schizophrenia; Anxiety; Depression

1. Introduction

The focus of this review is on neuropsychiatric risk associated with *in utero* exposure to maternal environmental stressors. The field of stress research has largely focused on the health effects of psychosocial or physiological stressors on hypothalamic–pituitary–adrenal (HPA) axis function in adult humans and animal model systems. Yet it has become increasingly clear that the HPA axis is not the only regulatory system sensitive to the effects of stress, and that these effects not only act on adults, but also occur throughout the lifespan.

*Corresponding author at: Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 618, Baltimore, MD 21205, USA., ktamashiro@jhmi.edu (K.L.K. Tamashiro).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The emergence of the concepts of “allostasis” and “allostatic overload” has broadened the definition of environmental stressors and study of pathophysiological mechanisms across a range of regulatory systems. In parallel, the developmental origins of health and disease (DOHaD) hypothesis has provided a developmental context.

The DOHaD, which emerged as a broadening of the “Barker hypothesis” and was named for epidemiologist David Barker, posits that early life environmental exposures can pattern risk for and severity of later life disease. Since Barker’s initial studies on the cardiovascular and metabolic effects of low birth weight (Barker, 2007; Barker and Osmond, 1986), epidemiological studies have associated exposure to under- and overnutrition (Armitage et al., 2008; Calkins and Devaskar, 2011), psychosocial stress and trauma (King et al., 2012; Van den Bergh et al., 2017; Vaiserman, 2015), infection (Bilbo and Schwarz, 2012; Izvolskaia et al., 2018), and toxins (Young et al., 2018; Drwal et al., 2019) during development with adverse effects on offspring across the lifespan and across a range of organ systems. To understand this mechanistically, we consider the concept of allostatic load. Pregnancy can be considered a state of allostasis, where the maternal-fetal dyad must balance dual goals of maternal and fetal stability across all organ systems, and across the developmental trajectory (Power and Schulkin, 2012). Additional environmental challenges during this time could result in allostatic overload that not only affects the health of the mother, but also impacts the health and resilience of the developing fetus.

It is clear that the developing brain, like other organ systems, is vulnerable to the effects of an adverse early environment (Giussani, 2011). Maternal adversity has been linked to a spectrum of neuropsychiatric problems – from neurodevelopmental diseases to psychiatric disorders to late life neurodegenerative disease – and some suggest that many brain diseases should be considered at least partially neurodevelopmental in origin (Levitt and Veenstra-VanderWeele, 2015; Heindel and Vandenberg, 2015). Here, we begin with an overview of the epidemiological and animal model evidence for two maternal stressors, psychosocial stress and infection, in priming offspring neuropsychiatric risk. In the current climate of increasing obesity and globalization of the Western-style diet model, maternal overnutrition is an emerging and pressing public health issue. We spend the majority of the review discussing the epidemiological and animal model evidence linking maternal overnutrition with increased neuropsychiatric risk in offspring. The overlapping neuropsychiatric consequences for offspring associated with these three maternal stressors suggests pathophysiological convergence, in line with our current understanding of allostatic overload. We discuss putative mechanisms linking maternal overnutrition and offspring neuropsychiatric risk, highlighting potential converging pathways and lessons learned from the infection and stress fields, and how existing model systems and current technologies may lead to better understanding of the multifactorial etiologies of neuropsychiatric illnesses. Finally, identification of common pathophysiological pathways shared between stressors opens the door to potential interventions that may be beneficial across stressors. We conclude with a brief discussion of potential future directions for the field and implications for intervention.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. Maternal psychosocial stress & immune activation

The contributions of perinatal stress (Van den Bergh et al., 2017; Bale, 2005; Bale et al., 2010; Boersma et al., 2014; Entringer et al., 2015; Chan et al., 2018) and maternal immune activation (Bilbo and Schwarz, 2012; Meyer et al., 2009; Solek et al., 2018; Meyer, 2014; Estes and McAllister, 2016) to offspring neuropsychiatric risk have been extensively reviewed. As such, we will touch on these topics only briefly as a framework to approach the less well-studied role of maternal overnutrition in neuropsychiatric vulnerability.

While it was long established that exposure to stress in adulthood negatively affects mental health, few studies evaluated risks of stress during gestation. Studies of children exposed *in utero* to disasters, like the 1986 Chernobyl accident or the 1988 Quebec ice storm, provided some of the first associations between perinatal stress exposure and neuropsychiatric outcomes (Boersma et al., 2014; Kolominsky et al., 1999; Laplante et al., 2008). Numerous other epidemiological studies have since expanded this association to prenatal psychosocial stressors of various type, duration, gestational timing, and severity, as well as a range of outcomes. However, recurring limitations in human studies include the difficulty in dissociating prenatal from early postnatal stress and reliance on retrospective self-report of stress experience, which may not adequately account for additional moderating variables.

In recent decades, a large number of studies using animal model systems have allowed for more controlled evaluation of the association between prenatal stress (PNS), timing and severity of stress exposure (Weinstock, 2017; Boersma and Tamashiro, 2015), and neuropsychiatric impairment in offspring. Broadly, offspring exposed to PNS demonstrate behavioral changes relevant to neuropsychiatric disease including but not limited to depression-like behavior (Morley-Fletcher et al., 2003; Morley-Fletcher et al., 2004), anxiety-like behavior (Vallee et al., 1997), alterations in stress coping style (Boersma et al., 2014), cognitive impairment (Vallee et al., 1999), decreased social interaction (Lee et al., 2007), and increased aggression (de Souza et al., 2013). While behavioral changes are consistently reported, phenotype appears highly dependent on type, degree, and timing of maternal stress, as well as sex and age of offspring at evaluation (Boersma et al., 2014). This variance highlights the importance of considering type and severity of stressor when interpreting offspring outcomes from PNS (Lesage et al., 2001), while also pointing to potential critical windows of exposure and thresholds of risk. Among the first investigations of time- and sex-dependent effects of PNS used mild chronic variable stress (CVS) applied to pregnant mice during early, mid, or late gestation (Mueller and Bale, 2006; Mueller and Bale, 2007; Mueller and Bale, 2008). For male offspring, only those exposed to early gestational PNS demonstrated neurobehavioral impairments as adults (Mueller and Bale, 2007; Mueller and Bale, 2008), which were accompanied by increased HPA axis responsivity (Mueller and Bale, 2008). Similarly, only those female offspring exposed to early gestational stress showed changes in behavior, but they exhibited improved learning performance, the opposite outcome compared to their male littermates (Mueller and Bale, 2007; Mueller and Bale, 2008). A growing body of work supports these findings suggesting that females may be less sensitive to the effects of PNS (Bale and Epperson, 2015). That is not to say that female offspring are completely resistant to stress. Instead, gestational stress, particularly in early development, seems to promote a more insidious risk for affective

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

disorders in females compared to risk of autism spectrum disorders (ASDs), behavioral, and intellectual disability in males (Bronson and Bale, 2016; Davis and Pfaff, 2014; Sandman et al., 2013). This dovetails with the sexual dimorphism in neuropsychiatric presentation: among males, the prevalence rates of neurodevelopmental disorders such as ASDs, attention deficit hyperactivity disorder (ADHD), and earlier-onset schizophrenia tend to be higher, whereas females have an increased prevalence of affective disorders (Davis and Pfaff, 2014; McLean et al., 2011; Hantsoo and Epperson, 2017; Fombonne, 2009; Bauermeister et al., 2007; Loomes et al., 2017; Zhang et al., 2012; Froehlich et al., 2007). Moving forward, understanding sexual dimorphism in the developing brain and further elucidating the effects of gestational timing and sex on offspring exposed to maternal stress remains an important direction for the field.

Several mechanisms have been proposed to underlie the relationship between maternal stress and offspring neuropsychiatric phenotypes. The most widely studied are alterations of the HPA axis, including potentially sex-specific changes in the circadian cycle of corticosterone (CORT), HPA axis responsivity, and impaired HPA axis negative feedback (Henry et al., 1994; Barbazanges et al., 1996; Maccari et al., 1995; Koehl et al., 1999). Within the brain, PNS is associated with decreased glucocorticoid and mineralocorticoid receptor binding capacities (Maccari et al., 1995; Koehl et al., 1999), which may alter hippocampal neurogenesis (Gould et al., 1992; Rodriguez et al., 1998; Montaron et al., 1999) and neuronal proliferation (Lemaire et al., 2000; Fujioka et al., 2006; Kawamura et al., 2006). Other mechanisms proposed to mediate the relationship between PNS and brain function include, but are not limited to, alterations in immune regulation and cytokines (Hantsoo et al., 2019), metabolic signaling (Tamashiro et al., 2009), placental function (Bronson and Bale, 2016), neurotrophic signaling (Ruf and Preissner, 2017), microbiome composition (Jasarevic et al., 2015), and epigenetic regulation (Boersma and Tamashiro, 2015), highlighting the diverse and complex actions of early life stress.

While many have focused on effects of PNS, others have studied another common early-life exposure, maternal immune activation (MIA), and there is now abundant evidence of overlapping neuropsychiatric risks between these two “stressors.” Though much of the early epidemiological work focused on links between maternal infection and schizophrenia (Mednick et al., 1988; Patterson, 2009; Meyer, 2014; Patterson, 2009) additional associations have been identified with ASDs (Patterson, 2011), developmental delay (Zerbo et al., 2013), cognitive impairment (Richetto and Riva, 2014; Knuesel et al., 2014), and affective disorders (Simanek and Meier, 2015; Murphy et al., 2017; Parboosing et al., 2013). Again similar to PNS, both clinical epidemiology and translational studies suggest that neuropsychiatric phenotypes associated with maternal infection appear to be influenced by gestational timing, duration, and severity of infectious stressor, as well as age and sex of the offspring (Brown and Meyer, 2018; Estes and McAllister, 2016; Schwartzer et al., 2013; Murray et al., 2019; de Souza et al., 2015; Giovanoli et al., 2015; Vernon et al., 2015). Overall, it appears that early immune stress leads to more extensive neuropsychological consequences, but that late gestation remains another critical and specific window for the effects of exposure (Meyer et al., 2007).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Mechanistically, recent evidence suggests that it is immune system activation, and not a specific pathogen, that is primarily responsible for negative effects on developing offspring (Estes and McAllister, 2016). This observation has been leveraged in pre-clinical studies that bypass specific pathogenic infection and instead directly activate the immune response with the viral mimetic polyinosinic:polycytidylic (poly[I:C]), the bacterial endotoxin lipopolysaccharide (LPS), or specific immune components such as cytokines. Doing so allows for study of generalizable and direct effects of MIA while tightly controlling the type, timing, duration, and intensity of the immune activation (Meyer et al., 2009; Brown and Meyer, 2018; Meyer et al., 2009). Offspring in these studies exhibit deficits in sensorimotor gating, attention, learning and memory, and social behavior, in addition to increased repetitive, anhedonic, and anxiety-like behaviors (Meyer, 2014; Estes and McAllister, 2016; Patterson, 2009; Knuesel et al., 2014). These changes have been linked to aberrations in brain structure and function including decreased cortical thickness, increased ventricular volume, and decreased regional volumes in the hippocampus, amygdala, and striatum (Estes and McAllister, 2016; Patterson, 2009; Piontkewitz et al., 2011). Emerging evidence suggests altered circuit connectivity and altered serotonergic, dopaminergic, and GABAergic signaling in some of these regions (Meyer et al., 2009; Estes and McAllister, 2016; Dickerson and Bilkey, 2013; Missault et al., 2019). At the synaptic level, reported changes include decreased dendritic spine density, shortened dendritic length, reductions in pre- and post-synaptic proteins, and deficits in synaptic transmission and long-term potentiation (Giovanoli et al., 2015; Choi et al., 2016; Coiro et al., 2015; Zhang and van Praag, 2015; Patrich et al., 2016). At the cellular level, there is evidence for altered neurogenesis and neuronal migration, as well as alterations in microglia and astroglia (Solek et al., 2018; de Souza et al., 2015; Zhang et al., 2018; Smolders et al., 2018; Prins et al., 2018; Liu et al., 2013; Oskvig et al., 2012).

While individual application of single immune factors has been shown to be sufficient to induce neuropsychiatric alterations (Smith et al., 2007; Ponzio et al., 2007), the immune system is in constant interplay with other biological systems including the placenta, HPA axis, gut microbiome, metabolism, oxidation, neurotrophic signaling, and epigenetic regulation, and changes within each of these systems are implicated in MIA (Estes and McAllister, 2016; Oskvig et al., 2012; Hsiao and Patterson, 2011; Udagawa and Hino, 2016; Gilmore et al., 2005; Babri et al., 2014; Reisinger et al., 2015; Simoes et al., 2018; Lammert et al., 2018). This reflects the complex nature of the etiology of neuropsychiatric risk, but it also points to commonalities between MIA and PNS in producing similar behavioral phenotypes – a concept we will return to at the end of this review.

3. Maternal overnutrition

3.1. Background and summarized clinical findings

While psychosocial stress and infection are among the most widely studied stressors experienced during pregnancy, another major stressor has emerged in the current climate of a global obesity epidemic: maternal overnutrition. Nearly two-thirds of women of reproductive age in the United States are overweight or obese, and rapidly climbing obesity rates in developing countries indicate that this is a worldwide public health problem (Flegal

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

et al., 2010; Hillemeier et al., 2011; Chen et al., 2018). Obesity and overweight are associated with a range of metabolic and cardiovascular comorbidities which, in pregnant women, increase risk for additional complications including pre-eclampsia and gestational diabetes mellitus (GDM) (Sohlberg et al., 2012; Mission et al., 2015; Stang and Huffman, 2016). Exposure to maternal obesity, high-energy diet, and associated metabolic consequences are consistently associated with a multitude of adverse health outcomes in offspring (Nguyen et al., 2015; Rivera et al., 2015; Maftei et al., 2015; Olson et al., 2009; Brekke et al., 2007), including neuropsychiatric disease (Rivera et al., 2015; Olfson et al., 2014; Boyle et al., 2011). Here we review epidemiological and animal model evidence for the association between these maternal conditions and offspring neuropsychiatric risk.

Epidemiological studies suggest a relationship between maternal overnutrition and both risk for and severity of several neurodevelopmental and psychiatric illnesses, including but not limited to ASDs, ADHD, affective disorders, and schizophrenia (Rivera et al., 2015) (Table 1). Maternal overnutrition is additionally associated with cognitive impairments in children and adolescents, and has been suggested to predispose the development of later-life cognitive dementias (Contu and Hawkes, 2017). However, it is important to acknowledge that across these studies there exists no consensus on how to determine or quantify “maternal overnutrition.” The most common determinations are based on body mass index (BMI, both pre- or post-pregnancy), weight gain during pregnancy (gestational weight gain, GWG), prepregnancy type 2 diabetes mellitus (T2DM), and the presence of gestational metabolic disorders including GDM (Rivera et al., 2015; Edlow, 2017). Given the high comorbidity and significant interplay between these conditions – and the resulting overlap in animal model systems used to investigate associated neuropsychiatric outcomes in offspring – we have grouped this discussion under “maternal overnutrition” as an umbrella terminology.

Despite a growing body of clinical evidence for a correlation between many of these markers of maternal metabolic state and adverse neuropsychiatric outcomes, not all studies support this. As an example, while several studies have linked high pre-pregnancy BMI with risk for ASD (Reynolds et al., 2014; Moss and Chugani, 2014; Krakowiak et al., 2012; Dodds et al., 2011; Getz et al., 2016), one study suggested that this association is due to residual confounds from familial risk factors (Gardner et al., 2015), and other studies found no association between BMI proximal to pregnancy onset and ASD (Bilder et al., 2013). GWG, while less studied, is consistently associated with ASD in all but one study (Reynolds et al., 2014), and numerous studies have identified metabolic complications prior to and during pregnancy, such as pre-existing diabetes, GDM, or hypertension, with ASD (Krakowiak et al., 2012; Dodds et al., 2011; Gardner et al., 2015; Bilder et al., 2013; Wallace et al., 2008). At least in part, these discrepancies likely arise from the fact that clinical studies are often difficult to control and confounders often difficult to identify. Animal models on the other hand, while less directly translatable, have allowed for more controlled studies aimed at disentangling the potential mechanistic players and pathways.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

3.2. Animal models

The majority of animal studies in this field use dietary manipulations that result in metabolic disturbances in the dam prior to and/or during pregnancy that can affect the developing fetus. These diets vary in their macronutrient content, but in general they are palatable, energy-dense, high in fat, and, in some cases, high in sugar (Winther et al., 2018; Zambrano and Nathanielsz, 2017; Musial et al., 2017; Mucellini et al., 2014; Bolton et al., 2017; Sun et al., 2012; Niculescu and Lupu, 2009; Tozuka et al., 2010; Wright et al., 2011). Diet exposure is usually continued until the end of gestation or lactation, at which point offspring are most commonly weaned onto a control diet. There is strong evidence that maternal overnutrition changes both behavior and brain physiology in offspring (Table 2). In the next several sections, behavioral and brain changes will be discussed as they relate to features of human neurodevelopmental and psychiatric disease.

3.2.1. Cognitive impairment—Cognitive impairment is a common feature of several neuropsychiatric and neurodevelopmental diseases, and in some cases is predictive of both severity and trajectory of disease course (Liu-Seifert et al., 2015; Pitteri et al., 2017; Treuer and Tohen, 2010; Stirling et al., 2003).

We have shown that as adults, male rat offspring from dams that were fed a 60% HFD during gestation and lactation are cognitively impaired. Male offspring exhibit slower learning acquisition and impaired memory retention in the Barnes maze as well as decreased novel object preference in the novel object recognition test in comparison to control offspring (Cordner et al., 2019). These behavioral changes were accompanied by decreased hippocampal brain-derived neurotrophic factor (BDNF), insulin receptor, and leptin receptor mRNA at weaning, and persistent downregulation of insulin receptor and leptin receptor in adulthood (Cordner et al., 2019). While BDNF is widely known for its neurotrophic properties, insulin and leptin signaling within the hippocampus are also key regulators of both neural development and function, and have been implicated in impaired cognition associated with adult consumption of HFDs (Van Doorn et al., 2017; Ferrario and Reagan, 2018; Cordner and Tamashiro, 2015). Evidence suggests that maternal overnutrition may additionally sensitize offspring to cognitive impairment associated with adult HFD exposure. Two studies have demonstrated impaired spatial cognition in maternal HFD rats that were also weaned onto HFD (White et al., 2009; Can et al., 2012). In one of these studies, White and colleagues found no significant deficit in maternal HFD rats who were weaned onto standard chow or in offspring of chow-fed dams weaned onto HFD, illustrating the potentially additive effects of both maternal and offspring exposure (White et al., 2009). Given the known comorbidity between obesity and cognitive impairment (Dye et al., 2017), it is critical for investigators to consider whether phenotypic outcomes are a *direct* consequence of developmental exposure to an insult (e.g. maternal overnutrition causes cognitive deficit) or *indirectly* related through a different, co-existing phenotype (e.g. maternal overnutrition causes offspring obesity which in turn results in cognitive deficits) (Tamashiro et al., 2009; Trandafir and Temneanu, 2016).

The lack of cognitive impairment seen from maternal HFD alone in White et al., in contrast to our findings, also highlights some inconsistency in the literature. Several studies have now

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

examined aspects of learning and memory in maternal HFD offspring with somewhat conflicting results. Like in the PNS and MIA literature, these discrepancies suggest how differences in experimental design – type, timing, and duration of maternal diet, species and strain differences, and how and when offspring are evaluated – can alter phenotypic outcomes. To the latter point, two studies thus far have found impaired spatial cognitive performance in adolescent but not adult offspring of HFD-fed dams. In one, adolescent offspring also exhibit increased peroxidized lipid accumulation, decreased BDNF, and impaired dendritic arborization within the hippocampus that is normalized by adulthood, suggesting a transient effect of maternal HFD (Tozuka et al., 2010). In the second study, while adult offspring from HFD-fed dams did not meet statistical criteria for cognitive impairment, the authors note that male offspring trend towards impaired performance (Robb et al., 2017). Given the findings by White and others, the question remains whether adult offspring from either study would demonstrate cognitive impairment if challenged with HFD themselves.

Other discrepancies include the nature of cognitive deficit, revealing nuances to seemingly similar outcomes. Two studies demonstrating impaired Morris water maze performance in adult offspring exposed to maternal HFD illustrate subtle variations in outcomes both classified as cognitive impairment (Moser et al., 2017; Page et al., 2014). In Page et al., offspring exhibited impaired retention but intact acquisition of learning, whereas Moser and colleagues found impaired acquisition with no deficits in retention upon acquisition. Other discrepancies in the literature are more striking, with at least one study finding improved spatial learning in adult offspring from HFD-fed dams (Bilbo and Tsang, 2010). Fewer studies have evaluated recognition memory, but with similarly inconsistent results, again perhaps reflecting differences in model and design. Consistent with our findings, in one study of mice exposed to maternal HFD, adult males exhibited impaired recognition memory, though this effect was absent in females (Graf et al., 2016). However, other studies of maternal overnutrition have found no deficits in offspring recognition memory (Winther et al., 2018; Moser et al., 2017).

The variation in the animal literature is reflected in the epidemiological literature. While several studies thus far have found an association between maternal overnutrition and cognitive problems in children, effect size and quality of cognitive deficit vary between studies (Basatemur et al., 2013; Bliddal et al., 2014; Brion et al., 2011; Casas et al., 2013; Craig et al., 2013; Eriksen et al., 2013; Hinkle et al., 2012; Huang et al., 2014; Li et al., 2016; Neggers et al., 2003; Krzeczkowski et al., 2018). Overnutrition in children is independently associated with reduced IQ, and while many of these studies adjusted for child BMI, BMI is only one index of metabolic dysregulation (Wraw et al., 2018). Given the known comorbidity between metabolic and cognitive impairment and the demonstrated influence of maternal metabolic dysregulation on the programming and regulation of offspring metabolism, dissociating direct and indirect maternal effects remains a priority.

3.2.2. Autism spectrum disorder (ASD)-like phenotypes—ASD in human patients has a considerably heterogeneous presentation largely characterized by impaired social interaction and patterns of restricted, repetitive behaviors (Ha et al., 2015). Female mice exposed to maternal HFD until weaning have decreased sociability compared to

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

controls, though this difference was not seen in male siblings or in females whose mothers were switched to a control diet upon delivery (Kang et al., 2014). Decreased sociability in female offspring was associated with increased microglial activation and levels of pro-inflammatory cytokines IL-1β and TNF-α within the brain, reminiscent of ASD-like behavior and associated cytokine changes in models of maternal immune activation (Estes and McAllister, 2016). In a similar model of murine HFD-induced maternal obesity, male offspring (females were not tested) display increased repetitive behavior and a complement of socially deficient behavior including fewer reciprocal interactions, decreased sociability, and no preference for social novelty (Buffington et al., 2016). Mechanistically, a synergistic interaction between oxytocin and dopamine is implicated in the processing of social cues (Modi and Young, 2012). These mice also demonstrated reduced oxytocin immunoreactivity in the paraventricular nucleus (PVN) of the hypothalamus and an absence of social interaction-induced long-term potentiation in ventral tegmental dopamine neurons, known projection targets for oxytocin-expressing PVN neurons (Melis et al., 2007). Taken together, these findings support the growing body of epidemiological evidence associating maternal overnutrition to ASD risk (Reynolds et al., 2014; Moss and Chugani, 2014; Krakowiak et al., 2012; Dodds et al., 2011; Getz et al., 2016; Gardner et al., 2015; Bilder et al., 2013; Wallace et al., 2008) and begin to link this risk to inflammatory and neuroendocrine mediated changes

3.2.3. Anxiety- and depression-like phenotypes—Several studies have associated maternal overnutrition with increased anxiety-like behavior in offspring (Wright et al., 2011; Bilbo and Tsang, 2010; Kang et al., 2014; Sasaki et al., 2013; Sasaki et al., 2014). Bilbo and Tsang found that adult male rat offspring exposed to maternal HFD swim faster within the MWM, suggesting an anxiety-like motivation to escape (Bilbo and Tsang, 2010). These animals also spent less time in the open arms of the EPM, supporting an anxiety-like phenotype. Female rats in this model did not exhibit anxiety-like behavior, and in fact several studies have demonstrated sexual dimorphism in the anxiety phenotype. These differences suggest sex effects in brain programming and its behavioral consequences, an assertion that appears to be true in other behavioral phenotypes associated with maternal overnutrition such as locomotor hyperactivity, but may also be indicative of variations in study design (Rivera et al., 2015; Kang et al., 2014; Sasaki et al., 2013). Few studies have evaluated females, and in studies that have, the female estrous cycle, which is known to affect behavior, is often not accounted for (Frye et al., 2000; D'Souza and Sadananda, 2017). There is also the possibility that some behavioral measures used to assess anxiety have different sensitivities in male versus female offspring. For example, Sasaki et al. found increased anxiety-like behavior in both male and female offspring of HFD dams, but this was specific to the elevated plus maze in females and the open field in males (Sasaki et al., 2013). In both males and females, increased anxiety-like behavior was accompanied by decreased baseline corticosterone, slower returns to baseline levels following an acute stress (restraint) challenge, increased gene expression of the glucocorticoid receptor within the amygdala, and altered gene expression of cytokines within limbic areas of the brain, suggesting a similar underlying physiology to sexually dimorphic anxiety-like behavioral phenotypes. In a follow up study, the same group found that as adolescents, male and female offspring of maternal HFD dams have decreased anxiety-like behavior, suggesting that

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

maternal overnutrition may have age-dependent influences on anxiety-like behavior (Sasaki et al., 2014). Fewer studies have evaluated depression-like behavior in offspring exposed to maternal overnutrition, though existing data suggest that maternal overnutrition may have a role in programming this set of behaviors as well. Two studies have found that as adults, rats exposed to maternal HFD exhibit depression-like behavior in the FST (Can et al., 2012; Giriko et al., 2013). Another study evaluating mild CVS in adult offspring exposed to maternal HFD found that maternal HFD sensitized offspring to stress-induced depression-like behavior, with stressed HFD offspring demonstrating reduced sucrose preference, decreased locomotor activity, and increased FST immobility in comparison to stressed offspring from dams fed a standard diet (Lin et al., 2015). In contrast, another group found that maternal HFD may actually mitigate stress-induced behavioral alterations in offspring exposed to early life stress, suggesting a potentially divergent interaction between discrete stressors across the course of development (Rincel et al., 2016).

Epidemiological studies suggest a link between maternal overnutrition and affective problems in children. To date multiple cohort studies have associated maternal overnutrition with increased internalizing pathology, including anxiety and depression symptomatology (Van Lieshout et al., 2013; Mina et al., 2017; Rodriguez, 2010; Robinson et al., 2013). Increasing maternal pre-pregnancy BMI attenuates the normal decline of internalizing symptoms across childhood and adolescence (Van Lieshout et al., 2013). While a positive association between maternal BMI and internalizing psychopathology emerged at age 8, this association increased in strength across childhood through age 17. These results suggest the continued potential for increased anxiety and depression in adults exposed to maternal HFD, but long-term prospective epidemiological studies on adult offspring remain to be conducted.

3.2.4. Schizophrenia-like phenotypes—Despite epidemiological evidence for increased schizophrenia risk in the offspring of obese mothers, few studies have examined models of maternal overnutrition in the context of schizophrenia-like behavior. Contrary to epidemiological data, one study in mouse dams fed HFD found facilitation of prepulse inhibition (PPI) in adult offspring, and no changes in cognition, social behavior, or locomotor behavior (Zieba et al., 2019). Another murine study also found improved PPI in adult offspring, however this was accompanied by cognitive impairment (Wolfrum and Peleg-Raibstein, 2018). It is possible that altered maternal care behavior during the lactation period may partially play into these results. In both studies, HFD exposure was continued until the end of lactation. We have previously shown in rats that dams fed HFD during gestation and lactation exhibit altered maternal care behavior, spending more time nursing their pups and doing so in a more optimal nursing posture (Purcell et al., 2011). In turn, while studies are limited, early-life maternal care appears to influence later-life sensorimotor gating. For example, one study in mice found that adult offspring of dams who spent less time engaged in pup-licking behavior during lactation exhibited impaired PPI compared to offspring of high pup-licking dams (Pedersen et al., 2011). While the limited evidence available creates a largely speculative discussion, it further highlights the importance of distinguishing between the prenatal and early postnatal environments.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In addition, the discrepancy between epidemiological work associating maternal overnutrition and schizophrenia and the limited animal literature suggests a gap that remains to be filled. Two cohort studies have associated elevated maternal BMI with multifold increased risk for schizophrenia in offspring (Jones et al., 1966; Schaefer et al., 2000), and one meta-analysis calculated that children of mothers with diabetes were over 7 times more likely to develop schizophrenia (Cannon et al., 2002). Kawai and colleagues report that schizophrenia risk increases by 24% for every maternal BMI unit increase in early pregnancy and 19% per unit in late pregnancy (Kawai et al., 2004). Considerable work remains to be done to evaluate schizophrenia-relevant phenotypes in animal models of overnutrition.

3.2.5. Summary and future directions—Maternal overnutrition has a significant long-term influence on brain function and behavior in offspring. Existing data suggest that maternal overnutrition is a risk factor for development of behavioral deficits consistent with a number of neuropsychiatric disorders. As with stress and infection, variation in outcomes could stem from differences in type and length of maternal exposure. As an example, obesity or HFD consumption during the pre-conception period alone has been shown to affect oocyte metabolism and morphology (Reynolds et al., 2015). In addition, the comorbidity between metabolic dysregulation and behavioral aberration calls to question whether behavioral phenotypes in offspring are due directly to maternal exposure or indirect, secondary to maternal programming of metabolic dysregulation in offspring. Future studies may be focused on sex differences, determining the degree of interdependence between cognitive and metabolic phenotypes, and determining critical periods of neuropsychiatric risk and resilience in response to maternal overnutrition. Despite these remaining questions, it is apparent that, like stress and infection, maternal overnutrition potentiates offspring neuropsychiatric risk. In the next sections, we examine putative mechanisms underlying this relationship.

4. Potential mechanisms linking maternal overnutrition and offspring neuropsychiatric outcomes

A range of mechanisms linking maternal nutrition to neuropsychiatric outcomes in offspring have been proposed. Like in both maternal psychosocial stress and maternal infection, these include changes to the HPA axis and neuroendocrine communication, metabolic hormones, immune regulation, placental structure and function, neurotrophic signaling, microbiome, and epigenetics. Here we will overview the rationale and evidence for some of the more well studied mechanisms and discuss how they may interact with one another (Table 2).

4.1. Metabolic regulation

Maternal overnutrition consistently results in metabolic impairment in the dam. We have shown that rat dams exposed to a HFD (60% kcal fat) during gestation only have increased plasma leptin by G10, lower plasma adiponectin by G14, impaired glucose tolerance and increased plasma insulin in a glucose tolerance test at G15, and increased adiposity at G21 (Song et al., 2017). Offspring in this model also exhibit metabolic impairment despite being weaned onto a standard chow diet (Tamashiro et al., 2009; Sun et al., 2012; Sun et al., 2014;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Sun et al., 2013). While overnutrition induced metabolic impairment in dams is likely important in patterning metabolic programming in offspring, evidence from our lab and others suggests it also has a role in patterning brain development and function (Cordner et al., 2019; Sun et al., 2014; Treesukosol et al., 2014). In addition to their role in energy balance and metabolism, metabolic hormones including insulin, leptin, and ghrelin have been shown to cross the blood brain barrier and act as key regulators of neural development and plasticity (Van Doorn et al., 2017; Ferrario and Reagan, 2018; Fadel et al., 2013; Bouret, 2017). Here we will discuss insulin and leptin as potential candidates linking maternal overnutrition and alterations in offspring brain and behavior.

The brain is densely populated with insulin receptors (Insr) (Abbott et al., 1999; Werther et al., 1987; Kar et al., 1993). Importantly, these receptors are not only found in areas of the brain involved in peripheral metabolic control, such as the hypothalamus, but also in regions relevant to cognition, motivation, and mood regulation (Ferrario and Reagan, 2018; Werther et al., 1987; Kar et al., 1993). These receptors bind peripheral insulin, which crosses the blood brain barrier throughout life (Banks et al., 2012; Banks, 2004). Receptor density is highest during early development, when their activation is postulated to play critical roles in a variety of functions including neurogenesis, neuronal maturation, and synaptogenesis (Kar et al., 1993; Chiu and Cline, 2010). In adulthood, regional insulin signaling is important not only for regulation of energy homeostasis (Schwartz et al., 2000), but also for behavior. Within the hippocampus, insulin signaling regulates structural and functional plasticity via facilitation of glutamatergic and GABAergic activity to promote cognition (Ferrario and Reagan, 2018). Recent evidence suggests that insulin signaling within the hippocampus and amygdala may also coordinate anxiety-like behavior; virally-mediated knockdown of insulin and insulin-like growth factor 1 receptors within either the hippocampus or amygdala increase anxiety-like behavior in adult mice (Soto et al., 2019). Finally, emerging evidence suggests a role for insulin signaling in coordinating neuro-transmitter activity within the nucleus accumbens – ventral tegmental area reward network (Ferrario and Reagan, 2018; Stouffer et al., 2015).

Exposure to overnutrition in adulthood is widely associated with central insulin resistance and resulting cognitive impairment (Fadel and Reagan, 2016). Recent evidence suggests that maternal overnutrition may program similar changes to offspring (Cordner et al., 2019; Schmitz et al., 2018). Insulin does not appear to cross the placental barrier, but glucose does. When glucose is transported in high amounts such as in the context of maternal overnutrition, it has been shown to increase production of insulin by the fetus, thereby exposing the developing fetal brain to a hyperinsulinemic environment (Sullivan et al., 2014; Ford et al., 2009; Oken and Gillman, 2003). Increased insulin action during this period may alter the development of neural circuitry involved in higher order processing (Sullivan et al., 2014). Further, it may prime for future insulin resistance within the offspring brain. A recent study demonstrated that maternal obesity in mice results in hippocampal insulin resistance within adult offspring along with decreased markers of neurogenesis, functional plasticity, and synaptic plasticity (Schmitz et al., 2018). We have shown that cognitive impairment in adult rat offspring exposed to maternal HFD during pregnancy and lactation is preceded by decreased hippocampal expression of *Insr* and glucose transporter 1 (*Slc2a1*) at P21, with

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

continued downregulation of *Insr* in adulthood, though we have not yet evaluated downstream markers of insulin resistance in the brain (Cordner et al., 2019).

Unlike insulin, maternal leptin can directly cross the placenta to act on the developing fetal brain (Luo et al., 2013; Djiane and Attig, 2008). Leptin acts through overlapping signaling cascades with insulin to promote neurodevelopment and cognitive function, and changes to leptin signaling during early life have been shown to alter the development of neural circuitry (Fadel and Reagan, 2016; Djiane and Attig, 2008; Bouret, 2010). We have shown that rat offspring exposed to maternal HFD also exhibit downregulation of hippocampal leptin receptor (*Lepr*) expression that persists into adulthood (Cordner et al., 2019). These animals additionally exhibit downregulated *Lepr* in the hypothalamus along with impaired signaling (Sun et al., 2012). It remains to be seen whether hippocampal expression changes in *Insr* and *Lepr* within the maternal HF diet model translate to signaling deficits, and the relative contributions of each to altered behavior.

4.2. Immune-related changes

Inflammatory mechanisms have a role in mediating maternal overnutrition-induced changes to brain and behavior. Obesity is considered a state of low-grade inflammation, and increasing adiposity is associated with greater circulating levels of both pro-inflammatory cytokines and markers of systemic inflammation (Hotamisligil, 2006; Howell and Powell, 2017; Segovia et al., 2014; Das, 2001). Overnutrition is additionally associated with inflammation at the level of the placenta, which may be stimulated not only through systemic inflammatory influences but also directly through activation of placental toll-like receptor (TLR)4 (Howell and Powell, 2017; Challier et al., 2008; Lackey and Olefsky, 2016; Basu et al., 2011; Roberts et al., 2011). TLR4, traditionally known to respond to bacterial endotoxin, also binds to and is activated by saturated fatty acids such as those found in HFDs, triggering an inflammatory cascade characterized by production and secretion of pro-inflammatory cytokines (Howell and Powell, 2017; Yang et al., 2016; Yang et al., 2015). In addition, the placenta expresses endogenous lipases, and in obesity possesses increased lipid storage capacity, suggesting that placental TLR4 activation in a state of maternal overnutrition may be induced by increases in both systemically circulating and local fatty acids (Pathmaperuma et al., 2010; Varastehpour et al., 2006; Qiao et al., 2015; Gauster et al., 2011). Obese women have a 3- to 9-fold increase in placental TLR4 expression, which positively correlates with pro-inflammatory interleukin(IL)-6 and IL-8 levels within both systemic circulation and the placenta (Yang et al., 2016). It is unclear to what degree systemic and placental inflammation contribute to fetal inflammation, though it is suggested that both may play a role. Evidence from MIA models suggests that both placental-derived and maternal circulating pro-inflammatory cytokines contribute to cytokine accumulation in the fetal brain (Ponzio et al., 2007; Hsiao and Patterson, 2011; Dahlgren et al., 2006).

While cytokines are well known for their roles in immune system regulation, strong evidence for their functions in neurodevelopment and function suggests that this may be a mechanism through which maternal overnutrition primes neuropsychiatric risk. First, cytokines have pleiotropic roles during normal neurodevelopment, including promotion of neurogenesis, neuronal migration, axon guidance, synapse formation, circuitry refinement,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and synaptic plasticity (Deverman and Patterson, 2009). These functions are under tight temporal and spatial regulation over the course of development, and altering the trajectory and magnitude of availability, localization, and balance between different cytokines could disrupt the neurodevelopmental trajectory. Increased pro-inflammatory cytokine levels within fetuses exposed to maternal overnutrition are associated with impaired cognition, increased anxiety-like behavior, and decreased social behavior (Rivera et al., 2015; White et al., 2009; Bilbo and Tsang, 2010; Sullivan et al., 2014; Sanders et al., 2014).

Second, an inflammatory milieu in early life may alter the development and function of astrocytes and microglia, the brain's resident immunocompetent cells that also perform essential neurodevelopmental functions including support of neuronal proliferation and differentiation, angiogenesis and vascular guidance, apoptosis and debris clearance, synaptogenesis, patterning, and pruning, myelination, and establishment of connectivity. Increased fetal brain inflammation associated with maternal overnutrition may prime microglia towards excessive production of pro-inflammatory cytokines and altered function, which may not only have consequences for the neurodevelopmental trajectory *in utero* but also persistent consequences, including increased sensitivity to future insult (Bilbo and Schwarz, 2009). For example, Edlow *et al.* found that maternal obesity in mice primes fetal microglia to overrespond to an immune challenge (Edlow et al., 2018). Bilbo and Tsang demonstrated further that offspring of maternal HFD-fed dams not only have increased microglial activation and Il-1β production within the hippocampus at birth, but also present as adults with increased hippocampal microglial activation at baseline and greater reactivity to an immune challenge, accompanied by increased anxiety-like behavior (Bilbo and Tsang, 2010). Maternal obesity increases proliferation of astrocytes within the hypothalamus, a relationship that is postulated to be mediated by IL-6 (Kim et al., 2016). Emerging evidence also implicates complement proteins and major histocompatibility complex class I molecules in mediating neurodevelopment and these may also be altered in maternal overnutrition (Estes and McAllister, 2015; Hsiao, 2013).

4.3. HPA axis and neuroendocrine hormones

The impact of early life insult on the development and function of the HPA axis has been demonstrated across several maternal stressors, including prenatal stress and immune activation. Neuroendocrine modulation may be a mechanism by which maternal overnutrition promotes neuropsychiatric risk in offspring (Sullivan et al., 2015). In response to stress, the PVN produces corticotropin releasing hormone (CRH) and arginine vasopressin, which stimulate the pituitary to release adrenocorticotropic hormone (ACTH) into systemic circulation. ACTH triggers the release of glucocorticoids from the adrenal cortex, which in turn act on brain regions including the pituitary, hypothalamus, hippocampus, and amygdala to regulate HPA axis activity and stress behavior. Extrahypothalamic populations of CRH in the amygdala and lateral bed nucleus of the stria terminalis are additionally thought to regulate fear and anxiety behavior (Schulkin et al., 1998). In addition to acute stress reactivity, aspects of the HPA axis demonstrate circadian biorhythmicity at baseline (Sage et al., 2001). It is suggested that maternal overnutrition affects both baseline HPA axis activity and stress responsivity in offspring, and that these changes may contribute to altered brain signaling and behavior (Sullivan et al., 2015).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In interpreting the mechanistic role of the HPA axis in behavioral outcomes within offspring exposed to maternal overnutrition, it is important to consider the developmental stage of the offspring at evaluation. In one study by Sasaki et al., adult offspring of rat dams fed a HFD during pregnancy and lactation exhibited decreased baseline corticosterone, increased glucocorticoid receptor expression in the amygdala, and increased anxiety-like behavior (Sasaki et al., 2013). In response to a restraint stress challenge, these offspring demonstrated a heightened corticosterone response followed by a slower return to baseline (Sasaki et al., 2013). Yet in a follow up study, this same group found that adolescent offspring exposed to the same maternal paradigm demonstrate decreased anxiety-like behavior and increased glucocorticoid receptor expression in the hippocampus but not the amygdala (Sasaki et al., 2014). Thus, these changes appear to be age-dependent, likely following the developmental trajectory of the HPA axis and maturation of feedback systems mediating corticosteroid sensitivity (McCormick et al., 2010; Romeo, 2013). Increased glucocorticoid receptor expression in the hippocampus is suggested to inhibit the HPA axis, whereas increased expression in the amygdala potentiates the stress response, demonstrating within this context the developmental and spatial relationship between HPA axis changes and behavior (Groeneweg et al., 2011). Additionally, it appears there may be a relationship between increased exploratory and risk-taking behaviors in adolescence and increased anxiety-like behaviors in adulthood, potentially implicating early stressor-induced alterations in the developmental trajectory of HPA regulation in different abnormal behaviors across development (Jacobson-Pick and Richter-Levin, 2010; Jacobson-Pick et al., 2011; McCormick and Green, 2013). Studies in neonate offspring are limited, but overall it appears that maternal overnutrition increases stress-induced corticosterone release and anxiety-like behavior in pre-weanlings, again reflecting the complexity of the developmental course (D'Asti et al., 2010; Abuaish et al., 2018). In conjunction with age, offspring sex is also of critical consideration as males and females have differential HPA axis responsivity at baseline as well as dimorphic development and maturation of stress circuitry beginning in gestation but continuing throughout life (Bale et al., 2010; Bale and Epperson, 2015).

The complex relationship between maternal overnutrition and neuroendocrine function not only exhibits spatial and temporal sensitivity in terms of developmental trajectory, but may also be highly dependent on type of maternal dietary intervention, diurnal rhythm for baseline measurements, and method of stress challenge. For example, Sasaki et al.'s finding of decreased basal corticosterone in adult offspring was conducted in the middle of the light cycle, whereas Walker and colleagues found increased basal corticosterone during the dark but not light cycle (Sasaki et al., 2013; Walker et al., 2008). Niu et al. sampled basal plasma corticosterone over a 24-h period and found an overall increase secondary to increases in both pulse frequency and amplitude of corticosterone secretion (Niu et al., 2019). Consistent with Sasaki's group, however, Niu and colleagues went on to demonstrate that offspring have heighted stress responsivity, exhibiting increased corticosterone levels and slower negative feedback following acute restraint stress, and additionally that they exhibit attenuated habituation to repeated restraint stress (Niu et al., 2019). Niu also showed that maternal HFD-induced stress sensitization was dependent on the amygdala (Niu et al., 2019). Overall, while methodological considerations appear to greatly influence findings,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

maternal HFD appears to change the developmental trajectory and function of the HPA axis in offspring, and these changes may underlie offspring changes to brain and behavior.

5. The placenta as an integrator and propagator of allostatic load

It is important to note that metabolic, immune, and neuroendocrine pathways exhibit significant co-regulation and crosstalk. Pregnancy is a state of normally occurring allostasis, where the body must maintain maternal health while changing physiological set points towards protection and resource allocation for the developing fetus (Power and Schulkin, 2012). These changes occur in temporal sequence across the metabolic, neuroendocrine, and immune systems, and changes within each system may influence one another. Disruption to any of these axes by maternal overnutrition may potentiate disruptions within the other systems towards a multisystem allostatic overload that can only be conveyed to the developing fetus through one organ: the placenta. The placenta serves as both messenger and sentinel between the mother and developing fetus, but its function in that role is adversely impacted by systemic dysregulation. For example, the placental inflammation associated with maternal overnutrition is not only the result of increased cytokine production from adipose tissue and direct effects of fatty acids at the placenta, but also likely impacted by dysregulation of metabolic hormones that can act as adipokine immune mediators. Leptin, high in obese pregnancy, has structural similarity to IL-6 and pro-inflammatory action (Iikuni et al., 2008; Lappas et al., 2005); adiponectin, low in obese pregnancy, has anti-inflammatory action (Ouchi and Walsh, 2007). Leptin and insulin also act through converging pathways with cytokine signaling (Iikuni et al., 2008; Shoelson et al., 2006). Thus, in gestational diabetes for example, inflammation at the placenta can promote both placental insulin resistance and maternal hyperglycemia, potentially increasing the metabolic dysregulation experienced by the fetus (Feng et al., 2016). In another example of placental pathway convergence, placental 11β-hydroxysteroid dehydrogenase type 2, an enzyme that inactivates glucocorticoids and protects the fetus from exposure to excess maternal glucocorticoids, is inhibited by pro-inflammatory cytokines, representing a mechanism by which maternal overnutrition-associated inflammation may increase fetal exposure to glucocorticoids (Kossintseva et al., 2006). Thus, the placenta is itself vulnerable to the effects of overload via alterations in its structure and function thereby amplifying an environment of dysregulation in the fetal compartment. In this section, we will use lessons learned from the stress and infection literature to comment on how maternal overnutrition may increase risk for offspring psychopathology by altering placental structural integrity, nutrient transfer, and neurotrophic communication (Table 2).

5.1. Structural integrity and nutrient transfer

Placental structure and sufficiency are critical for proper growth and development of the fetus. Placental insufficiency as seen in excessive maternal inflammation is associated with spontaneous miscarriage. Yet even mild disruptions of placental architecture can alter the capacity of the placenta to provide oxygen and nutrients to the fetus, changing the trajectory of fetal growth and development and potentially promoting neuropsychiatric risk. This mechanism has been studied more extensively in the context of MIA, where there is loss of placental integrity, decreased blood perfusion to the fetus, and perinatal brain damage.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Evidence suggests that maternal overnutrition may also alter placental cytoarchitecture and blood flow. In non-human primates (NHP), exposure to maternal HFD increases placental inflammation and decreases uterine blood flow volume even in lean, metabolically unimpaired mothers. In obese, hyperinsulinemic mothers, HFD exposure additionally reduces fetal compartment blood flow and induces placental infarctions, increasing frequency of stillbirth (Frias et al., 2011). Behaviorally, the offspring of HFD fed NHP mothers display greater anxiety despite weaning onto a low-fat control diet (Thompson et al., 2017). Studies in rodent models are consistent for placental structure changes, but mixed for blood flow capacity. Hayes et al. found that maternal HFD-induced obesity in rats increases placental inflammation, impairs vascular maturation, induces placental hypoxia, and compromises fetal growth and viability (Hayes et al., 2014), whereas Mark et al. showed decreased placental and fetal size and increased inflammation without changes to markers of vascular development (Mark et al., 2011). We have found that in rats provided maternal HFD the thickness of the placental labyrinth layer is reduced, suggesting reduced vascular capacity, but we have not examined hemodynamics in this model (Song et al., 2017). Even without frank changes to blood flow, reductions in placental thickness and integrity may alter the protective capacity of the placenta against systemic dysregulation.

The impact of maternal overnutrition on placental nutrient transfer has been more widely studied. The three major nutrient substrates for the growing fetus are glucose, lipids, and amino acids. Epidemiological and animal model studies suggest that maternal overnutrition may alter fetal exposure to these substrates by altering placental nutrient sensing, metabolism, and levels of nutrient transporters themselves (Song et al., 2017; Gallo et al., 2017). The variable interplay between reduced placental thickness and increased nutrient transporters may account for the range of aberrant birth weights associated with maternal overnutrition, from small for gestational age to macrosomia (Howell and Powell, 2017). This interplay may also reflect on the range of neuropsychiatric phenotypes associated with maternal overnutrition, as these nutrient substrates are also the building blocks for the developing brain.

5.2. Neurotrophic communication

In addition to its role as an arbiter of maternal signaling, the placenta is a significant source of neurotrophic signals to the developing fetal brain. Serotonin (5-HT) is produced by the placenta and is critical for normal brain development (Bonnin et al., 2011). In addition to its action in mood regulation, 5-HT signaling during fetal life has a significant role in promoting neurogenesis, neuronal migration, axon guidance, and synaptogenesis (Bonnin et al., 2011; Velasquez et al., 2013). Since the early fetal brain does not have the capacity to produce 5-HT, it is synthesized in the placenta from maternal l-tryptophan (TRP). Placental 5-HT is necessary for fetal brain development until the arrival of serotonergic projections from the dorsal raphe in mid-gestation (Bonnin et al., 2011). Too much or too little placental 5-HT availability during this early period leads to developmental alterations, including aberrant serotonergic outgrowth and abnormal development of the major thalamocortical axon tract (Goeden et al., 2016). A seminal study by Goeden et al. demonstrated that poly(I:C)-induced inflammation (a moderate immune challenge) in mouse dams increases placental synthesis of 5-HT via a transient increase in substrate availability of maternal TRP

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

to the placenta and subsequent increase in the expression and biosynthetic activity of placental tryptophan hydro-xylase 1 (TPH1). Increased placental output of 5-HT accumulates in the fetal forebrain and blunts serotonergic axon outgrowth from the hind-brain (Goeden et al., 2016). Proinflammatory cytokine treatment has additionally been shown to reduce survival of 5-HT neurons within the dorsal raphe and substantia nigra (Hochstrasser et al., 2011). Impairment of central serotonergic signaling is implicated across several neuropsychiatric illnesses associated with maternal overnutrition including ASD, ADHD, and mood disorders.

Indeed, animal models suggest that maternal overnutrition may impair development of the brain serotonergic system, resulting in lower 5-HT production and signaling. Non-human primates exposed to maternal HFD have reduced gene expression in the 5-HT synthesis pathway in the dorsal raphe and decreased serotonergic immunoreactivity in the prefrontal cortex, with concomitant anxiety and hyperactivity (Sullivan et al., 2015; Sullivan et al., 2010). Rats exposed to maternal HFD have increased expression of the 5HT1A receptor within the ventral hippocampus, maybe a compensatory response to reduced 5-HT availability, leading to increased anxiety-like behavior (Peleg-Raibstein et al., 2012).

In addition to potential consequences from overnutrition-induced placental inflammation, insulin appears to be a regulator of placentally sourced 5-HT by modulating cell surface localization of serotonin transporter (SERT) within the placenta, suggesting a potential convergence of mechanisms by which maternal overnutrition may alter the availability of 5-HT to the fetal brain and subsequent serotonergic system development (Murthi and Vaillancourt, 2019).

Importantly, 5-HT synthesis accounts for less than 5% of normal TRP metabolism, most of which occurs through the kynurenine (KYN) pathway (Gal and Sherman, 1980). Placental KYN pathway components are also upregulated in inflammation, and there is evidence for KYN system alterations within the brains of offspring exposed to maternal HFD, suggesting another possible pathway through which maternal overnutrition may promote neuropsychiatric risk (Winther et al., 2018; Schwarcz et al., 2012; Williams et al., 2017; Campbell et al., 2015; Manuelpillai et al., 2005). In the study by Goeden et al., in addition to augmenting TRP availability and upregulating TPH1 gene expression, maternal poly(I:C) injection also upregulated placental gene expression of indoleamine 2,3-dioxygenase (IDO1), responsible for converting maternal TRP to KYN, and subsequently increased KYN concentrations within the fetal brain (Goeden et al., 2016). In another, more severe model of intrauterine infection and inflammation, Williams et al. report upregulation of the placental KYN pathway and increased fetal brain accumulation of KYN (Williams et al., 2017). Here, the authors found decreased placental TRP and an increased KYN:TRP ratio, suggesting that TRP was shunted away from 5-HT synthesis pathway, potentially (placental 5-HT was not measured) resulting in a *decrease* in placental 5-HT availability for the developing fetal brain. There has been limited examination of the placental KYN pathway in maternal overnutrition, but one clinical study found a positive correlation between BMI and plasma KYN in pregnant women (Groer et al., 2018). High BMI was also associated with decreased plasma TRP, suggesting a potential reduction in substrate availability as well as possible shunting towards KYN production at the level of the placenta, though exact placental

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

changes remain to be determined (Groer et al., 2018). These examples illustrate that inflammation may have varying effects on placental 5-HT and that the severity of immune challenge or inflammatory response may dictate whether 5-HT production and signaling is decreased or increased. Nevertheless, such immune stressors ultimately lead to similar neuropsychiatric outcomes via an altered 5-HT system.

In addition to 5-HT, the placenta also produces BDNF which facilitates placental development and metabolism. Both maternal and placental BDNF cross the placental barrier into fetal circulation to reach the fetal brain (Kodomari et al., 2009; Antonakopoulos et al., 2018) where it plays a critical role in supporting neuronal survival, synaptic transmission, plasticity, growth, and repair (Reichardt, 2006). Maternal overnutrition decreases BDNF expression within the cortex and hippocampus of offspring, and the decrease in BDNF associates with cognitive impairment (Tozuka et al., 2010; Cordner and Tamashiro, 2015; Page et al., 2014; Arnold et al., 2014; Yamada-Goto et al., 2012). Maternal obesity has been shown to impair placental BDNF signaling (Prince et al., 2017). Additionally, elevated glucocorticoids associated with maternal stress has been shown to alter BDNF within the placenta and offspring brain (Suri and Vaidya, 2013; Kertes et al., 2017) and may thus contribute to maternal overnutrition and maternal stress associated behavioral deficits.

5.3. Sex differences and the placenta

The number of studies in which male and female offspring are both evaluated remain limited, but existing studies suggest sex differences in offspring behavior and physiology across stressors. Recent work has suggested that these differences may emerge in part at the level of the placenta, consistent with its role as an integrator and propagator of maternal stress. The placenta is sexually dimorphic, with differences emerging as early as the trophectoderm stage of embryogenesis (Bale, 2016; O'Connell et al., 2013; Sood et al., 2006). Studies across a variety of maternal insults have revealed sexually dimorphic placental responses to stressors (Bronson and Bale, 2016; Davis and Pfaff, 2014; Sandman et al., 2013; Mao et al., 2010; Howerton et al., 2013; Bronson and Bale, 2014; Dunn et al., 2011; Gabory et al., 2013; Clifton, 2010). In general, the XY placenta appears to be more sensitive to environmental change, whereas the XX placenta is relatively resistant (Bale, 2016), suggesting that such differential responses may, in part, underlie sexually divergent brain development and behavioral outcomes. As an example, Bale and colleagues have found that *O*-linked N-acetylglucosamine transferase (*OGT*), an X-linked gene expressed in the placenta, is decreased in response to maternal CVS during early gestation in both male and female offspring. Under normal conditions, *OGT* expression is lower in the XY placenta compared to XX placenta because OGT escapes X-inactivation and is biallelically expressed in XX placentas. Thus, maternal stress resulted in even lower *OGT* in stressed XY placentas compared to unstressed placentas from both sexes as well as stressed XX placentas (Howerton et al., 2013; Howerton and Bale, 2014). *OGT* plays a critical role in chromatin remodeling and reduced *OGT* was associated with significant transcriptional changes in the placenta and brain that was consistent with behavioral and physiological abnormalities in male, but not female, offspring exposed to maternal stress, as well as in unstressed mice with targeted placental deletion of *OGT* (Howerton et al., 2013; Howerton and Bale, 2014). The

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

OGT story thus illustrates one way in which the placenta may mediate sex-specific effects of gestational stress on offspring.

6. Final perspectives

It is now clear that diverse maternal stressors including psychosocial stress, infection, and overnutrition result in overlapping neuropsychiatric outcomes for offspring. Considering the shared outcomes across diverse stressors, some have started to investigate common etiologies, and evidence supporting this idea is growing. As has long been recognized in the adult stress literature, it is increasing clear that the concepts of allostatic load and allostatic overload apply to maternal stressors, with aberrant neurodevelopment and neuropsychiatric risks to offspring emerging from stress effects on interacting maternal regulatory systems, the placenta, and the developing fetal brain (Fig. 1).

Common risks and mechanisms across various stressors have attracted greater attention and the information gained will be critical in identifying potential interventions that could apply to a wide variety of developmental “stressors”. Collaboration across disciplines and innovations in design and analysis that can better account for the ways in which different stressors overlap and interact with each other will facilitate advancement in the field. Importantly, individuals exposed a particular stressor are often the same individuals at highest risk for facing other stressors, suggesting that successful interventions should also be broad in scale. As such, behavioral interventions may not only be more accessible to those at risk, but may also allow for more widespread mechanistic action, functioning across multiple systems to broadly promote neuropsychiatric resilience.

In the interest of translating findings to humans, pre-clinical studies that incorporate individual differences and experiences rather than simply single-variable group effects are needed. Thompson and colleagues recently utilized multivariate analysis in a non-human primate model of maternal overnutrition, concluding that maternal pre-pregnancy adiposity and gestational HFD consumption exert unique effects on offspring behavior (Thompson et al., 2018). Thompson’s work demonstrates the ability to utilize more sophisticated statistical modeling to go beyond single variable associations towards a more complex, nuanced understanding of underlying etiology. Although resources limit extensive collection of multisystem variables across all studies, more robust collaboration across disciplines and open-source reporting of raw data from individual studies may offer alternatives. Expanding such databases would significantly increase our ability to compare between studies and stressors, identify promising etiological pathways, and design and test interventions.

Acknowledgements

The authors thank Dr. Timothy H. Moran for enlightening conversations and his continual mentoring and guidance. This work was supported by the National Institutes of Health (NIH) HD093338 (S. G. K.), the Greif Family Scholar Fund (Z. A. C.), NIH MH108944 (K. L. T.), and the Dalio Philanthropies.

References

Abbott MA, Wells DG, Fallon JR, 1999 The insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses. J. Neurosci 19, 7300–7308. [PubMed: 10460236]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Abuaish S, Spinieli RL, McGowan PO, 2018 Perinatal high fat diet induces early activation of endocrine stress responsivity and anxiety-like behavior in neonates. Psychoneuroendocrinology 98, 11–21. [PubMed: 30086533]

Antonakopoulos N, Iliodromiti Z, Mastorakos G, Iavazzo C, Valsamakis G, Salakos N, Papageorghiou A, Margeli A, Kalantaridou S, Creatsas G, Deligeoroglou E, Vrachnis N, 2018 Association between brain-derived neurotrophic factor (BDNF) levels in 2(nd) trimester amniotic fluid and fetal development. Mediators Inflamm. 2018, 8476217. [PubMed: 30622436]

Armitage JA, Poston L, Taylor PD, 2008 Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity. Front. Horm. Res 36, 73–84. [PubMed: 18230895]

Arnold SE, Lucki I, Brookshire BR, Carlson GC, Browne CA, Kazi H, Bang S, Choi BR, Chen Y, McMullen MF, Kim SF, 2014 High fat diet produces brain insulin resistance, synaptodendritic abnormalities and altered behavior in mice. Neurobiol. Dis 67, 79–87. [PubMed: 24686304]

Babri S, Doosti MH, Salari AA, 2014 Strain-dependent effects of prenatal maternal immune activation on anxiety- and depression-like behaviors in offspring. Brain Behav. Immun 37, 164–176. [PubMed: 24326014]

Bale TL, 2005 Is mom too sensitive? Impact of maternal stress during gestation. Front. Neuroendocrinol 26, 41–49. [PubMed: 15862184]

Bale TL, 2016 The placenta and neurodevelopment: sex differences in prenatal vulnerability. Dialogues Clin. Neurosci 18, 459–464. [PubMed: 28179817]

Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ, 2010 Early life programming and neurodevelopmental disorders. Biol. Psychiatry 68, 314–319. [PubMed: 20674602]

Bale TL, Epperson CN, 2015 Sex differences and stress across the lifespan. Nat. Neurosci 18, 1413–1420. [PubMed: 26404716]

Banks WA, 2004 The source of cerebral insulin. Eur. J. Pharmacol 490, 5–12. [PubMed: 15094069]

Banks WA, Owen JB, Erickson MA, 2012 Insulin in the brain: there and back again. Pharmacol. Ther 136, 82–93. [PubMed: 22820012]

Barbazanges A, Piazza PV, Le Moal M, Maccari S, 1996 Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. J. Neurosci 16, 3943–3949. [PubMed: 8656288]

Barker DJ, 2007 The origins of the developmental origins theory. J. Int. Med 261, 412–417.

Barker DJ, Osmond C, 1986 Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1, 1077–1081. [PubMed: 2871345]

Basatemur E, Gardiner J, Williams C, Melhuish E, Barnes J, Sutcliffe A, 2013 Maternal prepregnancy BMI and child cognition: a longitudinal cohort study. Pediatrics 131, 56–63. [PubMed: 23230067]

Basu S, Haghiac M, Surace P, Challier JC, Guerre-Millo M, Singh K, Waters T, Minium J, Presley L, Catalano PM, Hauguel-de Mouzon S, 2011 Pregravid obesity associates with increased maternal endotoxemia and metabolic inflammation. Obesity (Silver Spring) 19 (2011) 476–82. [PubMed: 20930711]

Bauermeister JJ, Shrout PE, Chavez L, Rubio-Stipec M, Ramirez R, Padilla L, Anderson A, Garcia P, Canino G, 2007 ADHD and gender: are risks and sequela of ADHD the same for boys and girls? J. Child. Psychol. Psychiatry 48, 831–839. [PubMed: 17683455]

Bilbo SD, Schwarz JM, 2009 Early-life programming of later-life brain and behavior: a critical role for the immune system. Front. Behav. Neurosci 3, 14. [PubMed: 19738918]

Bilbo SD, Schwarz JM, 2012 The immune system and developmental programming of brain and behavior. Front. Neuroendocrinol 33, 267–286. [PubMed: 22982535]

Bilbo SD, Tsang V, 2010 Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB J. 24, 2104–2115. [PubMed: 20124437]

Bilder DA, Bakian AV, Viskochil J, Clark EA, Botts EL, Smith KR, Pimentel R, McMahon WM, Coon H, 2013 Maternal prenatal weight gain and autism spectrum disorders. Pediatrics 132, e1276–e1283. [PubMed: 24167172]

Bliddal M, Olsen J, Stovring H, Eriksen HL, Kesmodel US, Sorensen TI, Nohr EA, 2014 Maternal pre-pregnancy BMI and intelligence quotient (IQ) in 5-year-old children: a cohort based study. PLoS One 9, e94498. [PubMed: 24727836]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Boersma GJ, Moghadam AA, Cordner ZA, Tamashiro KL, 2014 Prenatal stress and stress coping style interact to predict metabolic risk in male rats. Endocrinology 155, 1302–1312. [PubMed: 24467745]

Boersma GJ, Tamashiro KL, 2015 Individual differences in the effects of prenatal stress exposure in rodents. Neurobiol. Stress 1, 100–108. [PubMed: 27589662]

Boersma GJ, Bale TL, Casanello P, Lara HE, Lucion AB, Suchecki D, Tamashiro KL, 2014 Long-term impact of early life events on physiology and behaviour. J. Neuroendocrinol 26, 587–602. [PubMed: 24690036]

Bolton JL, Wiley MG, Ryan B, Truong S, Strait M, Baker DC, Yang NY, Ilkayeva O, O'Connell TM, Wroth SW, Sanchez CL, Swamy G, Newgard C, Kuhn C, Bilbo SD, Simmons LA, 2017 Perinatal western-type diet and associated gestational weight gain alter postpartum maternal mood. Brain Behav 7, e00828. [PubMed: 29075574]

Bonnin A, Goeden N, Chen K, Wilson ML, King J, Shih JC, Blakely RD, Deneris ES, Levitt P, 2011 A transient placental source of serotonin for the fetal forebrain. Nature 472, 347–350. [PubMed: 21512572]

Bouret SG, 2010 Neurodevelopmental actions of leptin. Brain Res. 1350, 2–9. [PubMed: 20399755]

Bouret SG, 2017 Development of hypothalamic circuits that control food intake and energy balance. In: nd, and Harris RBS, (Eds.), Appetite and Food Intake: Central Control, Boca Raton (FL), pp. 135–154.

Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, Visser S, Kogan MD, 2011 Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics 127, 1034–1042. [PubMed: 21606152]

Brekke HK, van Odijk J, Ludvigsson J, 2007 Predictors and dietary consequences of frequent intake of high-sugar, low-nutrient foods in 1-year-old children participating in the ABIS study. Br. J. Nutr 97, 176–181. [PubMed: 17217574]

Brion MJ, Zeegers M, Jaddoe V, Verhulst F, Tiemeier H, Lawlor DA, Smith GD, 2011 Intrauterine effects of maternal prepregnancy overweight on child cognition and behavior in 2 cohorts. Pediatrics 127, e202–e211. [PubMed: 21187310]

Bronson SL, Bale TL, 2014 Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal antiinflammatory treatment. Endocrinology 155, 2635–2646. [PubMed: 24797632]

Bronson SL, Bale TL, 2016 The placenta as a mediator of stress effects on neurodevelopmental reprogramming. Neuropsychopharmacology 41, 207–218. [PubMed: 26250599]

Brown AS, Meyer U, 2018 Maternal immune activation and neuropsychiatric illness: a translational research perspective. Am. J. Psychiatry 175, 1073–1083. [PubMed: 30220221]

Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M, 2016 Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. Cell 165, 1762–1775. [PubMed: 27315483]

Calkins K, Devaskar SU, 2011 Fetal origins of adult disease. Curr. Probl. Pediatr. Adolesc. Health Care 41, 158–176. [PubMed: 21684471]

Campbell BM, Pocivavsek A, Notarangelo FM, Parachikova AI, 2015 The Role of Kynurenine Pathway Metabolites in Neuropsychiatric Disorders In: Mittal S (Ed.), Targetting the Broadly Pathogenic Kynurenine Pathway. Springer, Cham, pp. 241–254.

Can OD, Ulupinar E, Ozkay UD, Yegin B, Ozturk Y, 2012 The effect of simvastatin treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet. Behav. Pharmacol 23, 582–592. [PubMed: 22797467]

Cannon M, Jones PB, Murray RM, 2002 Obstetric complications and schizophrenia: historical and meta-analytic review. Am. J. Psychiatry 159, 1080–1092. [PubMed: 12091183]

Casas M, Chatzi L, Carsin AE, Amiano P, Guxens M, Kogevinas M, Koutra K, Lertxundi N, Murcia M, Rebagliato M, Riano I, Rodriguez-Bernal CL, Roumeliotaki T, Sunyer J, Mendez M, Vrijheid M, 2013 Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. Int. J. Epidemiol 42, 506–517. [PubMed: 23569191]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Challier JC, Basu S, Bintein T, Minium J, Hotmire K, Catalano PM, Hauguel-de Mouzon S, 2008 Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. Placenta 29 (2008) 274–81. [PubMed: 18262644]

Chan JC, Nugent BM, Bale TL, 2018 Parental advisory: maternal and paternal stress can impact offspring neurodevelopment. Biol. Psychiatry 83, 886–894. [PubMed: 29198470]

Chen C, Xu X, Yan Y, 2018 Estimated global overweight and obesity burden in pregnant women based on panel data model. PLoS One 13, e0202183. [PubMed: 30092099]

Chiu SL, Cline HT, 2010 Insulin receptor signaling in the development of neuronal structure and function. Neural. Dev 5, 7. [PubMed: 20230616]

Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, Hoeffer CA, Littman DR, Huh JR, 2016 The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 351, 933–939. [PubMed: 26822608]

Clifton VL, 2010 Review: Sex and the human placenta: mediating differential strategies of fetal growth and survival. Placenta 31 (Suppl), S33–S39. [PubMed: 20004469]

Coiro P, Padmashri R, Suresh A, Spartz E, Pendyala G, Chou S, Jung Y, Meays B, Roy S, Gautam N, Alnouti Y, Li M, Dunaevsky A, 2015 Impaired synaptic development in a maternal immune activation mouse model of neurodevelopmental disorders. Brain Behav. Immun 50, 249–258. [PubMed: 26218293]

Contu L, Hawkes CA, 2017 A review of the impact of maternal obesity on the cognitive function and mental health of the offspring. Int. J. Mol. Sci 18.

Cordner ZA, Tamashiro KL, 2015 Effects of high-fat diet exposure on learning & memory. Physiol. Behav 152, 363–371. [PubMed: 26066731]

Cordner ZA, Khambadkone SG, Boersma GJ, Song L, Summers TN, Moran TH, Tamashiro KLK, 2019 Maternal high-fat diet results in cognitive impairment and hippocampal gene expression changes in rat offspring. Exp. Neurol 318, 92–100. [PubMed: 31051155]

Craig WY, Palomaki GE, Neveux LM, Haddow JE, 2013 Maternal body mass index during pregnancy and offspring neurocognitive development. Obstet. Med 6, 20–25. [PubMed: 27757147]

Dahlgren J, Samuelsson AM, Jansson T, Holmang A, 2006 Interleukin-6 in the maternal circulation reaches the rat fetus in mid-gestation. Pediatr. Res 60, 147–151. [PubMed: 16864694]

Das UN, 2001 Is obesity an inflammatory condition? Nutrition 17, 953–966. [PubMed: 11744348]

D'Asti E, Long H, Tremblay-Mercier J, Grajzer M, Cunnane SC, Di Marzo V, Walker CD, 2010 Maternal dietary fat determines metabolic profile and the magnitude of endocannabinoid inhibition of the stress response in neonatal rat offspring. Endocrinology 151, 1685–1694. [PubMed: 20160134]

Davis EP, Pfaff D, 2014 Sexually dimorphic responses to early adversity: implications for affective problems and autism spectrum disorder. Psychoneuroendocrinology 49, 11–25. [PubMed: 25038479]

de Souza MA, Centenaro LA, Menegotto PR, Henriques TP, Bonini J, Achaval M, Lucion AB, 2013 Prenatal stress produces social behavior deficits and alters the number of oxytocin and vasopressin neurons in adult rats. Neurochem. Res 38, 1479–1489. [PubMed: 23624943]

de Souza DF, Wartchow KM, Lunardi PS, Brolese G, Tortorelli LS, Batassini C, Biasibetti R, Goncalves CA, 2015 Changes in astroglial markers in a maternal immune activation model of schizophrenia in wistar rats are dependent on sex. Front Cell Neurosci. 9, 489. [PubMed: 26733814]

Deverman BE, Patterson PH, 2009 Cytokines and CNS development. Neuron 64, 61–78. [PubMed: 19840550]

Dickerson DD, Bilkey DK, 2013 Aberrant neural synchrony in the maternal immune activation model: using translatable measures to explore targeted interventions. Front Behav. Neurosci 7, 217. [PubMed: 24409130]

Djiane J, Attig L, 2008 Role of leptin during perinatal metabolic programming and obesity. J. Physiol. Pharmacol 59 (Suppl 1), 55–63.

Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S, 2011 The role of prenatal, obstetric and neonatal factors in the development of autism. J. Autism Dev. Disord 41, 891–902. [PubMed: 20922473]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Drwal E, Rak A, Gregoraszczuk EL, 2019 Review: polycyclic aromatic hydrocarbons (PAHs)-Action on placental function and health risks in future life of newborns. Toxicology 411, 133–142. [PubMed: 30321648]

D'Souza D, Sadananda M, 2017 Estrous cycle phase-dependent changes in anxiety- and depression-like profiles in the late adolescent wistar-kyoto rat. Ann. Neurosci 24, 136–145. [PubMed: 28867895]

Dunn GA, Morgan CP, Bale TL, 2011 Sex-specificity in transgenerational epigenetic programming. Horm Behav. 59, 290–295. [PubMed: 20483359]

Dye L, Boyle NB, Champ C, Lawton C, 2017 The relationship between obesity and cognitive health and decline. Proc. Nutr. Soc 76, 443–454. [PubMed: 28889822]

Edlow AG, 2017 Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat Diagn 37, 95–110. [PubMed: 27684946]

Edlow AG, Glass RM, Smith CJ, Tran PK, James K, Bilbo S, 2018 Placental macrophages: a window into fetal microglial function in maternal obesity. Int. J. Dev. Neurosci

Entringer S, Buss C, Wadhwa PD, 2015 Prenatal stress, development, health and disease risk: a psychobiological perspective-2015 Curt Richter Award Paper. Psychoneuroendocrinology 62, 366–375. [PubMed: 26372770]

Eriksen HL, Kesmodel US, Underbjerg M, Kilburn TR, Bertrand J, Mortensen EL, 2013 Predictors of intelligence at the age of 5: family, pregnancy and birth characteristics, postnatal influences, and postnatal growth. PLoS One 8, e79200. [PubMed: 24236109]

Estes ML, McAllister AK, 2015 Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat. Rev. Neurosci 16, 469–486. [PubMed: 26189694]

Estes ML, McAllister AK, 2016 Maternal immune activation: implications for neuropsychiatric disorders. Science 353, 772–777. [PubMed: 27540164]

Fadel JR, Reagan LP, 2016 Stop signs in hippocampal insulin signaling: the role of insulin resistance in structural, functional and behavioral deficits. Curr. Opin. Behav. Sci 9, 47–54. [PubMed: 26955646]

Fadel JR, Jolivalt CG, Reagan LP, 2013 Food for thought: the role of appetitive peptides in age-related cognitive decline. Ageing Res. Rev 12, 764–776. [PubMed: 23416469]

Feng H, Su R, Song Y, Wang C, Lin L, Ma J, Yang H, 2016 Positive correlation between enhanced expression of TLR4/MyD88/NF-kappaB with insulin resistance in placentae of gestational diabetes mellitus. PLoS One 11, e0157185. [PubMed: 27340831]

Ferrario CR, Reagan LP, 2018 Insulin-mediated synaptic plasticity in the CNS: anatomical, functional and temporal contexts. Neuropharmacology 136, 182–191. [PubMed: 29217283]

Flegal KM, Carroll MD, Ogden CL, Curtin LR, 2010 Prevalence and trends in obesity among US adults, 1999–2008. JAMA 303, 235–241. [PubMed: 20071471]

Fombonne E, 2009 Epidemiology of pervasive developmental disorders. Pediatr. Res 65, 591–598. [PubMed: 19218885]

Ford SP, Zhang L, Zhu M, Miller MM, Smith DT, Hess BW, Moss GE, Nathanielsz PW, Nijland MJ, 2009 Maternal obesity accelerates fetal pancreatic beta-cell but not alpha-cell development in sheep: prenatal consequences. Am. J. Physiol. Regul. Integr. Comp. Physiol 297, R835–R843. [PubMed: 19605766]

Frias AE, Morgan TK, Evans AE, Rasanen J, Oh KY, Thornburg KL, Grove KL, 2011 Maternal high-fat diet disturbs uteroplacental hemodynamics and increases the frequency of stillbirth in a nonhuman primate model of excess nutrition. Endocrinology 152, 2456–2464. [PubMed: 21447636]

Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS, 2007 Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. Arch. Pediatr. Adolesc. Med 161, 857–864. [PubMed: 17768285]

Frye CA, Petralia SM, Rhodes ME, 2000 Estrous cycle and sex differences in performance on anxiety tasks coincide with increases in hippocampal progesterone and 3alpha,5alpha-THP. Pharmacol. Biochem. Behav 67, 587–596. [PubMed: 11164090]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Fujioka A, Fujioka T, Ishida Y, Maekawa T, Nakamura S, 2006 Differential effects of prenatal stress on the morphological maturation of hippocampal neurons. Neuroscience 141, 907–915. [PubMed: 16797130]

Gabory A, Roseboom TJ, Moore T, Moore LG, Junien C, 2013 Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics. Biol. Sex Differ 4, 5. [PubMed: 23514128]

Gal EM, Sherman AD, 1980 L-kynurenine: its synthesis and possible regulatory function in brain. Neurochem. Res 5, 223–239. [PubMed: 6154900]

Gallo LA, Barrett HL, Dekker Nitert M, 2017 Review: placental transport and metabolism of energy substrates in maternal obesity and diabetes. Placenta 54, 59–67. [PubMed: 27993398]

Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, Idring S, Dalman C, 2015 Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study. Int. J. Epidemiol 44, 870–883. [PubMed: 26045508]

Gauster M, Hiden U, van Poppel M, Frank S, Wadsack C, Hauguel-de Mouzon S, Desoye G, 2011 Dysregulation of placental endothelial lipase in obese women with gestational diabetes mellitus. Diabetes 60, 2457–2464. [PubMed: 21852675]

Getz KD, Anderka MT, Werler MM, Jick SS, 2016 Maternal pre-pregnancy body mass index and autism spectrum disorder among offspring: a population-based case-control study. Paediatr. Perinat. Epidemiol 30, 479–487. [PubMed: 27239935]

Gilmore JH, Jarskog LF, Vadlamudi S, 2005 Maternal poly I: C exposure during pregnancy regulates TNF alpha, BDNF, and NGF expression in neonatal brain and the maternal-fetal unit of the rat. J. Neuroimmunol 159, 106–112. [PubMed: 15652408]

Giovanoli S, Notter T, Richetto J, Labouesse MA, Vuillermot S, Riva MA, Meyer U, 2015 Late prenatal immune activation causes hippocampal deficits in the absence of persistent inflammation across aging. J Neuroinflammation 12, 221. [PubMed: 26602365]

Giriko CA, Andreoli CA, Mennitti LV, Hosoume LF, Souto Tdos S, Silva AV, Mendes-da-Silva C, 2013 Delayed physical and neurobehavioral development and increased aggressive and depression-like behaviors in the rat offspring of dams fed a high-fat diet. Int. J. Dev. Neurosci 31, 731–739. [PubMed: 24071008]

Giussani DA, 2011 The vulnerable developing brain. Proc. Natl. Acad. Sci. USA 108, 2641–2642. [PubMed: 21297035]

Goeden N, Velasquez J, Arnold KA, Chan Y, Lund BT, Anderson GM, Bonnin A, 2016 Maternal inflammation disrupts fetal neurodevelopment via increased placental output of serotonin to the fetal brain. J. Neurosci 36, 6041–6049. [PubMed: 27251625]

Gould E, Cameron HA, Daniels DC, Woolley CS, McEwen BS, 1992 Adrenal hormones suppress cell division in the adult rat dentate gyrus. J. Neurosci 12, 3642–3650. [PubMed: 1527603]

Graf AE, Lallier SW, Waidyaratne G, Thompson MD, Tipple TE, Hester ME, Trask AJ, Rogers LK, 2016 Maternal high fat diet exposure is associated with increased hepcidin levels, decreased myelination, and neurobehavioral changes in male offspring. Brain Behav. Immun 58, 369–378. [PubMed: 27519153]

Groeneweg FL, Karst H, de Kloet ER, Joels M, 2011 Rapid non-genomic effects of corticosteroids and their role in the central stress response. J. Endocrinol 209, 153–167. [PubMed: 21357682]

Groer M, Fuchs D, Duffy A, Louis-Jacques A, D'Agata A, Postolache TT, 2018 Associations among obesity, inflammation, and tryptophan catabolism in pregnancy. Biol. Res. Nurs 20, 284–291. [PubMed: 29141444]

Ha S, Sohn IJ, Kim N, Sim HJ, Cheon KA, 2015 Characteristics of brains in autism spectrum disorder: structure, function and connectivity across the lifespan. Exp. Neurobiol 24, 273–284. [PubMed: 26713076]

Hantsoo L, Epperson CN, 2017 Anxiety disorders among women: a female lifespan approach. Focus (Am Psychiatr Publ) 15, 162–172. [PubMed: 28966563]

Hantsoo L, Kornfield S, Anguera MC, Epperson CN, 2019 Inflammation: a proposed intermediary between maternal stress and offspring neuropsychiatric risk. Biol. Psychiatry 85, 97–106. [PubMed: 30314641]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Hayes EK, Tessier DR, Percival ME, Holloway AC, Petrik JJ, Gruslin A, Raha S, 2014 Trophoblast invasion and blood vessel remodeling are altered in a rat model of lifelong maternal obesity. Reprod. Sci 21, 648–657. [PubMed: 24155067]

Heindel JJ, Vandenberg LN, 2015 Developmental origins of health and disease: a paradigm for understanding disease cause and prevention. Curr. Opin. Pediatr 27, 248–253. [PubMed: 25635586]

Henry C, Kabbaj M, Simon H, Le Moal M, Maccari S, 1994 Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. J. Neuroendocrinol 6, 341–345. [PubMed: 7920600]

Hillemeier MM, Weisman CS, Chuang C, Downs DS, McCall-Hosenfeld J, Camacho F, 2011 Transition to overweight or obesity among women of reproductive age. J. Womens Health (Larchmt) 20, 703–710. [PubMed: 21599427]

Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ, 2012 Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. Int. J. Obes. (Lond) 36, 1312–1319. [PubMed: 22964791]

Hochstrasser T, Ullrich C, Sperner-Unterweger B, Humpel C, 2011 Inflammatory stimuli reduce survival of serotonergic neurons and induce neuronal expression of indoleamine 2,3-dioxygenase in rat dorsal raphe nucleus organotypic brain slices. Neuroscience 184, 128–138. [PubMed: 21501664]

Hotamisligil GS, 2006 Inflammation and metabolic disorders. Nat. 444, 860–867.

Howell KR, Powell TL, 2017 Effects of maternal obesity on placental function and fetal development. Reproduction 153, R97–R108. [PubMed: 27864335]

Howerton CL, Bale TL, 2014 Targeted placental deletion of OGT recapitulates the prenatal stress phenotype including hypothalamic mitochondrial dysfunction. Proc. Natl. Acad. Sci. USA 111, 9639–9644. [PubMed: 24979775]

Howerton CL, Morgan CP, Fischer DB, Bale TL, 2013 O-GlcNAc transferase (OGT) as a placental biomarker of maternal stress and reprogramming of CNS gene transcription in development. Proc. Natl. Acad. Sci. USA 110, 5169–5174. [PubMed: 23487789]

Hsiao EY, 2013 Immune dysregulation in autism spectrum disorder. Int. Rev. Neurobiol 113, 269–302. [PubMed: 24290389]

Hsiao EY, Patterson PH, 2011 Activation of the maternal immune system induces endocrine changes in the placenta via IL-6. Brain Behav. Immun 25, 604–615. [PubMed: 21195166]

Huang L, Yu X, Keim S, Li L, Zhang L, Zhang J, 2014 Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project. Int. J. Epidemiol 43, 783–792. [PubMed: 24569381]

Iikuni N, Lam QL, Lu L, Matarese G, La Cava A, 2008 Leptin and inflammation. Curr. Immunol. Rev 4, 70–79. [PubMed: 20198122]

Izvolskaia M, Sharova V, Zakharova L, 2018 Prenatal programming of neuroendocrine system development by lipopolysaccharide: long-term effects. Int. J. Mol. Sci 19.

Jacobson-Pick S, Audet MC, Nathoo N, Anisman H, 2011 Stressor experiences during the juvenile period increase stressor responsivity in adulthood: transmission of stressor experiences. Behav. Brain Res 216, 365–374. [PubMed: 20732357]

Jacobson-Pick S, Richter-Levin G, 2010 Differential impact of juvenile stress and corticosterone in juvenility and in adulthood, in male and female rats. Behav. Brain Res 214, 268–276. [PubMed: 20561965]

Jasarevic E, Rodgers AB, Bale TL, 2015 A novel role for maternal stress and microbial transmission in early life programming and neurodevelopment. Neurobiol. Stress 1, 81–88. [PubMed: 25530984]

Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P, 1998 Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. Am. J. Psychiat 155 (1998) 355–64. [PubMed: 9501745]

Kang SS, Kurti A, Fair DA, Fryer JD, 2014 Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. J. Neuroinflammation 11, 156. [PubMed: 25212412]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Kar S, Chabot JG, Quirion R, 1993 Quantitative autoradiographic localization of [125I]insulin-like growth factor I, [125I]insulin-like growth factor II, and [125I]insulin receptor binding sites in developing and adult rat brain. J. Comp. Neurol 333, 375–397. [PubMed: 8349849]

Kawai M, Minabe Y, Takagai S, Ogai M, Matsumoto H, Mori N, Takei N, 2004 Poor maternal care and high maternal body mass index in pregnancy as a risk factor for schizophrenia in offspring. Acta Psychiatr. Scand 110, 257–263. [PubMed: 15352926]

Kawamura T, Chen J, Takahashi T, Ichitani Y, Nakahara D, 2006 Prenatal stress suppresses cell proliferation in the early developing brain. Neuroreport 17, 1515–1518. [PubMed: 16957600]

Kertes DA, Bhatt SS, Kamin HS, Hughes DA, Rodney NC, Mulligan CJ, 2017 BNDF methylation in mothers and newborns is associated with maternal exposure to war trauma. Clin. Epigenetics 9, 68. [PubMed: 28680507]

Kim DW, Glendining KA, Grattan DR, Jasoni CL, 2016 Maternal obesity leads to increased proliferation and numbers of astrocytes in the developing fetal and neonatal mouse hypothalamus. Int. J. Dev. Neurosci 53, 18–25. [PubMed: 27326907]

King S, Dancause K, Turcotte-Tremblay AM, Veru F, Laplante DP, 2012 Using natural disasters to study the effects of prenatal maternal stress on child health and development. Birth Defects Res. C Embryo. Today 96, 273–288. [PubMed: 24203917]

Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, Toovey S, Prinssen EP, 2014 Maternal immune activation and abnormal brain development across CNS disorders. Nat. Rev. Neurol 10, 643–660. [PubMed: 25311587]

Kodomari I, Wada E, Nakamura S, Wada K, 2009 Maternal supply of BDNF to mouse fetal brain through the placenta. Neurochem. Int 54, 95–98. [PubMed: 19114070]

Koehl M, Darnaudery M, Dulluc J, Van Reeth O, Le Moal M, Maccari S, 1999 Prenatal stress alters circadian activity of hypothalamo-pituitary-adrenal axis and hippocampal corticosteroid receptors in adult rats of both gender. J. Neurobiol 40, 302–315. [PubMed: 10440731]

Kolominsky Y, Igumnov S, Drozdovitch V, 1999 The psychological development of children from Belarus exposed in the prenatal period to radiation from the Chernobyl atomic power plant. J. Child Psychol. Psychiatry 40, 299–305. [PubMed: 10188713]

Kossintseva I, Wong S, Johnstone E, Guilbert L, Olson DM, Mitchell BF, 2006 Proinflammatory cytokines inhibit human placental 11beta-hydroxysteroid dehydrogenase type 2 activity through Ca2+ and cAMP pathways. Am. J. Physiol. Endocrinol. Metab 290, E282–E288. [PubMed: 16174654]

Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, Hertz-Picciotto I, 2012 Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 129, e1121–e1128. [PubMed: 22492772]

Krzeczkowski JE, Boylan K, Arbuckle TE, Dodds L, Muckle G, Fraser W, Favotto LA, Van Lieshout RJ, Group MS, 2018 Neurodevelopment in 3–4year old children exposed to maternal hyperglycemia or adiposity in utero. Early Hum. Dev 125, 8–16. [PubMed: 30149267]

Lackey DE, Olefsky JM, 2016 Regulation of metabolism by the innate immune system. Nat. Rev. Endocrinol 12, 15–28. [PubMed: 26553134]

Lammert CR, Frost EL, Bolte AC, Paysour MJ, Shaw ME, Bellinger CE, Weigel TK, Zunder ER, Lukens JR, 2018 Cutting edge: critical roles for microbiota-mediated regulation of the immune system in a prenatal immune activation model of autism. J. Immunol 201, 845–850. [PubMed: 29967099]

Laplante DP, Brunet A, Schmitz N, Ciampi A, King S, 2008 Project Ice Storm: prenatal maternal stress affects cognitive and linguistic functioning in 5 1/2-year-old children. J. Am. Acad. Child Adolesc. Psychiatry 47, 1063–1072. [PubMed: 18665002]

Lappas M, Permezel M, Rice GE, 2005 Leptin and adiponectin stimulate the release of proinflammatory cytokines and prostaglandins from human placenta and maternal adipose tissue via nuclear factor-kappaB, peroxisomal proliferator-activated receptor-gamma and extracellularly regulated kinase 1/2. Endocrinology 146, 3334–3342. [PubMed: 15905315]

Lee PR, Brady DL, Shapiro RA, Dorsa DM, Koenig JI, 2007 Prenatal stress generates deficits in rat social behavior: Reversal by oxytocin. Brain Res. 1156, 152–167. [PubMed: 17540347]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Lemaire V, Koehl M, Le Moal M, Abrous DN, 2000 Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc. Natl. Acad. Sci. USA 97, 11032–11037. [PubMed: 11005874]

Lesage J, Blondeau B, Grino M, Breant B, Dupouy JP, 2001 Maternal under-nutrition during late gestation induces fetal overexposure to glucocorticoids and intrauterine growth retardation, and disturbs the hypothalamo-pituitary adrenal axis in the newborn rat. Endocrinology 142, 1692–1702. [PubMed: 11316731]

Levitt P, Veenstra-VanderWeele J, 2015 Neurodevelopment and the origins of brain disorders. Neuropsychopharmacology 40, 1–3. [PubMed: 25482168]

Li M, Fallin MD, Riley A, Landa R, Walker SO, Silverstein M, Caruso D, Pearson C, Kiang S, Dahm JL, Hong X, Wang G, Wang MC, Zuckerman B, Wang X, 2016 The association of maternal obesity and diabetes with autism and other developmental disabilities. Pediatrics 137, e20152206. [PubMed: 26826214]

Lin C, Shao B, Huang H, Zhou Y, Lin Y, 2015 Maternal high fat diet programs stress-induced behavioral disorder in adult offspring. Physiol. Behav 152, 119–127. [PubMed: 26423785]

Liu YH, Lai WS, Tsay HJ, Wang TW, Yu JY, 2013 Effects of maternal immune activation on adult neurogenesis in the subventricular zone-olfactory bulb pathway and olfactory discrimination. Schizophr. Res 151, 1–11. [PubMed: 24113206]

Liu-Seifert H, Siemers E, Price K, Han B, Selzler KJ, Henley D, Sundell K, Aisen P, Cummings J, Raskin J, Mohs R., 2015 Alzheimer's disease neuroimaging, cognitive impairment precedes and predicts functional impairment in mild Alzheimer's disease. J. Alzheimers Dis 47, 205–14. [PubMed: 26402769]

Loomes R, Hull L, Mandy WPL, 2017 What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J. Am. Acad. Child. Adolesc. Psychiatry 56, 466–474. [PubMed: 28545751]

Luo ZC, Nuyt AM, Delvin E, Fraser WD, Julien P, Audibert F, Girard I, Shatenstein B, Deal C, Grenier E, Garofalo C, Levy E, 2013 Maternal and fetal leptin, adiponectin levels and associations with fetal insulin sensitivity. Obesity (Silver Spring) 21, 210–216. [PubMed: 23505188]

Maccari S, Piazza PV, Kabbaj M, Barbazanges A, Simon H, Le Moal M, 1995 Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. J. Neurosci 15, 110–116. [PubMed: 7823121]

Maftei O, Whitrow MJ, Davies MJ, Giles LC, Owens JA, Moore VM, 2015 Maternal body size prior to pregnancy, gestational diabetes and weight gain: associations with insulin resistance in children at 9–10 years. Diabet. Med 32, 174–180. [PubMed: 25407383]

Manuelpillai U, Ligam P, Smythe G, Wallace EM, Hirst J, Walker DW, 2005 Identification of kynurenine pathway enzyme mRNAs and metabolites in human placenta: up-regulation by inflammatory stimuli and with clinical infection. Am. J. Obstet. Gynecol 192, 280–288. [PubMed: 15672037]

Mao J, Zhang X, Sieli PT, Falduto MT, Torres KE, Rosenfeld CS, 2010 Contrasting effects of different maternal diets on sexually dimorphic gene expression in the murine placenta. Proc. Natl. Acad. Sci. USA 107, 5557–5562. [PubMed: 20212133]

Mark PJ, Sisala C, Connor K, Patel R, Lewis JL, Vickers MH, Waddell BJ, Sloboda DM, 2011 A maternal high-fat diet in rat pregnancy reduces growth of the fetus and the placental junctional zone, but not placental labyrinth zone growth. J Dev Origins Health Disease 2, 63–70.

McCormick CM, Green MR, 2013 From the stressed adolescent to the anxious and depressed adult: investigations in rodent models. Neuroscience 249, 242–257. [PubMed: 22967838]

McCormick CM, Mathews IZ, Thomas C, Waters P, 2010 Investigations of HPA function and the enduring consequences of stressors in adolescence in animal models. Brain Cogn 72, 73–85. [PubMed: 19616355]

McLean CP, Asnaani A, Litz BT, Hofmann SG, 2011 Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J. Psychiatr. Res 45, 1027–1035. [PubMed: 21439576]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Mednick SA, Machon RA, Huttunen MO, Bonett D, 1988 Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch. Gen. Psychiatry 45, 189–192. [PubMed: 3337616]

Melis MR, Melis T, Cocco C, Succu S, Sanna F, Pillolla G, Boi A, Ferri GL, Argiolas A, 2007 Oxytocin injected into the ventral tegmental area induces penile erection and increases extracellular dopamine in the nucleus accumbens and paraventricular nucleus of the hypothalamus of male rats. Eur. J. Neurosci 26, 1026–1035. [PubMed: 17672853]

Meyer U, 2014 Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. Biol. Psychiatry 75, 307–315. [PubMed: 23938317]

Meyer U, Yee BK, Feldon J, 2007 The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? Neuroscientist 13, 241–256. [PubMed: 17519367]

Meyer U, Feldon J, Fatemi SH, 2009 In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. Neurosci. Biobehav. Rev 33, 1061–1079. [PubMed: 19442688]

Mina TH, Lahti M, Drake AJ, Raikkonen K, Minnis H, Denison FC, Norman JE, Reynolds RM, 2017 Prenatal exposure to very severe maternal obesity is associated with adverse neuropsychiatric outcomes in children. Psychol. Med 47, 353–362. [PubMed: 27776561]

Missault S, Anckaerts C, Ahmadoun S, Blockx I, Barbier M, Bielen K, Shah D, Kumar-Singh S, De Vos WH, Van der Linden A, Dedeurwaerdere S, Verhoye M, 2019 Hypersynchronicity in the default mode-like network in a neurodevelopmental animal model with relevance for schizophrenia. Behav. Brain Res 364, 303–316. [PubMed: 30807809]

Mission JF, Marshall NE, Caughey AB, 2015 Pregnancy risks associated with obesity. Obstet. Gynecol. Clin. North Am 42, 335–353. [PubMed: 26002170]

Modi ME, Young LJ, 2012 The oxytocin system in drug discovery for autism: animal models and novel therapeutic strategies. Horm. Behav 61, 340–350. [PubMed: 22206823]

Montaron MF, Petry KG, Rodriguez JJ, Marinelli M, Aurousseau C, Rougon G, Le Moal M, Abrous DN, 1999 Adrenalectomy increases neurogenesis but not PSANCAM expression in aged dentate gyrus. Eur. J. Neurosci 11, 1479–1485. [PubMed: 10103142]

Morley-Fletcher S, Darnaudery M, Koehl M, Casolini P, Van Reeth O, Maccari S, 2003 Prenatal stress in rats predicts immobility behavior in the forced swim test. Effects of a chronic treatment with tianeptine. Brain Res 989, 246–251. [PubMed: 14556947]

Morley-Fletcher S, Darnaudery M, Mocaer E, Froger N, Lanfumey L, Laviola G, Casolini P, Zuena AR, Marzano L, Hamon M, Maccari S, 2004 Chronic treatment with imipramine reverses immobility behaviour, hippocampal corticosteroid receptors and cortical 5-HT(1A) receptor mRNA in prenatally stressed rats. Neuropharmacology 47, 841–847. [PubMed: 15527818]

Moser VC, McDaniel KL, Woolard EA, Phillips PM, Franklin JN, Gordon CJ, 2017 Impacts of maternal diet and exercise on offspring behavior and body weights. Neurotoxicol. Teratol 63, 46–50. [PubMed: 28757311]

Moss BG, Chugani DC, 2014 Increased risk of very low birth weight, rapid postnatal growth, and autism in underweight and obese mothers. Am. J. Health Promot 28, 181–188. [PubMed: 23875984]

Mucellini AB, Goularte JF, de Araujo da Cunha AC, Caceres RC, Noschang C, da Silva Benetti C, Silveira PP, Sanvitto GL, 2014 Effects of exposure to a cafeteria diet during gestation and after weaning on the metabolism and body weight of adult male offspring in rats. Br. J. Nutr 111, 1499–506. [PubMed: 24330855]

Mueller BR, Bale TL, 2006 Impact of prenatal stress on long term body weight is dependent on timing and maternal sensitivity. Physiol. Behav 88, 605–614. [PubMed: 16828814]

Mueller BR, Bale TL, 2007 Early prenatal stress impact on coping strategies and learning performance is sex dependent. Physiol. Behav 91, 55–65. [PubMed: 17367828]

Mueller BR, Bale TL, 2008 Sex-specific programming of offspring emotionality after stress early in pregnancy. J. Neurosci 28, 9055–9065. [PubMed: 18768700]

Murphy SK, Fineberg AM, Maxwell SD, Alloy LB, Zimmermann L, Krigbaum NY, Cohn BA, Drabick DAG, Ellman LM, 2017 Maternal infection and stress during pregnancy and depressive symptoms in adolescent offspring. Psychiatry Res. 257, 102–110. [PubMed: 28750213]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Murray KN, Edye ME, Manca M, Vernon AC, Oladipo JM, Fasolino V, Harte MK, Mason V, Grayson B, McHugh PC, Knuesel I, Prinssen EP, Hager R, Neill JC, 2019 Evolution of a maternal immune activation (mIA) model in rats: early developmental effects. Brain Behav. Immun 75, 48–59. [PubMed: 30218784]

Murthi P, Vaillancourt C, 2019 Placental serotonin systems in pregnancy metabolic complications associated with maternal obesity and gestational diabetes mellitus. Biochim Biophys. Acta Mol. Basis Dis

Musial B, Vaughan OR, Fernandez-Twinn DS, Voshol P, Ozanne SE, Fowden AL, Sferruzzi-Perri AN, 2017 A Western-style obesogenic diet alters maternal metabolic physiology with consequences for fetal nutrient acquisition in mice. J. Physiol 595, 4875–4892. [PubMed: 28382681]

Neggers YH, Goldenberg RL, Ramey SL, Cliver SP, 2003 Maternal prepregnancy body mass index and psychomotor development in children. Acta Obstet. Gynecol. Scand 82, 235–240. [PubMed: 12694119]

Nguyen MU, Wallace MJ, Pepe S, Menheniott TR, Moss TJ, Burgner D, 2015 Perinatal inflammation: a common factor in the early origins of cardiovascular disease? Clin. Sci. (Lond) 129, 769–784. [PubMed: 26223841]

Niculescu MD, Lupu DS, 2009 High fat diet-induced maternal obesity alters fetal hippocampal development. Int. J. Dev. Neurosci 27, 627–633. [PubMed: 19695321]

Niu X, Wu X, Ying A, Shao B, Li X, Zhang W, Lin C, Lin Y, 2019 Maternal high fat diet programs hypothalamic-pituitary-adrenal function in adult rat offspring. Psychoneuroendocrinology 102, 128–138. [PubMed: 30544004]

O'Connell BA, Moritz KM, Walker DW, Dickinson H, 2013 Sexually dimorphic placental development throughout gestation in the spiny mouse (Acomys cahirinus). Placenta 34, 119–126. [PubMed: 23260227]

Oken E, Gillman MW, 2003 Fetal origins of obesity. Obes. Res 11, 496–506. [PubMed: 12690076]

Olfson M, Blanco C, Wang S, Laje G, Correll CU, 2014 National trends in the mental health care of children, adolescents, and adults by office-based physicians. JAMA Psychiatry 71, 81–90. [PubMed: 24285382]

Olson CM, Strawderman MS, Dennison BA, 2009 Maternal weight gain during pregnancy and child weight at age 3 years. Mat. Child Health J 13, 839–846.

Oskvig DB, Elkahloun AG, Johnson KR, Phillips TM, Herkenham M, 2012 Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. Brain. Behav. Immun 26, 623–634. [PubMed: 22310921]

Ouchi N, Walsh K, 2007 Adiponectin as an anti-inflammatory factor. Clin. Chim. Acta 380, 24–30. [PubMed: 17343838]

Page KC, Jones EK, Anday EK, 2014 Maternal and postweaning high-fat diets disturb hippocampal gene expression, learning, and memory function. Am. J. Physiol. Regul. Integr. Comp. Physiol 306, R527–R537. [PubMed: 24523341]

Parboosing R, Bao Y, Shen L, Schaefer CA, Brown AS, 2013 Gestational influenza and bipolar disorder in adult offspring. JAMA Psychiatry 70, 677–685. [PubMed: 23699867]

Pathmaperuma AN, Mana P, Cheung SN, Kugathas K, Josiah A, Koina ME, Broomfield A, Delghingaro-Augusto V, Ellwood DA, Dahlstrom JE, Nolan CJ, 2010 Fatty acids alter glycerolipid metabolism and induce lipid droplet formation, syncytialisation and cytokine production in human trophoblasts with minimal glucose effect or interaction. Placenta 31, 230–239. [PubMed: 20089301]

Patrich E, Piontkewitz Y, Peretz A, Weiner I, Attali B, 2016 Maternal immune activation produces neonatal excitability defects in offspring hippocampal neurons from pregnant rats treated with poly I:C. Sci. Rep 6, 19106. [PubMed: 26742695]

Patterson PH, 2009 Immune involvement in schizophrenia and autism: etiology, pathology and animal models. Behav. Brain Res 204, 313–321. [PubMed: 19136031]

Patterson PH, 2011 Maternal infection and immune involvement in autism. Trends Mol. Med 17, 389–394. [PubMed: 21482187]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Pedersen CA, Vadlamudi S, Boccia ML, Moy SS, 2011 Variations in maternal behavior in C57BL/6J mice: behavioral comparisons between adult offspring of high and low pup-licking mothers. Front. Psychiatry 2, 42. [PubMed: 21808624]

Peleg-Raibstein D, Luca E, Wolfrum C, 2012 Maternal high-fat diet in mice programs emotional behavior in adulthood. Behav. Brain Res 233, 398–404. [PubMed: 22633920]

Piontkewitz Y, Arad M, Weiner I, 2011 Risperidone administered during asymptomatic period of adolescence prevents the emergence of brain structural pathology and behavioral abnormalities in an animal model of schizophrenia. Schizophr. Bull 37, 1257–1269. [PubMed: 20439320]

Pitteri M, Romualdi C, Magliozzi R, Monaco S, Calabrese M, 2017 Cognitive impairment predicts disability progression and cortical thinning in MS: An 8-year study. Mult. Scler 23, 848–854. [PubMed: 27527906]

Ponzio NM, Servatius R, Beck K, Marzouk A, Kreider T, 2007 Cytokine levels during pregnancy influence immunological profiles and neurobehavioral patterns of the offspring. Ann N Y Acad. Sci 1107, 118–128. [PubMed: 17804539]

Power ML, Schulkin J, 2012 Maternal obesity, metabolic disease, and allostatic load. Physiol. Behav 106, 22–28. [PubMed: 21939681]

Prince CS, Maloyan A, Myatt L, 2017 Maternal obesity alters brain derived neurotrophic factor (BDNF) signaling in the placenta in a sexually dimorphic manner. Placenta 49, 55–63. [PubMed: 28012455]

Prins JR, Eskandar S, Eggen BJL, Scherjon SA, 2018 Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? J. Reprod. Immunol 126, 18–22. [PubMed: 29421625]

Purcell RH, Sun B, Pass LL, Power ML, Moran TH, Tamashiro KL, 2011 Maternal stress and high-fat diet effect on maternal behavior, milk composition, and pup ingestive behavior. Physiol. Behav 104, 474–479. [PubMed: 21605577]

Qiao L, Guo Z, Bosco C, Guidotti S, Wang Y, Wang M, Parast M, Schaack J, Hay WW Jr., Moore TR, Shao J, 2015 Maternal high-fat feeding increases placental lipoprotein lipase activity by reducing SIRT1 expression in mice. Diabetes 64, 3111–3120. [PubMed: 25948680]

Reichardt LF, 2006 Neurotrophin-regulated signalling pathways. Philos. Trans. R Soc. Lond. B Biol. Sci 361, 1545–1564. [PubMed: 16939974]

Reisinger S, Khan D, Kong E, Berger A, Pollak A, Pollak DD, 2015 The poly(I:C)-induced maternal immune activation model in preclinical neuropsychiatric drug discovery. Pharmacol. Ther 149, 213–226. [PubMed: 25562580]

Reynolds KA, Boudoures AL, Chi MM, Wang Q, Moley KH, 2015 Adverse effects of obesity and/or high-fat diet on oocyte quality and metabolism are not reversible with resumption of regular diet in mice. Reprod. Fertil. Dev 27, 716–724. [PubMed: 25775080]

Reynolds LC, Inder TE, Neil JJ, Pineda RG, Rogers CE, 2014 Maternal obesity and increased risk for autism and developmental delay among very preterm infants. J. Perinatol 34, 688–692. [PubMed: 24811227]

Richetto J, Riva MA, 2014 Prenatal maternal factors in the development of cognitive impairments in the offspring. J Reprod Immunol 104–105, 20–25.

Rincel M, Lepinay AL, Delage P, Fioramonti J, Theodorou VS, Laye S, Darnaudery M, 2016 Maternal high-fat diet prevents developmental programming by early-life stress. Transl. Psychiatry 6, e966. [PubMed: 27898075]

Rivera HM, Christiansen KJ, Sullivan EL, 2015 The role of maternal obesity in the risk of neuropsychiatric disorders. Front. Neurosci 9, 194. [PubMed: 26150767]

Robb JL, Messa I, Lui E, Yeung D, Thacker J, Satvat E, Mielke JG, 2017 A maternal diet high in saturated fat impairs offspring hippocampal function in a sexspecific manner. Behav. Brain. Res 326, 187–199. [PubMed: 28259676]

Roberts KA, Riley SC, Reynolds RM, Barr S, Evans M, Statham A, Hor K, Jabbour HN, Norman JE, Denison FC, 2011 Placental structure and inflammation in pregnancies associated with obesity. Placenta 32, 247–254. [PubMed: 21232790]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Robinson M, Zubrick SR, Pennell CE, Van Lieshout RJ, Jacoby P, Beilin LJ, Mori TA, Stanley FJ, Newnham JP, Oddy WH, 2013 Pre-pregnancy maternal overweight and obesity increase the risk for affective disorders in offspring. J. Dev. Orig Health Dis 4, 42–48. [PubMed: 25080181]

Rodriguez A, 2010 Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. J. Child. Psychol. Psychiatry 51, 134–143. [PubMed: 19674195]

Rodriguez JJ, Montaron MF, Petry KG, Aurousseau C, Marinelli M, Premier S, Rougon G, Le Moal M, Abrous DN, 1998 Complex regulation of the expression of the polysialylated form of the neuronal cell adhesion molecule by glucocorticoids in the rat hippocampus. Eur. J. Neurosci 10, 2994–3006. [PubMed: 9758169]

Romeo RD, 2013 The teenage brain: the stress response and the adolescent brain. Curr. Dir. Psychol. Sci 22, 140–145. [PubMed: 25541572]

Ruf W, Preissner KT, 2017 State of the Art 2017. J. Thromb. Haemost 15, 1239. [PubMed: 28589662]

Sage D, Maurel D, Bosler O, 2001 Involvement of the suprachiasmatic nucleus in diurnal ACTH and corticosterone responsiveness to stress. Am. J. Physiol. Endocrinol. Metab 280, E260–E269. [PubMed: 11158929]

Sanders TR, Kim DW, Glendining KA, Jasoni CL, 2014 Maternal obesity and IL-6 lead to aberrant developmental gene expression and deregulated neurite growth in the fetal arcuate nucleus. Endocrinology 155, 2566–2577. [PubMed: 24773340]

Sandman CA, Glynn LM, Davis EP, 2013 Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. J. Psychosom. Res 75, 327–335. [PubMed: 24119938]

Sasaki A, de Vega WC, St-Cyr S, Pan P, McGowan PO, 2013 Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood. Neuroscience 240, 1–12. [PubMed: 23454542]

Sasaki A, de Vega W, Sivanathan S, St-Cyr S, McGowan PO, 2014 Maternal high-fat diet alters anxiety behavior and glucocorticoid signaling in adolescent offspring. Neuroscience 272, 92–101. [PubMed: 24791714]

Schaefer CA, Brown AS, Wyatt RJ, Kline J, Begg MD, Bresnahan MA, Susser ES, 2000 Maternal prepregnant body mass and risk of schizophrenia in adult offspring. Schizophr. Bull 26, 275–286. [PubMed: 10885630]

Schmitz L, Kuglin R, Bae-Gartz I, Janoschek R, Appel S, Mesaros A, Jakovcevski I, Vohlen C, Handwerk M, Ensenauer R, Dotsch J, Hucklenbruch-Rother E, 2018 Hippocampal insulin resistance links maternal obesity with impaired neuronal plasticity in adult offspring. Psychoneuroendocrinol. 89, 46–52.

Schulkin J, Gold PW, McEwen BS, 1998 Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 23, 219–243. [PubMed: 9695128]

Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ, 2012 Kynurenines in the mammalian brain: when physiology meets pathology. Nat. Rev. Neurosci 13, 465–477. [PubMed: 22678511]

Schwartz MW, Woods SC, Porte D Jr., Seeley RJ, Baskin DG, 2000 Central nervous system control of food intake. Nature 404, 661–671. [PubMed: 10766253]

Schwartzer JJ, Careaga M, Onore CE, Rushakoff JA, Berman RF, Ashwood P, 2013 Maternal immune activation and strain specific interactions in the development of autism-like behaviors in mice. Transl. Psychiat 3, e240.

Segovia SA, Vickers MH, Gray C, Reynolds CM, 2014 Maternal obesity, inflammation, and developmental programming. Biomed. Res. Int 2014, 418975. [PubMed: 24967364]

Shoelson SE, Lee J, Goldfine AB, 2006 Inflammation and insulin resistance. J. Clin. Invest 116, 1793–1801. [PubMed: 16823477]

Simanek AM, Meier HC, 2015 Association between prenatal exposure to maternal infection and offspring mood disorders: a review of the literature. Curr. Probl. Pediatr. Adolesc. Health Care 45, 325–364. [PubMed: 26476880]

Simoes LR, Sangiogo G, Tashiro MH, Generoso JS, Faller CJ, Dominguini D, Mastella GA, Scaini G, Giridharan VV, Michels M, Florentino D, Petronilho F, Reus GZ, Dal-Pizzol F, Zugno AI, Barichello T, 2018 Maternal immune activation induced by lipopolysaccharide triggers immune

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

response in pregnant mother and fetus, and induces behavioral impairment in adult rats. J. Psychiatr. Res 100, 71–83. [PubMed: 29494891]

Smith SE, Li J, Garbett K, Mirnics K, Patterson PH, 2007 Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci 27, 10695–10702. [PubMed: 17913903]

Smolders S, Notter T, Smolders SMT, Rigo JM, Brone B, 2018 Controversies and prospects about microglia in maternal immune activation models for neurodevelop-mental disorders. Brain Behav. Immun 73, 51–65. [PubMed: 29870753]

Sohlberg S, Stephansson O, Cnattingius S, Wikstrom AK, 2012 Maternal body mass index, height, and risks of preeclampsia. Am. J. Hypertens 25, 120–125. [PubMed: 21976280]

Solek CM, Farooqi N, Verly M, Lim TK, Ruthazer ES, 2018 Maternal immune activation in neurodevelopmental disorders. Dev. Dyn 247, 588–619. [PubMed: 29226543]

Song L, Sun B, Boersma GJ, Cordner ZA, Yan J, Moran TH, Tamashiro KLK, 2017 Prenatal high-fat diet alters placental morphology, nutrient transporter expression, and mtorc1 signaling in rat. Obesity (Silver Spring) 25, 909–919. [PubMed: 28332771]

Sood R, Zehnder JL, Druzin ML, Brown PO, 2006 Gene expression patterns in human placenta. Proc. Natl. Acad. Sci. USA 103, 5478–5483. [PubMed: 16567644]

Soto M, Cai W, Konishi M, Kahn CR, 2019 Insulin signaling in the hippocampus and amygdala regulates metabolism and neurobehavior. Proc. Natl. Acad. Sci. USA 116, 6379–6384. [PubMed: 30765523]

Stang J, Huffman LG, 2016 Position of the academy of nutrition and dietetics: obesity, reproduction, and pregnancy outcomes. J. Acad. Nutr. Diet 116, 677–691. [PubMed: 27017177]

Stirling J, White C, Lewis S, Hopkins R, Tantam D, Huddy A, Montague L, 2003 Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. Schizophr Res 65, 75–86. [PubMed: 14630300]

Stouffer MA, Woods CA, Patel JC, Lee CR, Witkovsky P, Bao L, Machold RP, Jones KT, de Vaca SC, Reith ME, Carr KD, Rice ME, 2015 Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. Nat. Commun 6, 8543. [PubMed: 26503322]

Sullivan EL, Grayson B, Takahashi D, Robertson N, Maier A, Bethea CL, Smith MS, Coleman K, Grove KL, 2010 Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring. J. Neurosci 30, 3826–3830. [PubMed: 20220017]

Sullivan EL, Nousen EK, Chamlou KA, 2014 Maternal high fat diet consumption during the perinatal period programs offspring behavior. Physiol. Behav 123, 236–242. [PubMed: 23085399]

Sullivan EL, Riper KM, Lockard R, Valleau JC, 2015 Maternal high-fat diet programming of the neuroendocrine system and behavior. Horm. Behav 76, 153–161. [PubMed: 25913366]

Sun B, Purcell RH, Terrillion CE, Yan J, Moran TH, Tamashiro KL, 2012 Maternal high-fat diet during gestation or suckling differentially affects offspring leptin sensitivity and obesity. Diabetes 61, 2833–2841. [PubMed: 22751689]

Sun B, Liang NC, Ewald ER, Purcell RH, Boersma GJ, Yan J, Moran TH, Tamashiro KL, 2013 Early postweaning exercise improves central leptin sensitivity in offspring of rat dams fed high-fat diet during pregnancy and lactation. Am. J. Physiol. Regul. Integr. Comp. Physiol 305, R1076–R1084. [PubMed: 24026073]

Sun B, Song L, Tamashiro KL, Moran TH, Yan J, 2014 Large litter rearing improves leptin sensitivity and hypothalamic appetite markers in offspring of rat dams fed high-fat diet during pregnancy and lactation. Endocrinology 155, 3421–3433. [PubMed: 24926823]

Suri D, Vaidya VA, 2013 Glucocorticoid regulation of brain-derived neurotrophic factor: relevance to hippocampal structural and functional plasticity. Neuroscience 239, 196–213. [PubMed: 22967840]

Tamashiro KL, Terrillion CE, Hyun J, Koenig JI, Moran TH, 2009 Prenatal stress or high-fat diet increases susceptibility to diet-induced obesity in rat offspring. Diabetes 58, 1116–1125. [PubMed: 19188431]

Thompson JR, Valleau JC, Barling AN, Franco JG, DeCapo M, Bagley JL, Sullivan EL, 2017 Exposure to a high-fat diet during early development programs behavior and impairs the central

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

serotonergic system in juvenile non-human primates. Front. Endocrinol. (Lausanne) 8, 164. [PubMed: 28785241]

Thompson JR, Gustafsson HC, DeCapo M, Takahashi DL, Bagley JL, Dean TA, Kievit P, Fair DA, Sullivan EL, 2018 Maternal diet, metabolic state, and inflammatory response exert unique and long-lasting influences on offspring behavior in non-human primates. Front. Endocrinol. (Lausanne) 9, 161. [PubMed: 29740395]

Tozuka Y, Kumon M, Wada E, Onodera M, Mochizuki H, Wada K, 2010 Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring. Neurochem. Int 57, 235–247. [PubMed: 20538025]

Trandafir LM, Temneanu OR, 2016 Pre and post-natal risk and determination of factors for child obesity. J. Med. Life 9, 386–391. [PubMed: 27928443]

Treesukosol Y, Sun B, Moghadam AA, Liang NC, Tamashiro KL, Moran TH, 2014 Maternal high-fat diet during pregnancy and lactation reduces the appetitive behavioral component in female offspring tested in a brief-access taste procedure. Am. J. Physiol. Regul. Integr. Comp. Physiol 306, R499–R509. [PubMed: 24500433]

Treuer T, Tohen M, 2010 Predicting the course and outcome of bipolar disorder: a review. Eur. Psychiat 25, 328–333.

Udagawa J, Hino K, 2016 Impact of maternal stress in pregnancy on brain function of the offspring. Nihon Eiseigaku Zasshi 71, 188–194. [PubMed: 27725421]

Vaiserman AM, 2015 Epigenetic programming by early-life stress: evidence from human populations. Dev. Dyn 244, 254–265. [PubMed: 25298004]

Vallee M, Mayo W, Dellu F, Le Moal M, Simon H, Maccari S, 1997 Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. J. Neurosci 17, 2626–2636. [PubMed: 9065522]

Vallee M, MacCari S, Dellu F, Simon H, Le Moal M, Mayo W, 1999 Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: a longitudinal study in the rat. Eur. J. Neurosci 11, 2906–2916. [PubMed: 10457187]

Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, Hoyer D, Roseboom T, Raikkonen K, King S, Schwab M, 2017 Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci. Biobehav. Rev

Van Doorn C, Macht VA, Grillo CA, Reagan LP, 2017 Leptin resistance and hippocampal behavioral deficits. Physiol. Behav 176, 207–213. [PubMed: 28267584]

Van Lieshout RJ, Robinson M, Boyle MH, 2013 Maternal pre-pregnancy body mass index and internalizing and externalizing problems in offspring. Can. J. Psychiatry 58, 151–159. [PubMed: 23461886]

Varastehpour A, Radaelli T, Minium J, Ortega H, Herrera E, Catalano P, Hauguel-de Mouzon S, 2006 Activation of phospholipase A2 is associated with generation of placental lipid signals and fetal obesity. J. Clin. Endocrinol. Metab 91, 248–255. [PubMed: 16249288]

Velasquez JC, Goeden N, Bonnin A, 2013 Placental serotonin: implications for the developmental effects of SSRIs and maternal depression. Front. Cell Neurosci 7, 47. [PubMed: 23630464]

Vernon AC, So PW, Lythgoe DJ, Chege W, Cooper JD, Williams SC, Kapur S, 2015 Longitudinal in vivo maturational changes of metabolites in the prefrontal cortex of rats exposed to polyinosinic-polycytidylic acid in utero. Eur. Neuropsychopharmacol 25, 2210–2220. [PubMed: 26475576]

Walker CD, Naef L, d'Asti E, Long H, Xu Z, Moreau A, Azeddine B, 2008 Perinatal maternal fat intake affects metabolism and hippocampal function in the offspring: a potential role for leptin. Ann. N Y Acad. Sci 1144, 189–202. [PubMed: 19076377]

Wallace AE, Anderson GM, Dubrow R, 2008 Obstetric and parental psychiatric variables as potential predictors of autism severity. J. Autism. Dev. Disord 38, 1542–1554. [PubMed: 18324467]

Weinstock M, 2017 Prenatal stressors in rodents: effects on behavior. Neurobiol. Stress 6, 3–13. [PubMed: 28229104]

Werther GA, Hogg A, Oldfield BJ, McKinley MJ, Figdor R, Allen AM, Mendelsohn FA, 1987 Localization and characterization of insulin receptors in rat brain and pituitary gland using in vitro autoradiography and computerized densitometry. Endocrinology 121, 1562–1570. [PubMed: 3653038]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

White CL, Pistell PJ, Purpera MN, Gupta S, Fernandez-Kim SO, Hise TL, Keller JN, Ingram DK, Morrison CD, Bruce-Keller AJ, 2009 Effects of high fat diet on Morris maze performance, oxidative stress, and inflammation in rats: contributions of maternal diet. Neurobiol. Dis 35, 3–13. [PubMed: 19374947]

Williams M, Zhang Z, Nance E, Drewes JL, Lesniak WG, Singh S, Chugani DC, Rangaramanujam K, Graham DR, Kannan S, 2017 Maternal inflammation results in altered tryptophan metabolism in rabbit placenta and fetal brain. Dev. Neurosci 39, 399–412. [PubMed: 28490020]

Winther G, Elfving B, Muller HK, Lund S, Wegener G, 2018 Maternal high-fat diet programs offspring emotional behavior in adulthood. Neuroscience 388, 87–101. [PubMed: 30025860]

Wolfrum C, Peleg-Raibstein D, 2018 Maternal overnutrition leads to cognitive and neurochemical abnormalities in C57BL/6 mice. Nutr. Neurosci 1–12.

Wraw C, Deary IJ, Der G, Gale CR, 2018 Maternal and offspring intelligence in relation to BMI across childhood and adolescence. Int. J. Obes. (Lond) 42, 1610–1620. [PubMed: 29515207]

Wright T, Langley-Evans SC, Voigt JP, 2011 The impact of maternal cafeteria diet on anxiety-related behaviour and exploration in the offspring. Physiol. Behav 103, 164–172. [PubMed: 21241725]

Yamada-Goto N, Katsuura G, Ochi Y, Ebihara K, Kusakabe T, Hosoda K, Nakao K, 2012 Impairment of fear-conditioning responses and changes of brain neurotrophic factors in diet-induced obese mice. J. Neuroendocrinol 24, 1120–1125. [PubMed: 22487415]

Yang X, Haghiac M, Glazebrook P, Minium J, Catalano PM, Hauguel-de Mouzon S, 2015 Saturated fatty acids enhance TLR4 immune pathways in human trophoblasts. Hum. Reprod 30, 2152–2159. [PubMed: 26202921]

Yang X, Li M, Haghiac M, Catalano PM, O'Tierney-Ginn P, Hauguel-de Mouzon S, 2016 Causal relationship between obesity-related traits and TLR4-driven responses at the maternal-fetal interface. Diabetologia 59, 2459–2466. [PubMed: 27535280]

Young JL, Cai L, States JC, 2018 Impact of prenatal arsenic exposure on chronic adult diseases. Syst. Biol. Reprod. Med 64, 469–483. [PubMed: 29873257]

Zambrano E, Nathanielsz PW, 2017 Relative contributions of maternal Western-type high fat, high sugar diets and maternal obesity to altered metabolic function in pregnancy. J. Physiol 595, 4573–4574. [PubMed: 28513863]

Zerbo O, Iosif AM, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I, 2013 Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. J. Autism. Dev. Disord 43, 25–33. [PubMed: 22562209]

Zhang XY, Chen DC, Xiu MH, Yang FD, Haile CN, Kosten TA, Kosten TR, 2012 Gender differences in never-medicated first-episode schizophrenia and medicated chronic schizophrenia patients. J. Clin. Psychiatry 73, 1025–1033. [PubMed: 22901352]

Zhang J, Jing Y, Zhang H, Bilkey DK, Liu P, 2018 Maternal immune activation altered microglial immunoreactivity in the brain of postnatal day 2 rat offspring. Synapse e22072. [PubMed: 30256454]

Zhang Z, van Praag H, 2015 Maternal immune activation differentially impacts mature and adult-born hippocampal neurons in male mice. Brain Behav. Immun 45, 60–70. [PubMed: 25449671]

Zieba J, Uddin GM, Youngson NA, Karl T, Morris MJ, 2019 Long-term behavioural effects of maternal obesity in C57BL/6J mice. Physiol. Behav 199, 306–313. [PubMed: 30414884]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

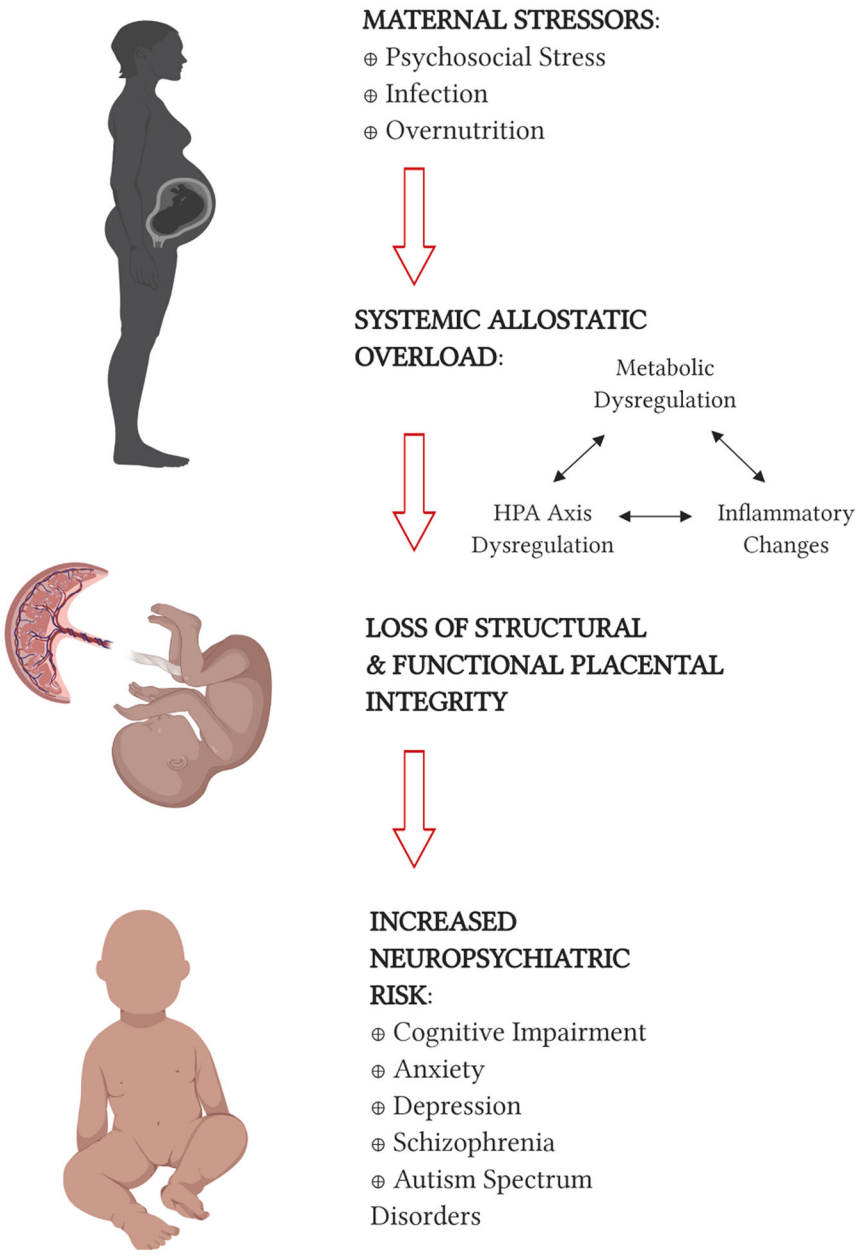

Fig. 1.

Different maternal environmental stressors lead to common neuropsychiatric risk profiles in offspring. Epidemiological and animal model studies associate maternal stress, infection, and altered nutrition with increased risk for an overlapping range of neuropsychiatric outcomes in offspring, including cognitive impairment, anxiety, depression, schizophrenia, and autism spectrum disorders. Evidence suggests that these stressors act via converging pathophysiological pathways characterized by systemic allostatic overload across regulatory systems including the hypothalamic–pituitary–adrenal (HPA) axis, metabolic signaling, and inflammatory pathways. The placenta acts as an integrator and propagator of allostatic overload, not only communicating the maternal environment to the fetus but also altering its own structural and functional capacity in response. The developing fetus, patterned in an

environment of dysregulation, is programmed towards increased neuropsychiatric risk. Created with BioRender.com.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Table 1

Summarized clinical studies associating maternal overnutrition with neuropsychiatric risk to offspring. Studies referenced are limited to the present review.

Offspring outcome	Measure of maternal overnutrition	Ref #	Concluded association	Study design	Notes
↑ Risk and Severity of ASDs	↑ Pre-pregnancy BMI	(Reynolds et al, 2014)	Yes	Cohort	
		(Moss and Chugani, 2014)	Yes	Cohort	
		(Krakowiak et al, 2012)	Yes	Case-Control	
		(Dodds et al., 2011)	Yes	Cohort	
		(Getz et al., 2016)	Yes	Case-Control	
		(Gardner et al., 2015)	Inconclusive	Cohort	Population-based association disappears in matched sibling analysis
		(Li et al., 2016)	Inconclusive	Case-Control	Association in combination with maternal diabetes
		(Bilder et al., 2013)	No	Cohort, Case-Control	
	↑ Gestational weight gain (GWG)	(Dodds et al., 2011)	Yes	Cohort	
		(Gardner et al., 2015)	Yes	Cohort	
		(Bilder et al., 2013)	Yes	Cohort, Case-Control	
		(Reynolds et al., 2014)	No	Cohort	
	Metabolic Complications (Diabetes,	(Krakowiak et al., 2012)	Yes	Case-Control	
	Hypertension, Pre-Eclampsia)	(Dodds et al., 2011)	Yes	Cohort	
		(Wallace et al., 2008)	Yes	Cohort	
		(Li et al., 2016)	Yes	Case-Control	
		(Reynolds et al., 2014)	No	Cohort	
↑ Risk of Cognitive	↑ Pre-pregnancy BMI	(Basatemur et al., 2013)	Yes	Cohort	
Impairment		(Bliddal et al., 2014)	Yes	Cohort	
		(Casas et al., 2013)	Yes	Cohort	
		(Craig et al., 2013)	Yes	Case-Control	
		(Eriksen et al., 2013)	Yes	Cohort	
		(Hinkle et al., 2012)	Yes	Cohort	
		(Huang et al., 2014)	Yes	Cohort	
		(Neggers et al., 2003)	Yes	Cohort	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Offspring outcome	Measure of maternal overnutrition	Ref #	Concluded association	Study design	Notes
		(Brion et al., 2011)	Inconclusive	Cohort	Inconsistent between cohorts; potential confounder effect
		(Li et al., 2016)	Inconclusive	Case-Control	Association in combination with maternal diabetes
		(Krzeczkowski et al., 2018)	Inconclusive	Cohort	Association disappears when accounting for maternal diet
	Metabolic Complications (Diabetes, Hypertension, Pre-Eclampsia)	(Li et al., 2016)	Yes	Case-Control	
		(Krzeczkowski et al., 2018)	Inconclusive	Cohort	Association disappears when accounting for maternal diet
↑ Risk of Anxiety or Depression	↑ Pre-pregnancy BMI	(Van Lieshout et al., 2013)	Yes	Cohort	
		(Mina et al., 2017)	Yes	Cohort	
		(Rodriguez, 2010)	Yes	Cohort	
		(Robinson et al., 2013)	Yes	Cohort	
↑ Risk of Schizophrenia	↑ Pre-pregnancy BMI	(Jones et al., 1966)	Yes	Cohort	
		(Schaefer et al., 2000)	Yes	Cohort	
	↑ GWG	(Kawai et al., 2004)	Yes	Case-Control	
	Metabolic Complications (Diabetes, Hypertension, Pre-Eclampsia)	(Cannon et al., 2002)	Yes	Meta-analysis	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Table 2

Findings from animal models of maternal overnutrition. Models of maternal overnutrition are presented with resulting changes to offspring behavior, brain, and peripheral outcomes; maternal physiology; and placental physiology. Studies referenced are limited to the present review.

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
(Winther et al., 2018)	Rat [Sprague-Dawley (SD)]	60% High-Fat Diet (HFD), 8 w pre-conception (PC) through gestation (G) and lactation (L)	Anxiety-like behaviour	Hippocampus • ↑ Corticotropin releasing hormone receptor 2 mRNA • ↓ Mineralocorticoid receptor mRNA • ↑ Pro-inflammatory cytokine mRNA • Alterations in kynurenine pathway gene expression	Pre- / at weaning • ↑ Body weight (BW) Adult • ↑ BW ♂	• ↑ BW	_	
(Musial et al., 2017)	Mouse (C57)	30% kcal fat, 36% kcal sugar (HFHS diet), through G Dam sacrifice G16 or G19	-	-	Fetal, G16 • ↑ BW Fetal, G19 • ↔ BW	G16 • ↑ Blood glucose • ↑ Plasma insulin • ↑ Plasma leptin • ↑ Plasma cholesterol G19 • ↓ Plasma free fatty acids (FFA) • ↓ Glucose tolerance • ↓ Insulin sensitivity	• ↓ Weight (G16, G19) • ↓ Prolactin / placental lactogen-related mRNA (G19)	
(Sun et al., 2012)	Rat(SD)	60% HFD, through G and L; Offspring cross-fostered to same- or opposite-diet dam at PI	-	Hypothalamus, pre- /atweaning • ↓ Leptin sensitivity at P10 (any HFD	Pre- /at weaning, L HFD • ↑ BW • ↑ Adiposity	• ↑ Plasma leptin (P10) • ↑ Milk leptin (P21)	-	Differential effects by exposure window: ↑ impact on

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
		• HFD-HFD (G-L) • Control diet (Con)-HFD • HFD-Con		exposure ♂, G HFD ♀) • ↑ Baseline pSTAT3 (L HFD ♀) • ↓ Leptin sensitivity at P21 (L HFD)	• ↑ Plasma leptin • ↓ Glucose tolerance Adult, L HFD • ↑ BW (♂) • ↑ Adiposity (♂)	• ↑ Milk fat content(P21)		offspring metabolic phenotype with L HFD
(Niculescu and Lupu, 2009)	Mouse (C57)	60% HFD, 10 w PC through G Dam sacrifice G17	-	Hippocampus, fetal • ↑ Neural progenitor proliferation (neuroepithelium) • ↓ Neural progenitor proliferation (dentate gyrus, DG) • ↓ Neuronal differentiation (DG) Cortex, fetal • ↑ Neural progenitor proliferation (neuroepithelium)	Fetal • ↓ BW • ↑ Fetal resorption	• ↑ BW	-	
(Tozuka et al., 2010)	Mouse (C57)	57.5% HFD, 6 w PC through G and L until P16	Cognitive impairment (adolescent)	Hippocampus, adolescent • ↑ Peroxidized lipid accumulation • ↓ BDNF mRNA/ protein • Impaired dendritic arborization of neurons	-	• ↑ BW • ↑ Serum cholesterol • ↑ Serum FFA • ↑ Serum triglycerides (TG)	-	Cognitive phenotype normalized by adulthood
(Wright et al., 2011)	Rat (Wistar)	Cafeteria diet, 11 w PC through G and L 8 experimental groups	Decreased anxiety-like	-	• ↑ Adiposity (L exposure)	• ↑ BW (PC exposure)	-	Differential effects by

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
		limiting HFD to PC, G, L, or a combination of exposure windows (e.g. PC & L only)	behavior (L exposure, ♂)					exposure window
(Cordner et al., 2019)	Rat (SD)	60% HFD, through G and L	Cognitive impairment	Hippocampus, weaning • ↓ Insr mRNA • ↓ Lepr mRNA • ↓ Slc2al mRNA Hippocampus, adult • ↓ Insr mRNA • ↓ Lepr mRNA	• ↑ BW	-	-	
(White et al., 2009)	Rat (Long Evans)	60% HFD, 4 w PC through G and L Offspring placed as adults onto HFD or Con	Cognitive impairment (HFD offspring exposed to adult HFD)	With maternal HFD • ↑ markers oxidative stress • ↓ IL-6 cortex	• ↑ BW (HFD offspring exposed to adult HFD) • ↑ adiposity (with maternal HFD)	• ↑ BW	-	Maternal + offspring diet exposure
(Can et al., 2012)	Rat(SD)	65% HFD, through G and L Offspring weaned onto respective dam diet	Anxiety-like behavior Depression-like behavior Cognitive impairment	Hippocampus • ↓ Number pyramidal neurons	• ↑ Serum TG	-	-	Maternal + offspring diet exposure
(Robb et al., 2017)	Rat (SD)	45% HFD, 10 w PC through G and L	Cognitive impairment (adolescent ♂, trend in adult ♂)	-	• ↑ Fasting blood glucose (♀)	• ↑ BW • ↑ Adiposity • ↑ Plasma leptin • ↓ Glucose tolerance		Cognitive phenotype normalized by adulthood; Sex differences: ↑ effect ♂
(Moser et al., 2017)	Rat (Long Evans)	60% HFD, 6 w PC through G and L	Cognitive impairment	-	Pre- /at weaning • ↑ BW	• ↑ BW	-	
(Page et al., 2014)	Rat (SD)	45% HFD, 1 m PC through G and L Offspring weaned onto HFD or Con	Cognitive impairment (maternal HFD exposure)	Hippocampus, maternal HFD exposure • ↓ BDNF mRNA/ protein	Maternal HFD exposure • ↑ BW • ↑ Adiposity • ↑ Plasma CORT	-	-	

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
				• ↓ nerve growth factor mRNA/ protein • ↓ Arc mRNA/ protein • ↓ Synaptophysin mRNA • ↑ Synaptotagmin mRNA • ↓ Glutamate NMDA receptor 2b	• ↑ Serum glucose (only if weaned to HFD)			
(Bilbo and Tsang, 2010)	Rat (SD)	60% high saturated fat HFD (SFD) or 60% high trans fat HFD (TFD), 4 w PC through G and L	Anxiety-like behavior (SFD or TFD ♂) Improved cognitive performance (SFD or TFD ♂)	Hippocampus, neonate • ↑ Microglial activation markers mRNA Hippocampus, weaning • ↑ Basal, LPS-stimulated IL-1β (SFD) Hippocampus, adult • ↑ Basal microglial activation (SFD) • ↑ Microglial LPS reactivity (SFD > TFD) Pre- /at weaning	Pre- /at weaning • ↑ BW (SFD) • ↑ Plasma leptin (SFD > TFD) Adult • ↑ BW (SFD ♂) • ↑ Plasma leptin (SFD > TFD ♂, SFD ♀)	• ↑ BW • ↑ Plasma leptin (SFD)		
(Graf et al., 2016)	Mouse (C57)	60% HFD, 8 w PC through G and L	Cognitive impairment (♂)	Pre- /at weaing • ↑ Pro-inflammatory cytokine mRNA • ↑ Nurr77 mRNA (inflammation-mediated TF) • Changes to iron metabolism-related gene expression	Pre- /at weaning • ↑ BW • ↑ Serum IL-5 • ↓ Serum IL-10	• ↑ BW • ↑ Serum leptin • ↑ Circulating proinflammatory cytokines	-	Sex differences: ↑ effect ♂

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
				• ↓ Myelination media cortex (♂)				
(Kang et al., 2014)	Mouse (C57)	60% HFD, • 6 w PC through G and L (HFD-HFD), OR • 6 w PC through G only (HFD-Con), OR • Through L only (Con-HFD)	Anxiety-like behavior (♀; HFD-HFD, HFD-Con) Social interaction deficits (♀; HFD-HFD only) Hyperactivity (♂; HFD-HFD, HFD-Con)	Adult • ↑ Microglial activation in whole brain and amygdala (♀, HFD-HFD) • ↑ Pro-inflammatory cytokines (♀, HFD-HFD)	• ↑ BW P21 (HFD-HFD) • ↑ BW adolescence (HFD-HFD, HFD-Con)	• ↑ BW with PC/G exposure	-	Timing of exposure: ↑ impact PC/G v L HFD, partial mitigation with L switch
(Buffington et al., 2016)	Mouse (C57)	60% HFD, 8 w PC through G and L	Social interaction deficits	• ↓ Oxytocin in hypothalamus • ↓ Social interaction-induced LTP in VTA DA neurons	• Gut dysbiosis	• ↑ BW	-	
(Sasaki et al., 2013)	Rat (Long Evans)	60% HFD, 4 w PC through G and L	Anxiety-like behavior	Amygdala • ↑ Mineralocorticoid receptor mRNA (♀) • ↑ Glucocorticoid receptor mRNA (♀) • ↑ Pro-inflammatory gene mRNA • ↑/↓ Anti-inflammatory gene mRNA Hippocampus	Pre- /at weaning • ↑ BW Adult • ↔BW • ↓ Baseline CORT • ↑ CORT elevation following stress challenge	• ↑ BW	-	Timing of offspring effect: altered phenotype in adolescent (Sasaki et al., 2014) v adult animals

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
				• ↓ Anti-inflammatory mRNA (♀)				
(Sasaki et al., 2014)	Rat (Long Evans)	60% HFD, 4 w PC through G and L	Decreased anxiety-like behavior (adolescent)	Amygdala, adolescent • ↓ Pro-inflammatory gene mRNA (♀ • ↓ Anti-inflammatory gene mRNA Hippocampus, adolescent • ↑ Glucocorticoid receptor mRNA • ↑ Pro-inflammatory cytokine mRNA • ↑ Anti-inflammatory gene mRNA	Pre- /at weaning • ↑ BW Adolescent • ↔BW	• ↑ BW	-	Timing of offspring effect: altered phenotype in adolescent v adult (Sasaki et al., 2013) animals
(Giriko et al., 2013)	Rat (Wistar)	52% HFD, through L	Delayed reflex development (early life) Depression-like behavior (adult)	-	Pre- / at weaning • ↔ BW • ↓ Mediolateral head axis • ↑ BW Adult • ↓ Anteroposterior head axis	• ↔ BW	-	
(Lin et al., 2015)	Rat (SD)	45% HFD, 10 d PC through G and L Adult offspring subjected to chronic unpredictable mild stress (CUMS)	Sensitization to stress-induced depression-like behavior	• ↑ CUMS-associated ↑ in CSF calcitonin gene-related peptide • ↑ CUMS-associated ↑ in hippocampal calcitonin gene-related peptide	• ↔ BW bymaternal diet • ↑ CORT in restraint challenge • ↓ CORT response habituation torepeated restraint			Maternal HFD ↑ sensitization to stress

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
					• ↑ BW			
(Zieba et al., 2019)	Mouse (C57)	43% HFD, 5 w PC through G and L	Facilitation of PPI	-	• ↑ BW	• ↑ BW	-	
(Wolfrum and Peleg-Raibstein, 2018)	Mouse (C57)	60% HFD, 3 w PC through G and L	Cognitive impairment (adult, ↑ severity in aged adult)Facilitation of PPI (adult, aged adult)	Ventral hippocampus, adult • ↓ Glutamate • ↓ Tyrosine • ↓ Taurine Medial PFC, adult • ↓ GABA • ↓ Aspartate • ↓ Taurine	-	-	-	
(Song et al., 2017)	Rat(SD)	60% HFD, through G	-	-	-	• ↔ BW • ↑ Adiposity • ↑ Plasma leptin • ↓ Plasma adiponectin • ↓ Plasma triglycerides • ↓ Glucose tolerance	• ↓ Labyrinth thickness • ↑ Nutrient transporter mRNA and protein ♂ • ↑ Growth-related mRNA ♀ • ↔ Weight	
(Sun et al., 2014)	Rat(SD)	60% HFD, through G and L	-	Hypothalamus, pre- /at weaning • Baseline alterations to leptin signaling pathway mRNA (↓ ObRb, ↓ STAT3, ↑ SOCS3) • ↓ Leptin sensitivity in arcuate • ↓ Appetite-related genes mRNA (NPY, AgRP)	Pre- / at weaning • ↑ BW • ↑ Adiposity • ↑ Plasma leptin • ↑ Plasma triglycerides • ↓ Plasma cholesterol • ↑ Glucose tolerance Adult • ↔ BW	• ↔ BW • ↑ Adiposity • ↑ Plasma leptin • ↑ Milk leptin	-	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
				Hypothalamus, adult • ↓ ObRb ♂ • ↓ CRH mRNA ♂	• ↑ Adiposity • ↑ Plasma leptin ♂			
(Schmitz et al., 2018)	Mouse (C57)	60% HFD, 9–11 w PC through G and L	-	Hippocampus, adult • ↓ Insulin signaling pathway components (insulin resistance) • ↓ Neurogenesis • ↓ Synaptic plasticity markers	Pre- /at weaning • ↑ BW • ↑ Adiposity • ↑ Serum insulin • ↓ Glucose tolerance Adult • ↔ BW • ↔ Adiposity • ↔ Serum insulin • ↔ Glucose tolerance	• ↑ BW	-	
(Ford et al., 2009)	Sheep	150% of recommended intake sheep diet by body weight, 60 d PC through G Dam sacrifice mid-gestation (G75 of 150 d G course)	-	-	Fetal • ↑ BW, length • ↑ Plasma glucose • ↑ serum insulin • ↑ serum CORT	• ↑ BW • ↑ adiposity • ↑ plasma glucose & serum insulin at baseline • ↓ glucose tolerance • ↑ serum CORT		
(Qiao et al., 2015)	Mouse (C57)	60% HFD, through G	-	-	Fetal • ↑ adiposity • ↑ serum free fatty acids	• ↑ BW • ↑ adiposity • ↓ serum triglycerides • ↑ serum insulin	• ↑ triglycerides • ↑ lipoprotein lipase mRNA, protein, activity • ↑ lipid transport genes mRNA	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
							• ↑ lipogenic transcription factors • ↓ SIRT1	
(Sanders et al., 2014)	Mouse (C57)	45% HFD, 8 w PC through G	-	Hypothalamus, fetal • ↓, NPY innervation of paraventricular nucleus • Altered arcuate mRNA levels of neurite growth regulators	Fetal • ↑ BW • ↑ plasma IL-6	• ↑ BW • ↑ plasma IL-6	-	
(Edlow et al., 2018)	Mouse (C57)	60% HFD, 12–14 w PC through G	-	Fetal • ↑ microglia number • ↑ microglial reactivity to LPS immune challenge(♂)	Fetal • ↔ Fetal BW	• ↑ BW	• ↑ CDllb + macrophage reactivity to LPS immune challenge (♂) • ↔ weight	
(Kim et al., 2016)	Mouse (C57)	45% HFD, 8 w PC through G	-	Hypothalamus, fetal • ↑ astrocyte proliferation, number in arcuate and supraoptic nucleus Hypothalamus, neonate • ↑ astrocyte proliferation, number in arcuate and supraoptic nucleus	-	-	-	
(D'Asti et al., 2010)	Rat(SD)	30%* *by weight* high n-6 fat HFD OR 30% by weight high n-3 fat HFD, GD 14 through L;* *By % weight; % kcal fat not reported*	-	Hypothalamus, pre-weaning • ↓ arachidonic acid content (n-3 HFD) Hippocampus, pre-weaning	Pre- / at weaning • ↑ BW (n-6 HFD) • ↑ plasma leptin (n-6 HFD)	• ↓ n-6/n-3 ratio in milk (n-3 HFD)	-	

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
				• ↓ arachidonic acid (n-3 HFD) • ↓ endocannabinoids (n-3 HFD)	• ↑ subcutaneous fat depot leptin mRNA (n-6 HFD) • ↑ baseline plasma CORT • ↑ stress-induced CORT AUC (n-3 HFD)			
(Abuaish et al., 2018)	Rat (Long Evans)	60% HFD, 3 w PC through G and L	Anxiety-like behavior (neonate)	PVN, pre- /at weaning • ↑ corticotropin releasing hormone mRNA Ventral hippocampus, pre-/at weaning • ↓ glucocorticoid receptor mRNA	Pre- /at weaning • ↑ BW • ↑ stress-induced CORT at P7 • ↑ stress-induced ACTH elevation, absence of CORT response at P13	• ↑ BW • ↑ stress-induced CORT peak • ↑ nursing time, dark cycle	-	
(Walker et al, 2008)	Rat (SD)	30%* *by weight* HFD, GD 14 through L; * *By % weight; % kcal fat not reported*	-	-	Pre- /at weaning • ↑ plasma leptin • ↑ adiposity • ↑ BW Adult • ↑ plasma leptin • ↑ BW • ↑ basal CORT, dark cycle	-	-	
(Niu et al, 2019)	Rat (SD)	27.5%* *by weight* HFD, 10 d PC through G and L; **By % weight; % kcal fat not reported*	-	Hypothalamus • ↑ basal corticotropin releasing hormone mRNA in paraventricular nucleus • ↑ corticotropin releasing hormone mRNA	• ↑ plasma CORT across light/dark cycle, f pulse # and pulse amplitude CORT secretion • ↑ restraint and LPS challenge CORT, ↔ insulin-induced	-	-	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
				in paraventricular nucleus following repeated restraint stress Amygala • ↑ glucocorticoid receptor	hypoglycemia challenge CORT • ↓ CORT response habituation to restraint stress			
(Frias et al., 2011)	Non-Human Primate (Japanese macaque)	32% HFD, ≤ 4y PC through G	-	-	Fetal, sensitive/obese • ↑ stillbirthn	Sensitive/obese dams • ↑ BW • ↑ plasma insulin • ↓ glucose tolerance • ↑ plasma leptin All HFD (sensitive/obese and resistant/lean) • ↑ plasma TG	Sensitive/obese dams • ↓ fetal side blood flow • ↑ infarction All HFD (sensitive/obese and resistant/lean) • uteroplacental blood • perfusion • ↑ TG • ↑ pro-inflammation (↑ TLR4, ↑ MCP-1, ↑ IL-lβ)	
(Thompson et al., 2017)	Non-Human Primate (Japanese macaque)	32% HFD + calorically dense treats, ≥ 1 y PC through G and L; Offspring weaned to HFD or Con	Anxiety-like behavior (juvenile, with maternal HFD) Increased stereotypic behaviors (juvenile, postweaning HFD)	Dorsal raphe, juvenile • ↓ TPH2 (with maternal HFD) Median raphe, juvenile • ↑ TPH2 (with postweaning HFD) Prefrontal cortex, juvenile • ↓ 5-HT immunoreactivity (with postweaning HFD)	Pre- /at weaning • ↑ hair cortisol Juvenile • ↑ plasma cortisol (with postweaning HFD)	• ↑ pre-pregnancy BW • ↓ glucose tolerance • ↑ plasma insulin • ↑ plasma leptin	-	Differential effects of maternal and postweaning HFD
(Hayes et al., 2014)	Rat (SD)	45% HFD, 16 w PC through G	-	-	-	• ↑ monocyte chemoattractant protein 1	• ↑ trophoblast invasion	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
						(MCP-1), marker of systemic inflammation	• Impaired spiral artery remodeling • ↑ matrix metalloproteinase • 9	
(Mark et al., 2011)	Rat (Wistar)	45% HFD, through G	-	-	Fetal • ↓ BW • ↑ plasma leptin	• ↑ BW gain • f↑ adiposity • ↑ plasma leptin	• ↓ junctional weight • ↔ markers of vascular development	
(Sullivan et al., 2010)	Non-Human Primate (Japanese macaque)	32% HFD + calorically dense treats, ≤ 4 y PC through G	Anxiety-like behavior (♀, infant)	Dorsal raphe, fetal • 5-HT system perturbations (↑ TPH2 mRNA, ↑ 5-HT1AR mRNA) Juvenile • ↓ CSF 5-HT	-	-	-	
(Peleg-Raibstein et al., 2012)	Mouse (C57)	60% HFD, 3 w PC through G and L	Anxiety-like behavior	Dorsal hippocampus • ↑ BDNF Ventral hippocampus • ↑ 5-HT1AR • ↑ GABAAR α2	-	-	-	
(Mao et al., 2010)	Mouse (NIH Swiss)	60% HFD, 30–35 w PC through G (sacrifice at mid-gestation)	-	-	-	• ↑ BW	• Sexual dimorphism in placental gene expression, ♀ more altered than ♂	
(Thompson et al., 2018)	Non-Human Primate (Japanese macaque)	32% HFD + calorically dense treats, ≥ 1 y PC through G and L	Anxiety-like behavior (juvenile)	-	• ↑ Systemic proinflammatory profile in gestation • ↑ Pre-pregnancy adiposity	-	-	

Front Neuroendocrinol. Author manuscript; available in PMC 2020 May 22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ref	Species (Strain)	Model	Offspring Behavioral Phenotype	Offspring Physiology, Central	Offspring Physiology, Peripheral	Maternal Physiology	Placental Physiology	Notes
					• ↓ Glucose tolerance			