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Prenatal Programming of Mental Illness: Current Understanding of Relationship and Mechanisms

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Abstract The British epidemiologist Dr. David J. Barker documented the relationship between infant birth weight and later onset of hypertension, coronary heart disease, insulin resistance, and type II diabetes. A stressful in utero environment can cause long-term consequences for offspring through prenatal programming. Prenatal programming most commonly occurs through epigenetic mechanisms and can be dependent on the type and timing of exposure as well as the sex of the fetus. In this review, we highlight the most recent evidence that prenatal programming is implicated in the development of psychiatric disorders in offspring exposed to maternal stress during pregnancy. Methodological differences between studies contribute to unavoidable heterogeneity in study findings. Current data suggest that fetal exposure to maternal hypothalamic-pituitary-adrenal axis dysregulation, excessive glucocorticoids, and inflammation with resulting epigenetic changes at both the placental and fetal levels are important areas of continued investigation.

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Introduction

The British epidemiologist Dr. David J. Barker introduced the concept that the "the womb may be more important than the home." Documenting the relationship between infant birth weight and adult disorders such as hypertension, metabolic disorders, and ischemic heart disease, Barker laid the groundwork for his "thrifty phenotype" hypothesis and more generally decades of research focusing on the *fetal and developmental origins of adult disease* [1–7]. Barker posited that maternal malnutrition or other factors lead to poor fetal growth "program" the offspring to prepare for future dietary intake resulting in health or disease depending upon the nutritional intake of the individual across the lifespan [8].

In the intervening years, we have come to appreciate that prenatal programming occurs, in part, through epigenetic mechanisms by which genes are activated or deactivated based on environmental influences during fetal development [9•]. Epigenetics is the modification of the genome that changes a gene's expression without altering the nucleotide sequence. DNA methylation and histone modifications are the most commonly studied epigenetic mechanisms by which cell structure and function can be altered during embryogenesis [10]. Though Dr. Barker's original concept—the womb may be more important than the home—likely underestimates the role of the postnatal environment on the development of disease; the prenatal period is certainly critical to the evolving "three-hit hypothesis of disease vulnerability and resilience." With genetic predisposition as "hit 1," the prenatal environment could be viewed as "hit 2," altering gene expression and leading to phenotypes with differing susceptibility to later life experiences and exposures (hit 3) [11]. Prenatal programming

may lead to a "mismatch" between the offspring's central nervous system activity and mental states or behavior that are required to function optimally in future environmental conditions [10]. This review focuses on the recent data regarding the relationship between prenatal programming and risk for mental illness.

Programming Factors

The type and timing of exposure as well as the offspring sex are critical factors to consider in evaluating the importance of prenatal programming on mental health outcomes.

Type of Stress

While some studies suggest that severe emotional distress experienced by the mother during pregnancy such as death of an older child increases the rate of serious malformations in the developing fetus [12, 13], most studies have examined the impact of less aversive and more common life events or maternal conditions during pregnancy on fetal, child, and long-term health outcomes [14]. Common environmental factors that are studied in preclinical models and/or human subject studies include diet, basal or manipulated glucocorticoid levels, and physiologic or psychological stressors. Whether maternal psychosocial stress or frank mental illness during pregnancy exerts programming effects on the developing fetus through enhanced fetal exposure to glucocorticoids [15, 16], inflammation [17–19], placental modifications [20, 21], suboptimal maternal health behaviors (such as poor nutritional intake and nicotine, drug, or alcohol use) [22–26], or factors yet to be identified is an area of active investigation requiring a translational approach to determine mechanisms and potential interventions.

Timing of Stress

The outcome of aversive maternal conditions on prenatal programming is time dependent and contingent on the maturational stage of the fetal brain [27•]. Early gestational insults could impact systems such as the hypothalamic-pituitary-adrenal (HPA) axis that are critical for the modulation of circadian rhythms, physical growth, and limbic-cortical processes [10]. In a sample of approximately three million Swedes, extreme maternal stress due to exposure to the death of a first-degree relative significantly increased the risk of infant mortality if the stress occurred in the immediate preconception period (6 to 0 months), but not if the stress occurred during pregnancy [28•]. In contrast, heightened maternal anxiety during late gestation was associated with behavioral/emotional problems in the offspring during childhood in one study [29], while another study documented adverse effects of daily hassles and pregnancy-specific anxiety during early and mid-gestation on infant mental and motor development [30]. Reflecting species variations in the timing of brain development, rodent studies emphasize the importance of early postnatal development in the "unmasking" of programming effects of prenatal stressors [31]. The apparent contradictory nature of the literature regarding the importance of timing with respect to environmental factors may be secondary to the difficulty inherent in isolating exposures to one point in gestation, particularly when considering human subject studies.

Offspring Sex

Preclinical research indicates that offspring sex plays a critical role in the maternal transmission of prenatal stress to the fetus [31]. Early gestation has been identified as a particularly important time during which maternal stress (chronic variable stress over 7 days such as new odors, changes in light exposure, or exposure to novel objects) impacts rodent offspring cognition and stress-coping strategies [32–34]. Male offspring exposed to maternal prenatal stress demonstrate impaired learning in a modified version of the Barnes maze task, while female offspring perform better following exposure to maternal stress during early gestation. Interestingly, the strategies for completing this spatial memory task varied in sex [33]. Similarly, male rodents are more sensitive to the effects of maternal stress-induced placental inflammation, displaying enhanced stress-induced locomotor hyperactivity when tested during adulthood [35]. Female rodents appear to be more sensitive to the activating effects of prenatal stress on hypothalamic-pituitary-adrenal axis function [36]. Likewise, some but not all human subject studies have suggested that maternal psychological distress impacts male and female offspring differently [25, 37–40]. Compared to females, male offspring of mothers who were stressed during pregnancy display relatively poor-state regulation during infancy and may be at relatively greater risk of attention deficit hyperactivity disorder symptoms during childhood and even schizophrenia later in life (reviewed in [41]). Maternal anxiety was associated with depression in adolescent girls but not in boys in one study [42]. Whether these sex differences in relationship to exposure to maternal prenatal distress can be observed because the frequency of specific behavioral/psychiatric disorders varies between males and females or because maternal stress actually contributes to these epidemiologic differences is worthy of further investigation.

Prenatal Programming of Neuropsychiatric Disorders

Research into the heritability of neuropsychiatric disorders suggests that while genetic and epigenetic factors play an important role, the manifestation of these disorders is likely

to be multifactorial, requiring pre- and/or postnatal insults. We provide a brief overview of the role of prenatal events in programming risk for several neuropsychiatric disorders, highlighting the importance of the type of stress, timing of exposure, and offspring sex where data are available.

Schizophrenia

Schizophrenia affects 0.5–1 % of the population [43] and is currently hypothesized to be a neurodevelopmental disorder [25]. Nongenetic, environmental risk factors for the development of schizophrenia include maternal viral infections, obstetric hypoxic complications, and maternal stress [44]. Given that schizophrenia is more common in males, it has been hypothesized that the male fetal brain may be more sensitive to certain prenatal stressors and neuroendocrine perturbations than females [45]. A Danish registry study of 1.38 million births from 1973 to 1995 found that the risk of schizophrenia was increased in the offspring (as of 2005) of mothers who were exposed to death of a relative during the first trimester of pregnancy (adjusted relative risk 1.67, 95 % confidence interval 1.02–2.73) [46]. Interestingly, a greater proportion of male offspring (n=4287) developed schizophrenia than female offspring (n=3044) with the adjusted model that included offspring sex as a covariate. Exposure to bereavement stress during the second or third trimester did not substantially increase the risk for schizophrenia, suggesting that the first trimester is a particularly sensitive window for the programming effects of extreme stress, particularly among male offspring. In a large Swedish cohort study, a preconception (6 days to 0 month) loss of a maternal first-degree relative was associated with an increased risk of bipolar disorder or schizophrenia among the offspring. Unfortunately, pregnancy exposure to bereavement was not addressed by gestational age in this study of over two million individuals [47]. The sex interaction was explored, however, but was not found to impact the relationship between bereavement stress and risk for schizophrenia. Neither study measured the mother's subjective experience of the loss, which may be an important factor in understanding how stress affects prenatal programming.

In a population-based study in the UK (n=4673), the experience of stressful life events (more generally defined) during pregnancy was weakly associated with psychosis in offspring at 12 years of age with events experienced earlier in pregnancy strengthening the relationship [48]. Similar to the Swedish study, this association was not dependent on the offspring sex. In an older study, adolescents whose fathers had died when they were in utero were more likely to develop symptoms of schizophrenia by the age of 15 compared to teens who lost their fathers during their first year of life [49]. In this study, there was no increase in birth complications, and a perinatal loss of the father at 3–5 or 9–10 months of gestation was mostly associated with the onset of psychosis. In a large cohort from Northern Finland, unwanted pregnancies were associated with a twofold increased risk of schizophrenia compared to wanted or mistimed pregnancies after controlling for socioeconomic, perinatal, and birth factors [50]. Maternal factors such as smoking and stress during pregnancy, rather than birth complications, increased the risk of adolescent psychosis in a cohort of 963 adolescents aged 15–20 years old [37]. Controlling for offspring sex did not change these outcomes. These studies suggest that while birth complications and poor maternal health behaviors are higher in persons who develop schizophrenia [51], prenatal stress is an independent risk factor. In contrast, several studies have not found a relationship between infection or wartime stress and schizophrenia [22, 52, 53].

Fetal hypoxia [54–56], maternal infections resulting in increased levels of maternal serum IgG and IgM class immunoglobulins at delivery [17], maternal exposure to influenza or toxoplasmosis [19], and maternal malnutrition [22, 24] have all been related in epidemiologic samples to increase the risk for the offspring development of psychosis, particularly schizophrenia. Mild to moderate maternal infection may be associated with heightened placental inflammation and change in the fetal immune system. With this prenatal background, the offspring may be at greater risk of psychosis with additional postnatal stress and/or infection exposures [18]. With this said, studies indicating a relationship between maternal infection and in utero inflammation with a heightened risk for schizophrenia have not been consistently replicated [57]. Many studies rely on retrospective methodology and utilize varying concepts of stress [11] and should, therefore, be interpreted with caution.

Animal models have provided mechanistic insight regarding perinatal programming and schizophrenia risk [25, 26]. Cognitive deficits, similar to those seen in schizophrenia, are seen in rodents subjected to maternal stress [25]. Both protein and vitamin D deficiency during preconception and pregnancy have been associated with decreased attentional control of selective learning as well as increased novelty-induced hyperlocomotion, NMDA receptor, and dopamine D_2 receptor sensitivity in rodents [25], but this finding has not been explored in detail in humans. Offspring of pregnant mice that experienced restraint stress showed abnormalities such as hyperactivity, deficits in social interaction, prepulse inhibition, and fear conditioning that were reversed with clozapine treatment [26]. These offspring were also born earlier and at lower birth weights than control mice [26]. Prenatal stress also increases serotonin 5-HT_{2A} receptors and decreases metabotropic glutamate 2 receptors in offspring; neurotransmitter systems implicated in the pathophysiology of schizophrenia, and important receptor targets for the pharmacologic treatment of schizophrenia [58]. Since behaviors and cognitive deficits which mimic those seen in schizophrenia were observed only in postpubertal rodents, this strengthens the

hypothesis that prenatal stress programs the fetus to respond abnormally to neuroendocrine changes occurring during and after puberty, a time of increased energy demand, hormonal production, and brain maturation.

Autism Spectrum Disorders

Autism spectrum disorders (ASDs) affect 1–2 % of the population [59] and symptoms of poor sociability and communication skills, repetitive behaviors, and circumscribed interests tend to become apparent by the age of 3 years. Inflammatory responses in the mother may affect fetal and postnatal brain development [60]. Originally, based on the knowledge that ASD was associated with season of birth [60], exposure to viral infections has been shown to increase the risk of ASD in many [61–63] but not all [64] studies. However, since a number of different infections have been associated with the increased risk for ASD, it is not a specific infective agent that is thought to be responsible but rather perinatal programming as a result of the maternal, placental, and/or fetal immune response [65]. Human studies suggest that infection may be most important in the first trimester as ASD is more common in children whose mothers are hospitalized for viral infections in the first trimester, although this needs further study [60]. Animal models are also consistent with alterations in maternal immune responses leading to autistic-like behaviors [60, 66, 67].

Affecting a third of pregnant women, obesity has important implications for prenatal programming and mental health outcomes [68]. Diabetes, obesity, and hypertension during pregnancy were associated with a higher risk of ASD in one population-based, case-control study (odds ratio (OR) 1.61, 95 % confidence interval 1.10–2.37) [69]. Maternal obesity also increased the risk for ASD among 2-year-old children born at a gestational age of ≤30 weeks [70]. Leptin, high in obesity, is a hormone produced by fat cells that communicates satiety to the brain. Higher levels of maternal leptin in obese pregnant women have been associated with placental dysfunction and abnormal brain development [69, 71, 72]. Children with ASD have higher plasma leptin levels than controls [73]. In addition, a high-fat diet can increase inflammation through inducing levels of cytokines that have been associated with ASD in humans [74], and there is evidence that increased cytokine levels during pregnancy negatively impact neural development [72]. High-fat diets can affect neurodevelopment by increasing levels of inflammatory cytokines and hormones, such as C-reactive protein, IL-6, IL-1β, and tumor necrosis factor [75], and suppressing the serotonergic system [72]. Few studies have examined whether offspring sex is a factor for exposures and autism risk. A study of 194 twins found that respiratory distress and hypoxia increased the risk of ASD in males, while jaundice was associated with its increased risk in female offspring [76]. They hypothesized that males may be more prone to hypoxic brain injury (HI) than females as testosterone can potentiate HI and progesterone and allopregnanolone can be protective in animal models. Whether this is the mechanism of offspring differences in humans who have a different reproductive development from animals is unknown. Taking perinatal programming a step further, a recent breakthrough in understanding how abnormal gamma-aminobutyric acid (GABA) activity results from a shift in intracellular chloride concentrations in two different animal models of the ASD phenotype has led to speculation that prenatal pharmacological treatment may be a future possibility [77].

The association of ASD with prenatal stress has been inconsistent, and in the largest population-based study to date, third trimester prenatal stress only (defined as loss of a first-degree relative) increased the risk of ASD in offspring born between 1992 and 2000 [hazard ratio (HR) 1.58, 95 % confidence interval (CI) 1.15–2.17] [47]. Offspring sex did not moderate this effect. Taken together, these studies suggest that prenatal stress, perhaps interacting with alterations in immune function, contributes to risk for ASD. However, the magnitude of this contribution that may be necessary to observe a relationship between maternal stress and ASD risk in the offspring is not yet clear.

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) has a worldwide prevalence of 2.5 % with most symptoms appearing by the age of 6 years [78]. General prenatal stress and stressful life events during pregnancy increase the risk of having a child who develops ADHD. Prenatal exposure (especially during the first trimester) to perceived general stress was associated with an increased risk of ADHD diagnosis, especially in boys [38]. In a retrospective case-control study, maternal stressful events during pregnancy was significantly associated with ADHD (OR 6.3, 95 % CI 1.5–27.3) compared to an unaffected sibling, with males more likely than females to be affected (OR 16.4, 95 % CI 3.3–79.15) [40]. Examining a large Danish cohort, Class et al. found that severe bereavement stress was associated with an increased risk of ADHD (HR 1.31, 95 % CI 1.04–1.66) [47]. Similarly, an earlier study of Danish children born between 1987 and 2001 found that boys born to mothers who experienced the unexpected death of a child or a spouse during pregnancy had a 72 % increased risk of a hospital diagnosis of ADHD or receiving ADHD medication (HR 1.72, 95 % CI 1.09–2.73) [79]. However, unlike the findings with maternal perception of general stress levels during pregnancy [38], there was a trend for the risk of ADHD to be greatest if the loss of a first-degree relative was during the third trimester. The death of a non-first-degree relative did not increase the risk. In addition, the risk was gender specific such that it is only applicable to males. Neither of the bereavement studies measured the mother's subjective response to her loss or the impact of maternal exposure to less aversive stressors. In a small retrospective case-control study, positive life events

and marital satisfaction were significantly lower during pregnancy in mothers who gave birth to children who were later diagnosed with ADHD [80]. A prospective cohort study found that maternal-state anxiety at 12–22 weeks of gestational age (but not later in pregnancy) was related to ADHD symptoms in 8 and 9-year-old children [81]. In contrast, maternal anxiety diagnosis was not related to the later development of ADHD in another study of a larger sample of women and their offspring [82]. These studies further emphasize the potential interaction between timing of adversity, severity of the stressor, and sex of the offspring in the programming of risk for mental disorders.

Preclinical research conducted by our group supports the human subject findings that early gestation may be the period of greatest vulnerability to relatively milder or chronic stressors with respect to ADHD-like phenotypes [35]. Using the chronic variable stress model, investigators induced placental inflammation that was then associated with hyperlocomotion in male but not female offspring. Interestingly, treatment with a nonsteroidal anti-inflammatory drug (NSAID) during maternal stress exposure decreased expression of the inflammatory marker interleukin-6 in the placenta of male offspring and rescued the male behavioral phenotype. Whether hyperlocomotion in rodents is an adequate model of ADHD symptoms in humans is debatable, but these data provide further support for the importance of inflammation in prenatal programming of ADHD-like phenotypes.

In addition to inflammation, excess in utero glucocorticoid (GC) exposure has been linked to risk for later development of ADHD symptoms. Exogenous GCs are given during pregnancy to women at risk of preterm delivery to improve infant outcomes. A retrospective study showed that repeated doses of exogenous GCs improved health outcomes in general but was associated with ADHD-like symptoms in children at ages 3 and 6 years [83].

Prenatal Programming of Mood and Anxiety Disorders

Depression

Major depressive disorder (MDD) is the number 1 cause of disease burden among women worldwide [84]. Yet, there are relatively few studies examining the impact of maternal stress, inflammation, or exposure to excess GCs on the programming of risk for MDD among the offspring. A few studies have focused on the impact of prenatal programming on depression risk using fetal growth restriction as a proxy for fetal well-being, but the results have been inconsistent [85]. In a cohort born between 1959 and 1966 (n=1101), no association between low birth weight, preterm birth, and small birth size for gestational age and the development of depression, severity, or number of episodes was found [86]. Factors such as offspring sex, age at offspring assessment, and whether a "second hit" such as whether a major stressor occurred later in life were not determined in this cohort, limiting the investigators' ability to observe a possible connection between prenatal factors and adult outcomes. One study that did examine outcomes by sex found that low-birth-weight females were at greater risk of developing depression by the age of 21 years than males [87]. Finally, in a study of both male and female adolescents, low birth weight was a predictor of depression risk only in females who had experienced childhood adversity [39]. Without lifetime adversity, there was no difference between depression rates in adolescent males and females regardless of birth weight.

One mechanism by which antenatal depression (depression during pregnancy) has been hypothesized to increase risk for future depression among the offspring is through alterations in fetal exposures to GC and, hence, HPA axis development [88]. Due to the general change in the HPA axis during pregnancy such that there is increased cortisol and placental cortisol-releasing hormone (CRH), it may be that chronic pregnancy stress is more likely to lead to abnormal fetal HPA axis development rather than acute pregnancy stresses [89]. Maternal depression is frequently chronic as many women are reticent to seek mental health treatment while pregnant. While there are no definitive studies, prospective data are starting to emerge, suggesting that significant depression during pregnancy is an independent risk factor for the later onset of depression in the adult human offspring [90, 91]. One study found that 18-year-old offspring were 1.28 times (95 % CI 1.08–1.51) more likely to report depression for each standard deviation increase in maternal depression score, controlling for postpartum maternal depression [90]. Since the presence of paternal depression while the mother is pregnant did not increase the risk of depression in the offspring, biological programming due to in utero exposure to maternal depression is suggested. Animal data suggest that prenatal restraint stress leads to depressive-like behavior in both male and female rodents [92]. While exposure to GC may be one mechanism for maternal transmission of risk to the offspring, multiple mechanisms are likely. For example, maternal depression is associated with alterations in the placental monoamine oxidase A enzyme, possibly altering fetal exposure to neurotransmitters such as serotonin which are implicated in the brain development and regulation of affective states [93].

Anxiety

In a large cohort (N=7944) from the Avon Longitudinal Study of Parents and Children, prenatal maternal anxiety has been predicted to lead the offspring to develop a mental disorder which may persist into adolescence [94•]. Prenatal anxiety leads to changes in cortisol awakening responses and diurnal regulation in adolescents [95]. Anxiety-like behavior and blunted stress responses have been reported in rodents after in utero exposure to lipopolysaccharide (LPS) which mimics exposure

to an infective agent [96]. In addition, LPS-treated animals also show increase autonomic nervous system (ANS) responsiveness, suggesting that both the HPA axis and the ANS are persistently and abnormally affected by perinatal immune dysregulation [97]. This suggests that an anxiety phenotype can be prenatally programmed by exposure to in utero infections that result in maternal immune dysregulation [98]. As mentioned previously, maternal high-fat diets can cause both immunologic and glucocorticoid dysregulation. High-fat diets fed to pregnant rodent mothers led to offspring who, as adults, showed anxiety behavior, increased stress responses associated with increased corticosterone receptors in the amygdala, and changes in inflammatory gene expression in both the hippocampus and the amygdala [99]. A high-fat diet appears to expose the neonate to increased inflammatory cytokines that adversely affect neural development [72]. Whether one offspring might develop an anxiety phenotype while another might develop a neurodevelopmental disorder has yet to be determined. It may be that the timing of the exposure and the sex of the offspring are important in the differential outcomes [72].

Conclusion

Over the past several decades, the prenatal or fetal programming of risk for adult disorders has become an area of considerable investigation and consequence. While early studies focused on factors such as maternal diet and offspring risk for cardiovascular and metabolic disorders, recent large-scale cohort and smaller studies have examined the impact of maternal psychological distress and risk for offspring neurodevelopmental and psychiatric sequelae. In conjunction with preclinical studies, these latter investigations have provided some interesting clues with regard to the importance of the type and timing of exposure as well as the offspring sex with respect to a risk for specific behavioral disorders.

Although somewhat inconsistent, there are compelling data which suggest that exposures to severe stressors such as loss of a first-degree relative or a spouse early in pregnancy or even immediately prior to conception increase the risk of schizophrenia primarily in male offspring, while bereavement stress during the third trimester is associated with an increased risk for externalizing behaviors and ADHD. Sex differences in schizophrenia risk were not as prominent in studies focusing on less aversive stressors. Again, the type of stressor and the degree to which the stress activates the maternal HPA axis, immune system, placental function, or all three are likely to play a critical role in the degree of fetal programming and particular disease outcome. For example, both the programming effects of the loss of a first-degree relative and exposure to exogenous GC administration on a risk for ADHD-like symptoms seem to be more prominent with late gestation exposures. Whether these symptoms are limited in duration to prepubertal childhood or continue into adulthood is not yet known. Maternal depression and anxiety appear to program an increased risk for externalizing behaviors among male offspring, but whether the degree to which externalizing behaviors and ADHD among prepubescent boys are greater than those among age-matched girls is due to prenatal programming effects or other factors is not yet known. Interestingly, the increased risk for depression observed among girls exposed in utero to maternal depression or anxiety was noted only in postpubertal girls with a history of adversity, both known risk factors for depression onset particularly among females. Hence, the degree to which prenatal programming interacts with subsequent life events and hormonal changes to render risk is yet to be determined.

Methodological differences between studies contribute to unavoidable heterogeneity in study findings. Large cohort studies such as those conducted in Denmark and Sweden have the power to address the programming effect of a specific stressor such as loss of a loved one. However, they cannot address the possible programming effects of maternally perceived stress or less severe stressors as these studies utilize a retrospective design to measure maternal factors. This distinction is important as greater perceived distress in response to an event or condition is associated with greater activation of the HPA axis and immune response. Findings from animal studies can provide clues to the mechanism, but they lack face validity for the emotional and psychological responses that humans experience in the face of stress. In addition, they tend to focus on one type of stress (restraint, tail suspension, etc.), which lacks the complexity of the human day-to-day experience. The chronic variable stress model utilized by our center and others may have greater ecological validity as the types of stress exposures differ across the study period.

Although these "post-Barker" decades have witnessed an explosion of interest in the role of prenatal and early life events on programming offspring for a host of adverse health outcomes, our understanding of the mechanism by which maternal psychosocial distress and physical stressors such as obesity and poor diet program the fetal brain for a greater risk of adult psychiatric disorders remains in its infancy. In addition, little attention is paid to the ways in which prenatal programming may lead to increased resiliency in the face of later life stressors. While far from conclusive, the data presented here implicate fetal exposure to maternal HPA axis dysregulation, excessive GCs, and inflammation with resulting epigenetic changes at both the placental and fetal levels as productive areas of continued investigation. Finally, we offer a slight modification of Dr. Barker's concept of the relative importance of pre- versus postnatal life by suggesting that the womb may be as important as the home. The bulk of the data, particularly those related to sex differences in psychiatric disorders, highlight the importance of the interaction

between fetal and later life exposures in the manifestation of disease states and/or resiliency.

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Compliance with Ethics Guidelines

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