



Published in final edited form as:

Annu Rev Clin Psychol. 2019 May 07; 15: 317–344. doi:10.1146/annurev-clinpsy-050718-095539.

Prenatal Developmental Origins of Future Psychopathology: Mechanisms and Pathways

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Abstract

The developmental origins of health and disease hypothesis applied to neurodevelopmental outcomes asserts that the fetal origins of future development are relevant to mental health. There is a third pathway for the familial inheritance of risk for psychiatric illness beyond shared genes and the quality of parental care: the impact of pregnant women's distress—defined broadly to include perceived stress, life events, depression, and anxiety—on fetal and infant brain–behavior development. We discuss epidemiological and observational clinical data demonstrating that maternal distress is associated with children's increased risk for psychopathology: For example, high maternal anxiety is associated with a twofold increase in the risk of probable mental disorder in children. We review several biological systems hypothesized to be mechanisms by which maternal distress affects fetal and child brain and behavior development, as well as the clinical implications of studies of the developmental origins of health and disease that focus on maternal distress. Development and parenting begin before birth.

Keywords

prenatal stress; DOHaD; brain development; depression; placenta

INTRODUCTION

Development begins before birth. During the prenatal period, along with the ultrasound-observable physical and organ maturation, extensive neural formation and circuit organization occur; as in postnatal life, the interplay of inherent genetic programs and genetic predispositions with a wide range of environmental exposures shapes individual differences in neurobehavioral trajectories. This assertion of the fetal origins of future development as relevant to mental health commenced, in part, with the Fels Longitudinal Study in the 1930s that examined the effects of maternal smoking on fetal behavior and

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DISCLOSURE STATEMENT

C.M. sits on the boards of Zero to Three and the Bezos Family Foundation Scientific Advisors; she has received a research grant from Johnson & Johnson. C.L.-C. has worked as a consultant for Forest/Allergan. Other than that consulting work, the authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

development (DiPietro et al. 2015). In the 1980s, the epidemiologist David Barker related an indicator of the intrauterine environment, lower birth weight, to subsequent risk for adult cardiovascular disease, thereby originating what has come to be known variously as the Barker hypothesis, the developmental origins of health and disease (DOHaD) model, and prenatal programming; this hypothesis now is applied to neurodevelopmental outcomes (van den Bergh et al. 2017). The recent ascendance of a developmental perspective in understanding and, thus ideally, preventing psychopathology (Nat. Advis. Mental Health Council. 2008, Sroufe 1997) has dramatically increased interest in the prenatal period as a key time point relevant to neurobehavioral outcomes. In what follows, we consider the prenatal developmental origins of risk for future psychopathology as a potential consequence of exposure to maternal affect dysregulation. Some DOHaD studies demonstrate associations between prenatal environmental exposure to household chemicals and child neurodevelopmental outcomes (Lam et al. 2017), while others assert that one form of maternal distress has more of an impact on the developing child (Glover 2011). We focus on research relevant to the idea that there is a third pathway for the familial inheritance of risk for psychiatric illness beyond shared genes and the quality of parental care: the impact of pregnant women's distress—defined broadly to include perceived stress, life events, depression, and anxiety—on fetal and infant brain–behavior development. We begin with a brief overview of prenatal brain development as a critical developmental period and a discussion of nuances of the DOHaD conceptual model with respect to illness risk; then, we move to a description of epidemiological data demonstrating that maternal distress is associated with children's increased risk for psychopathology. We then review several biological systems hypothesized to be mechanisms through which maternal distress affects fetal and child brain–behavior development. We also cover possible confounding maternal preclinical health and lifestyle pathways that deserve more attention in DOHaD studies of maternal distress. We next consider the clinical implications of DOHaD studies that have focused on maternal distress, as well as challenges to the overall scientific findings. Finally, we touch on future directions for this line of DOHaD work. Of note, two important moderators in DOHaD research do not have consistent results despite their centrality to understanding the fetal origins of child psychopathology: timing and sex effects. Briefly, we provide some discussion of each.

There is significant knowledge regarding the time course of fetal brain development (see the section titled Prenatal Brain Development: A Critical Period for Environmental Influences) (Tau & Peterson 2010), as well as of protective attributes of placental functioning (Monk et al. 2016), yet there is a lack of specificity with respect to the gestational timing of prenatal maternal distress and differentiated child outcomes (van den Bergh et al. 2017). Significant challenges exist in finding such unique associations: (a) few studies systematically assess women across pregnancy to identify one period as influential; (b) with more than 50% of pregnancies in the United States being unplanned, women rarely are available for distress assessment during the first trimester; (c) throughout gestation, the fetal brain changes as does the maternal brain and stress-related biology (e.g., women tend to be less responsive to stressors in the second trimester) so that there are two dynamic systems to consider. We aim to specify the timing of gestational exposure, but the field, especially concerning human

studies, cannot yet describe differential effects based on different timing of gestational exposure (van den Bergh et al. 2017).

Sex differences are evident in research into maternal prenatal distress, yet they are remarkably varying; for example, some studies show that males are more likely to be affected and have a 72% increased risk of developing childhood attention-deficit/hyperactivity disorder (ADHD) if their mother lost a spouse or child during pregnancy (van den Bergh et al. 2017) and others identify girls as evincing more compromised mental health outcomes, particularly later in development, and, specifically, a significant association between maternal prenatal depression and risk for depression at 18 years old in females but not males (Quarini et al. 2015). Other reports identify comparable magnitudes of effects yet with differentiated outcomes, such as high maternal prenatal anxiety related to greater likelihood of ADHD in 4-year-old males and emotion regulation problems in females (O'Donnell et al. 2014). Sex differences identifying greater male vulnerability point to the slower development of the male brain—such that there is an extended critical period of prenatal vulnerability—as an explanatory model; another lead considers hormone exposure, especially to testosterone, given its role of organizing sexual variation in the developing brain and association with risk of neurodevelopmental disease (Bale 2016). Finally, the placenta, an important part of the fetus and, thus, XX or XY, is a transient, highly dynamic endocrine organ that transports nutrients and oxygen to the growing fetus, removes waste products, maintains a protective barrier, and responds with sex-varying transcriptional changes to maternal perturbations (Bale 2016). In one elegant model in mice based on the X-linked gene *OGT* (*O*-linked *N*-acetylglucosamine transferase), male placentas with typically lower levels of OGT are poised for epigenetic alterations that appear to produce robust transcriptional responses to maternal prenatal stress that result in increased stress sensitivity as adults (Bale 2016). Consistent with the US National Institutes of Health's (NIH's) mandate to consider sex as a biological variable in biomedical research aimed at understanding disease risk, sex as it moderates fetal brain development and placental functioning [and possibly maternal stress biology (DiPietro et al. 2011)] is central to characterizing prenatal programming processes and neurobehavioral trajectories; much remains to be discovered. We provide sex differences in study outcomes, although a coherent integration of the range of sex differences in outcomes is not yet possible (see Sandman et al. 2013 for an insightful review of sex differences).

Prenatal Brain Development: A Critical Period for Environmental Influences

The interplay of inherent genetic programs along with genetic variation interact with characteristics of the fetus's environment to organize neural elements into complex structural and functional networks referred to as the connectome. This critical period, also subserving corticogenesis, is characterized by considerable plasticity and, thus, vulnerability, yet also opportunity (Scheinost et al. 2017, Werker & Hensch 2015). Briefly, we review aspects of fetal brain development, which typically is divided into three primary phases: embryonic (from conception to the eighth gestational week), the early fetal period (up to mid-gestation), and the late fetal period (lasting until birth). During the early and late fetal periods, brain development centers on the processes of neuron production, migration, connection, and differentiation.

At the midpoint of gestation, 20 weeks, the end of the early fetal period, the brain has the necessary structures for mature functioning, albeit with a smooth, lissencephalic versus ridged cortical plate, as the ridges (gyri) and depressions (sulci) are just beginning to form (Encha-Razavi & Sonigo 2003, Fogliarini et al. 2005). These fissures begin to appear at between 18 and 24 weeks and distinguish the four lobes of the brain that make up the cerebral cortex (frontal, parietal, occipital, and temporal). The development of secondary and tertiary sulci continues through the end of gestation. These fissures—the wrinkled appearance—increase the brain’s efficiency by enlarging the brain’s surface area and the neurons within it.

The early fetal period is critical for the development of the neocortex, as most cortical neurons are generated during this period and many have migrated to their positions in the neocortex and begun to form essential connections for future neural circuits. The human brain contains billions of neurons, most of which are produced by mid-gestation. Neuronal migration peaks between gestational weeks 12 and 20 and is largely complete by weeks 26 to 29. The late fetal period sees significant specialization in each neural region and the formation of different cortical layers, as well as the overall maturation of the brain. With respect to communication or connections, early neurons, known as subplate neurons, are capable of propagating neural signals across different neurotransmitter systems, for example, across monoaminergic, cholinergic, and glutamatergic synapses. The formation of these neuronal connections, called dendritic arborization and synaptogenesis, accelerates in the late fetal period to produce a thickening of the developing cortex. At week 34, approximately 40,000 new synapses are formed every second, a process that continues into early postnatal life. Finally, while the number of neurons in the human brain peaks at 28 weeks, as many as half of these neurons die as a result of naturally occurring cell death (apoptosis). Myelin, which is first detected at between 20 and 28 weeks, enhances the speed and accuracy of neuronal communication (Tau & Peterson 2010). Because the foundations of the central nervous system develop prenatally, variations originating from this critical period will impact subsequent neural network patterns and have significant relevance for neurobehavioral development (Anderson & Thomason 2013).

Different Theoretical Models: Does Maternal Distress Program Risk or Plasticity?

In broad terms, DOHaD research falls under the diathesis–stress model, which is so prominent in developmental psychopathology research (Sroufe 1997). In this model, some individuals are more vulnerable to adversity due to endogenous characteristics, such as genes of risk or negative emotionality; prenatal studies of future risk for mental health problems identify prenatal exposures as contributing to a child’s vulnerability, or his or her diathesis. Unique to DOHaD studies are specific tenets, such as fetal adaptation, programming, and the match between pre- and postnatal environments, that emphasize the ongoing malleability of the organism over time (i.e., developmental plasticity) and children’s outcomes as products of successive adaptations to environmental cues.

Barker (1995) describes the fetus as adapting to his or her environment with changes in their biology that become programmed, meaning embedded and long-lasting, with the idea that these programmed changes potentially put the offspring at risk for future disease. Glover

(2011) and Sandman et al. (2013) suggest that fetal adaptations are aimed at ensuring survival and that exposure to maternal prenatal distress functions as a communication foreshadowing characteristics of the postnatal world for which the fetus can begin to prepare via biological adaptations. The developmental outcomes partly depend on the match or mismatch between the in utero cues foreshadowing the postnatal environment and the environment actually encountered. From an evolutionary perspective, behaviors that may have been programmed in utero to be advantageous could be incongruent with the demands of the modern world. For example, as Glover (2011) summarizes, children's outcomes related to prenatal exposure to maternal distress—*anxiety, ADHD, impulsivity, aggression*—may have been adaptive in life-threatening environments by increasing vigilance and prioritizing attunement to danger cues, more exploration, and a willingness to fight predators. We have found higher levels of maternal distress related to greater fetal heart rate in response to stimuli, an early marker of heightened alertness (Posner et al. 2016). The adaptation itself is not viewed as pathogenic; instead, pathology can emerge from the mismatch between the pre- and postnatal environments. In one provocative paper, concordance between maternal prenatal (at 25 gestational weeks) and postpartum depression versus nonconcordance (so, two hits of depression versus only one in a traditional diathesis model) was associated with superior scores on the Bayley Scales of Infant and Toddler Development at 3, 6, and 12 months (Sandman et al. 2012). Alternatively, prenatal adaptations are hypothesized as inherently coming at a cost—that is, a short-term survival benefit associated with future risk for poor neurodevelopmental outcomes. Finally, a newer premise in the DOHaD model is that adaptation itself is being programmed prenatally. Here, exposure to prenatal distress fosters offspring's sensitivity to the environmental context, which is viewed as a risk or opportunity factor, depending on the qualities of the child's life (Hartman et al. 2018). In one study, prairie voles exposed to prenatal maternal stress showed varying levels of behavioral and physiological stress reactivity as adults, depending on the quality of their rearing environments, while controls showed no effect of rearing condition (Hartman et al. 2018). The DOHaD model offers innovative and potentially testable hypotheses regarding the succession of processes by which prenatal exposure to maternal distress affects development and contributes to compromised neurobehavioral outcomes in children. The concept of adaptation is an important lens for this research, with theoretical specificity that can be operationalized and optimism with respect to opportunities for clinical intervention, as adaptations are not viewed as pathology or risk per se.

Maternal Prenatal Distress Is a Risk Factor for Future Psychopathology in Children

Approximately 10–12% of pregnant women meet the criteria for a mental disorder, most often anxiety or a depressive disorder. This rate more than doubles in women from low-income samples. An estimated 30% report some kind of stress in their daily lives (van den Bergh et al. 2017). Two recent papers (O'Donnell et al. 2014, van den Bergh et al. 2017) describe the substantial evidence demonstrating that elevated maternal distress during pregnancy increases the future child's risk for mental health disorders, including anxiety, depression, ADHD, and schizophrenia. In an extensive systematic review of all published studies in humans conducted between 2010 and 2017 that were longitudinal, prospective epidemiological, or clinical observational, and that reported on maternal distress and children's outcomes, van den Bergh et al. (2017) concluded that maternal distress across

different gestational time points predicts behavioral problems in both males and females, such as externalizing or internalizing symptoms, anxiety, and depression, as well as conduct problems and overall psychiatric disturbances, although they also reported the existing negative findings. The papers reviewed tended to have solid methodology, including less reliance on maternal report for the mother and her child's functioning; the inclusion of key moderators, such as family support; and postnatal contextual factors, such as family functioning. The other paper (O'Donnell et al. 2014) leveraged the Avon Longitudinal Study of Parents and Children cohort of nearly 8,000 children followed from the third trimester to 13 years of age and showed the following: High levels of maternal anxiety were associated with a twofold increased risk in probable mental disorder in male and female children at ages 4, 7, 9, 11.5, and 13 years. Results were similar for prenatal depression and included potential confounders (i.e., maternal postnatal anxiety and depression, socioeconomic factors, obstetrical risks, and maternal parenting) in the statistical models. One weakness in the study—that mental disorder outcomes were based on maternal report (also the source of the pregnancy anxiety evaluation)—is overcome by other studies of the same cohort showing an increased risk for child and adolescent depression and anxiety based on children's reports or standardized clinical interviews with the child, or both (van den Bergh et al. 2017).

The data supporting an association between prenatal maternal distress and the offspring's risk for psychopathology provide strong rationale for the public health relevance of this line of DOHaD studies. Yet the nuances of the DOHaD conceptual model that include fetal adaptation and developmental plasticity, in line with the developmental approach to psychopathology (Sroufe 1997) emphasizing equifinality—multiple pathways leading to the common manifest outcomes (mental health diagnosis)—as well as multifinality—different outcomes (diagnosis) resulting from the same pathways (Cicchetti & Rogosch 1996)—frequently are outside the scope of this research. The most robust support of the DOHaD hypothesis that maternal distress affects children's future brain–behavior development that is relevant to psychopathology may come from an examination of proximal outcomes or intermediate phenotypes or endophenotypes that may reveal adaptation and mark a risk for future psychopathology, as well as from preclinical animal studies. Research on mechanisms—variations in maternal, fetal, and placental child biology and behavior—provides this evidence.

MATERNAL DISTRESS GETS UNDER FETAL SKIN

Mechanisms: How Maternal Distress Reaches the Fetal Brain and Alters Development

Here, we review several biological systems hypothesized to be mechanisms by which maternal distress affects fetal and child brain–behavior development. Some of these intermediate phenotypes focus on maternal biology, while others concern the offspring; these systems are described independently as that is how they most often are studied, and yet they are functioning concurrently with multiple influencing pathways. See Figure 1 for a visual representation of some of the processes and pathways reviewed here.

Hypothalamic–pituitary–adrenal axis.—The hypothalamic–pituitary–adrenal (HPA) axis is a central component of the hormonal stress response system. It is responsible for

secreting glucocorticoids, including cortisol, which alerts the organism to potential threat and maintains homeostasis (Herman & Cullinan 1997). Abnormal functioning of the HPA axis is implicated in the pathophysiological mechanisms underlying a range of psychiatric illnesses (Buitelaar 2013). Since prenatal maternal distress may be associated with alterations in HPA axis regulation and higher levels of circulating glucocorticoids—which can affect placenta functioning and cross the placenta and reach the fetus (Monk et al. 2016, Stirrat et al. 2018)—it is likely that maternal distress affects the development of the offspring’s HPA circuitry and brain development, as well as the subsequent risk for psychopathology.

Prenatal programming of the offspring’s HPA axis functioning has been extensively investigated. A recent meta-analysis supports small-to-moderate effects of maternal distress on an offspring’s glucocorticoid levels across preclinical and human studies (Thayer et al. 2018). Overall, animal studies suggest that prenatal stress (PS for animal models) results in elevated levels of basal and reactivity (i.e., poststressor) corticosteroids and decreased negative feedback of the HPA axis (Maccari et al. 1995). Further, PS exposure affects stress neurocircuitry in mice, including increasing corticotropin-releasing factor in the amygdala and reducing hippocampal glucocorticoid receptor expression (Mueller & Bale 2008). These changes have been documented in rats alongside increased cognitive problems in offspring, anxiety, and depression-like behaviors, even through adulthood (Brunton & Russell 2010, St-Cyr et al. 2017).

An offspring’s sex appears to play a critical role in determining outcomes and, further complicating matters, interacts with the timing and type of PS exposure (Brunton & Russell 2010). For example, juvenile and adult male guinea pigs exposed to late-gestation PS [gestational day (GD) 50 or 60; gestation length approximately 65–70 days] had increased basal and adrenocorticotrophic hormone–stimulated cortisol levels (Kapoor & Matthews 2005). Juvenile and adult female offspring, however, had increased basal levels only in response to GD50 PS (Kapoor & Matthews 2008). In many studies, male offspring appear to be the most strongly affected. Interestingly, they often present with what is known as a dysmasculinized phenotype (i.e., with behaviors and gene expression patterns most commonly seen in females) (Bale 2016). Preclinical models traditionally have used a range of prenatal stressors (e.g., handling, strobe lights, nutrient restriction, cortisol injections, and electric shocks) to investigate HPA axis functioning in offspring. More recently, greater attention has been paid to tailoring animal models to mimic stressors relevant to human experiences (e.g., social stressors). Exposure to these more ecologically valid social stressors early in gestation often results in pregnancy loss, whereas later exposure appears to have long-lasting cognitive, neurological, and behavioral effects in offspring, including hyperresponsiveness to stress and increased anxiety (Brunton 2013).

Human studies relate maternal prenatal distress and maternal HPA activation to an increased risk for autism spectrum disorder (ASD), schizophrenia, depression, anxiety, and ADHD in offspring (Chan et al. 2018). Higher prenatal levels of maternal plasma corticotropin-releasing hormone are associated with greater cortical thinning and decrements in cognitive functioning in school-age children (Sandman et al. 2018). Birth cohorts and longitudinal studies have expanded our understanding of the fetal programming of the HPA axis, yet

findings have been equivocal in associating maternal distress with HPA axis dysfunction and psychopathology. For example, one study of 116 women with elevated cortisol levels during the second and third trimesters found increased stress responses in newborns but did not find an association between maternal distress and cortisol (Davis et al. 2011), and another found an association only between maternal distress and slightly lower awakening, and not diurnal, cortisol ($N = 170$ mothers) (van den Heuvel et al. 2018). A recent prospective longitudinal study documented that both prenatal maternal depression and cortisol levels during the first and second trimesters were related to emotional reactivity in preschool-age offspring, suggesting that both of these prenatal exposures may have independent, sex-specific effects (Swales et al. 2018). The direction of findings has also varied, with some studies documenting blunted HPA axis and stress responses in offspring (Vedhara et al. 2012) and others documenting the opposite (Capron et al. 2015). Further, one study found initial increases in early offspring cortisol reactivity (at 5 weeks), but decreases in later reactivity (at 8 weeks and 12 months); stressors have varied across offspring assessments, possibly contributing to the variability (Tollenaar et al. 2011). Seemingly contradictory offspring sex effects have also been found. For example, the Iowa Flood Study of pregnant women found increased cortisol in response to stress in female toddlers, but not in male toddlers (aged 2.5 years) (Yong Ping et al. 2015).

Maternal immune activation.—Maternal immune activation (MIA, denoting during pregnancy) can occur in response to a number of triggers, including infection, diet, and psychosocial stress. The relation between MIA and compromised neurodevelopmental and psychiatric functioning has been widely investigated in recent years, with both animal models and studies in humans predominantly supporting such an association.

Animal models support MIA leading to increased risk for psychopathology in offspring. Findings include symptoms and behaviors representative of autism (Kang et al. 2014), schizophrenia (Li et al. 2009), and anxiety and depression (Depino 2018). There are several proposed mechanisms, as maternal cytokines can impact the fetus by (a) crossing the placenta and entering the fetal compartment (see the section titled Placental Functioning: DNA Modification), (b) affecting the placenta itself and causing placental inflammation and associated cytokine production, (c) creating fetal immune dysregulation, or (d) a combination of the three (Meltzer & Van de Water 2016). Because cytokines are known to be involved in dendritic growth and neuronal survival and differentiation (Marx et al. 2001), MIA may exert its effect on offspring's outcomes through multiple aspects of brain development [see Gumusoglu & Stevens 2019 for a recent review of MIA, including new findings on the changes in microglia (brain immune cells) influencing outcomes]. Given the array of disorders that have been associated with maternal perinatal inflammation, it is likely that the specific cause of inflammation (i.e., in response to bacterial infection versus experienced stress), the timing of exposure, and other environmental and individual factors (e.g., the offspring's sex, genetic risk for a specific disease) interact and result in different processes leading from MIA to risk for a range of psychopathologies in offspring.

A recent review (Depino 2018) underscores these issues by documenting that in animal models the specific methodology used to elicit maternal perinatal inflammation often results in different symptomatology. For example, administering bacterial versus viral insults at the

same time (GD 9) in males results in, respectively, brain and behavioral differences associated with schizophrenia [i.e., enlarged ventricles and reduced prepulse inhibition in males (Li et al. 2009)] or increases in anxiety and depression-like behaviors (Depino 2018). Further, there is significant variation in outcomes depending on the timing of inflammation, even when the methods utilized to elicit it are kept constant (Li et al. 2009). For instance, a viral challenge with polyinosinic:polycytidylic acid on GD9 resulted in hindered spatial exploration in offspring, whereas the same exposure on GD17 led to poorer performance on a discrimination reversal learning task (i.e., increased perseverative behavior) (Meyer et al. 2006). Notably, offspring sex effects, when explored, have been frequently identified. Sex steroids (i.e., estrogens, androgens, and progesterone) are known to have a role in regulating the immune system and influence HPA axis activity. Thus, it is likely that the type of infectious agent and timing of maternal inflammation interact with an offspring's sex and possibly underlie some of the inconsistency in findings (Rana et al. 2012).

Studies on MIA in humans also document an increased risk for offspring psychopathology, notably ASD and schizophrenia. The vast majority of this work has examined infection-related MIA, and as in the rodent literature, findings vary depending on the timing of inflammation and type of infectious agent (Careaga et al. 2017). For example, a Danish study that included 10,000 children with autism found associations between maternal viral infection during the first trimester and maternal bacterial infection during the second trimester and ASD risk in children (Atladóttir et al. 2010). Maternal infection also may be a risk factor for affective disorders in offspring (reviewed in Simanek & Meier 2015). Another study showed an increased proportion of affective disorders occurring in children conceived during the influenza type A2/Singapore epidemic in Helsinki, Finland (Machon et al. 1997). It is important to consider that maternal stress—versus a subclinical or clinical infection—may have a more pervasive inflammatory profile, as studies find elevated serum levels of proinflammatory cytokines across trimesters in mothers with high psychological stress and low social support (Coussons-Read et al. 2007).

An emerging line of research has documented that MIA [indexed via levels of interleukin-6 (IL-6) and C-reactive protein] is related to potentially important intermediate phenotypes in the fetus and infant: decreased fetal heart rate variability (considered a physiological substrate of emotion regulation), alterations in functional connectivity between the medial prefrontal cortex and temporoparietal junction, and larger right amygdala volume and increased amygdala connectivity to a number of structures across the brain (Rudolph et al. 2018, Spann et al. 2018). Together, these studies suggest that prenatal MIA exposure can impact the early development of the autonomic nervous system and brain networks involved in cognition, sensory processing, learning, and emotion. These studies show great promise, given that by detecting brain alterations at such an early age, there is reduced confounding from postnatal exposures. However, the specific functional significance of these alterations is yet to be determined; results from one study indicated that maternal inflammation was related to decreased working memory at 24 months (Rudolph et al. 2018), yet another found a positive association with overall cognition at 14 months (Spann et al. 2018). Extended longitudinal follow up and further replication are needed.

Placental functioning: DNA modification.—Environmental insults can alter placental biology, in part via epigenetic modifications, and lead to perturbation of the transport and waste removal functions, such as a deficiency in nutrient transport leading to altered fetal growth (Angiolini et al. 2006).

The term epigenetics refers to heritable changes in gene expression (activation or suppression) that occur without alterations to the DNA. Epigenetic mechanisms include DNA methylation, histone modification, and the presence of noncoding RNA; the most broadly studied is DNA methylation. Several studies suggest that changes in placental DNA methylation at least partly mediate the effect of environmental factors on an offspring's future risk for behavioral problems.

The placenta regulates fetal cortisol exposure, in part via placental DNA methylation of glucocorticoid-related genes such as *FKBP5*, *HSD11B2*, and *NR3C1*. Deregulation of this placental function has been shown to impact the offspring's neurobehavioral development (Conradt et al. 2013, Monk et al. 2016, Paquette et al. 2014). In humans, placental DNA methylation of *FKBP5* (FK506 binding protein, a molecular chaperone of glucocorticoid receptor regulation) has been associated with reduced placental *FKBP5* gene expression and increased risk of high arousal in newborns ($N = 61$, 49% female) (Paquette et al. 2014). Maternal depression has been associated with greater placental DNA methylation of *NR3C1*, a gene encoding for a glucocorticoid receptor, and *HSD11B2*, a gene producing an enzyme that converts active cortisol into inactive cortisone. Placental DNA methylation of these two genes predicted poorer self-regulation, lower muscle tone, and more lethargy in neonates ($N = 482$, 47% female) (Conradt et al. 2013). In another study, maternal stress was associated with increased placental DNA methylation of *HSD11B2*, which, in turn, was associated with a reduction in fetal coupling, indicative of delayed neurobehavioral development ($N = 61$, 51% female) (Monk et al. 2016). None of these papers identified sex effects in infant outcomes. Finally, maternal socioeconomic adversity has been associated with lower levels of placental *HSD11B2* methylation, with greater effects in males than females (Appleton et al. 2013).

The placenta: mitochondrial dysfunction.—Mitochondria are organelles present in every cell of the body and contain their own DNA; they are essential for several biological functions, including energy production. DNA methylation processes are mechanistically linked to mitochondrial functioning. Mitochondria are involved in the one-carbon metabolism pathway that uses nutrients from the diet to provide methyl (CH_3) groups for the methylation of DNA (Bao et al. 2016). In addition, mitochondrial signaling regulates gene expression in the cell nucleus and the DNA methylation machinery, DNA methyltransferases, which contribute to DNA methylation and transcriptional reprogramming in the placenta (Picard et al. 2014). In a preclinical study, PS induced in rats was associated with depression-like behavior and with a reduction of PGC-1 α protein (a regulator of mitochondrial biogenesis) in the frontal cortex and hippocampus of their 3-month-old male offspring (Glombik et al. 2015). In human pregnancies, one study found a decrease in placental mitochondrial copy number with exposure to prenatal stress (Brunst et al. 2017). The mitochondrial copy number is the ratio of a mitochondrial gene to a reference nuclear gene (designated as mtDNA/nDNA) and is often considered an index of

mitochondria content per cell, although this interpretation has been criticized. A study investigating DNA gene expression found an association between prenatal stress and changes in placental mitochondrial DNA gene expression of oxidative phosphorylation subunits involved in energy production; higher self-reported trait anxiety, state anxiety, and perceived stress were associated with increased *MT-ND2* gene expression, and increased expression was negatively correlated with infant temperament indices of activity, smile, and laughter at 6 months of age (Lambertini et al. 2015).

The gut microbiome.—It has become increasingly evident that the gut microbiome has a significant role in health and disease, including in neurodevelopment and psychiatric functioning (Lima-Ojeda et al. 2017). Alterations in the composition of the gut microbiota have been found in clinical populations, including populations with depression, stress, anxiety, and autism (Cenit et al. 2017). Our understanding of the establishment and development of the gut microbiome is limited, yet there is evidence that this process begins perinatally and that birth strongly influences it. For example, infants born via vaginal delivery show a bacterial composition resembling their mothers' vaginal microbiome, whereas babies born via Cesarean section show more skin-like microbiomes (Dominguez-Bello et al. 2010). Moreover, recent rodent studies challenge the existence of a sterile in utero environment, suggesting an even earlier mother–infant microbiome transmission, likely through the placental barrier or fetal ingestion of amniotic fluid (Walker et al. 2017). Microbiota colonize the infant gut and guide critical processes, such as metabolism and nutrient extraction (Cilieborg et al. 2012). Because the developing brain exerts a high metabolic demand, microbial colonization may significantly influence brain maturation and, potentially, the risk for neuropsychiatric disease (Keunen et al. 2014). As prenatal stress is known to alter the composition of the maternal microbiota, the maternal microbiome may be another plausible pathway for prenatal maternal stress to exert an influence on an offspring's neurodevelopment (Culhane et al. 2001).

Animal studies support this mechanistic model. A study in nonhuman primates demonstrated that the offspring of prenatally stressed mothers showed altered gut microbiomes (Bailey et al. 2004). Of note, this study found that the early versus late gestational induction of stress predicted different types of bacterial depletion: *Lactobacillus* versus both *Bifidobacterium* and *Lactobacillus*, respectively (Bailey et al. 2004). A number of studies have suggested that administering these probiotics can result in symptom reduction across neurological and psychiatric disorders, including ASD, schizophrenia, and depression. Preclinical studies provide some evidence of probiotic administration influencing concentrations of inflammatory cytokines, gamma-aminobutyric acid, glutamate, and brain-derived neurotrophic factor, all of which play important parts in cognitive functioning and are implicated across psychiatric diseases (Cerdó et al. 2017). Rodent models show early and late gestational stress resulting in *Lactobacillus* depletion in both the maternal vaginal microbiome and the offspring's gut microbiome (Gur et al. 2017), and this depletion lasts even through adulthood (Jašarević et al. 2015). Further, the offspring of stressed dams showed altered brain development, including reductions in amino acid concentrations across a host of brain regions. These reductions were more pronounced in male offspring, suggesting increased susceptibility to metabolic programming of the

developing brain in males (Jašarević et al. 2015), perhaps stemming from its typically larger overall size, slower developmental course, and associated increased energy demands.

These studies point to the important role of the maternal and infant microbiomes in offspring's neuropsychiatric development, although several gaps in the research remain. Importantly, no direct human evidence of in utero infant gut colonization exists (although see Oki et al. 2018 for emerging work in this area). Further, neither human nor rodent studies have examined the long-term behavioral and psychiatric implications of prenatal maternal stress-related alterations in offspring's microbiomes.

Sensory experiences.—Before birth, fetuses register sensory experience, and there is evidence of transnatal learning—that is, learning that occurs as a fetus is carried across the birth divide (Busnel et al. 2017, Moon & Fifer 2000). The extent to which prenatal sensory exposures related to maternal affect influence individual differences in offspring's neurodevelopment is only beginning to be studied.

Decades of innovative work have demonstrated late-term fetal discrimination of various sound categories, including musical tones and short melodies (Busnel et al. 2017), as well as voice preference, in particular, for the mother's. Based on a nonnutritive sucking paradigm, 3-day-old infants showed they identified their mother's voice (reading Dr. Seuss) over another woman's and sucked more to elicit hearing it (DeCasper & Fifer 1980). Later work, again using maternal recitation as well as singing, replicated newborn discrimination of the maternal voice as well as memory for a spoken passage or melody even if produced by an unfamiliar speaker. As DeCasper et al. have described (Busnel et al. 2017, DeCasper & Fifer 1980), this preference for the maternal voice over another woman's likely subserves bonding while transnatal memory for language-specific properties may undergird language development. A recent novel experiment (Tallet et al. 2016) extended prenatal auditory learning, asking whether pairing prenatal auditory voice exposure with a maternal aversive versus positive experience would influence postnatal behavior when the familiar voice was heard. Late-gestation pregnant sows underwent soft brushing versus electrical prodding manipulation while hearing a tape-recorded voice. At 3 weeks postpartum (1 pig year = 18 human years), piglets were given a social isolation test; compared with control piglets whose mothers did not undergo manipulation and with those exposed to the voice paired with positive brushing, those exposed to the voice paired with maternal aversive prenatal treatment emitted more distress calls. Given emerging fetal imaging studies demonstrating sensory-driven plasticity (Anderson & Thomason 2013), these findings suggest the possibility of in utero shaping of fetal neural organization and infant postnatal behavior based on the pairing of varying maternal emotions (which the fetus experiences as stimuli via maternal hormone and/or cardiorespiratory activation) with external auditory stimuli. Future key areas of research concern (a) replication, (b) identification of the biological pathways by which maternal prenatal emotional experience may contribute to neurodevelopment and behavior consonant with the valence of the maternal prenatal experience, and (c) the extension to infant studies and overcoming of the challenges for operationalization. If the fetus is exposed to maternal biological stress cues and angry speech, would this amplify infant sensitivity to the composite cues of maternal affect dysregulation? Would this have possible implications for future development or adaptively

prime a child to register sounds associated with intimate partner violence that they heard in utero?

Pathways: Is it Maternal Distress or an Unexamined Variable Associated with Distress?

In studies showing associations between prenatal maternal distress and increased risk for child psychopathology, lifestyle characteristics as well as relevant disease states often are not simultaneously examined. Yet many such factors commonly covary with distress and may be the agent of influence. That is, maternal distress may be a marker variable for unexamined subclinical health and lifestyle factors that also affect fetal and child development.

Sleep.—Maternal sleep patterns undergo changes throughout pregnancy due to alterations in reproductive hormones, increased nocturia, and body aches (Pien & Schwab 2004). Studies report increased sleep duration during the first trimester that gradually decreases throughout pregnancy, with sleep becoming shorter and more fragmented during the last trimester. Altered sleep is a common occurrence, yet any further sleep loss—including that associated with maternal distress—can place both mother and offspring at risk for negative health trajectories, including poor birth outcomes (reviewed elsewhere, see Palagini et al. 2014).

No studies in humans have tested specific associations between maternal prenatal sleep disturbance and children's future risk for psychopathology. Nevertheless, there are some studies that indirectly support the probability. For example, one study of 74 mothers found evidence for delays in social development in 1-year-olds born to mothers who experienced sleep-disordered breathing during pregnancy (Tauman et al. 2015). A study from our group showed that in a sample of 292 teenage mothers (ages 14–19 years), emotional abuse during childhood was indirectly associated with lower third-trimester fetal heart rate variability via abuse-related maternal sleep disturbances throughout pregnancy (Gustafsson et al. 2017). Studies also have reported a positive correlation between maternal prenatal sleep and offspring sleep (Armstrong et al. 1998). Because childhood sleep problems are predictive of future psychopathology (Gregory & O'Connor 2002), it is possible that poor maternal prenatal sleep increases offspring's risk of mental illness through this pathway. Finally, because poor prenatal sleep is related to elevations in both maternal circulating cytokines (Okun et al. 2009) and cortisol levels (Bleker et al. 2017), the pathways previously described may underlie the potential associations between maternal sleep and children's risk for psychopathology, yet these hypotheses remain to be tested.

In contrast, animal studies have significantly contributed to our understanding of the association between disrupted or diminished prenatal maternal sleep and offspring's risk for psychopathology, and they may prove to be particularly helpful in specifying the pathways by which maternal prenatal sleep affects offspring's psychopathology. Studies of prenatal maternal sleep deprivation (MSD) have consistently documented compromised development and functioning in offspring of dams with MSD. Findings include increased hyperactivity (Radhakrishnan et al. 2015), risk-taking behaviors (Gulia et al. 2014), anxiety and depression-like symptoms (Yu et al. 2018), and cognitive deficits (e.g., spatial learning and memory; Yu et al. 2018, Zhao et al. 2015). MSD has been found to impair hippocampal

neurogenesis (Zhao et al. 2015) and synaptic plasticity (Yu et al. 2018), which have been causally linked to disruptions in emotional and cognitive functioning.

The rodent literature is mostly consistent in documenting emotional and cognitive sequelae in offspring of dams with MSD, yet several questions remain. Rodent models have typically examined a gestational period comparable to third-trimester human MSD (Radhakrishnan et al. 2015, Yu et al. 2018, Zhao et al. 2015), and the studies examining first- and second-trimester MSD have been inconsistent in documenting emotional deficits (Calegare et al. 2010). It remains to be determined whether these different sequelae truly reflect the timing of sleep deprivation effects or differing MSD methods [e.g., gentle handling versus placing rats on platforms surrounded by water to prevent rapid eye movement (REM)-related muscle relaxation; Silva et al. 2004] or are due to varying offspring outcome measures. Also, because the type of sleep loss (i.e., total MSD, REM-only deprivation) has been found to produce differing offspring behavior (Gulia et al. 2014), future human research will have to include objective sleep measures to create a complete understanding of the possible influence of and mechanisms by which disruptions in maternal prenatal sleep may influence offspring's development. Finally, it must be noted that sleep restriction also is stress inducing.

Nutrition.—Stress and depression often co-occur with inadequate nutrition, are highly interrelated, and have been associated with similar adverse neurobehavioral outcomes in offspring. Both maternal experiences of stress and inadequate nutrition may affect the fetus via related biological pathways (Monk et al. 2013).

Concerns about the long-term effects of maternal prenatal malnutrition initially arose from epidemiological studies of the Dutch famine (1944–1945) showing that children conceived during a period of starvation had a higher risk of disease later in life, including neurodevelopmental disorders such as schizophrenia (Hoek et al. 1998). Clinical, epidemiological, and basic science research have shown that macronutrient deficiencies (i.e., reduced general caloric intake, and deficiencies in glucose, fat, and protein) and micronutrient deficiencies (i.e., in minerals such as zinc, iron, copper, or iodine, or in vitamins, such as choline, folate, and vitamin A) are associated with increased risks of adverse neurobehavioral developmental outcomes (such as cognitive delays, ADHD, ASD, and schizophrenia) in humans and with alterations in stress- and behavior-related brain regions in animals (i.e., the hippocampus and dopamine circuitry involved in the reward system) (Monk et al. 2013, Prado & Dewey 2014). Nutrient deficiency is more likely to impair brain development if the deficiency occurs during a period when the need for that nutrient for neurodevelopment is high. Early in pregnancy, deficits in maternal nutrient intake have been shown to affect cell proliferation, while deficits later in pregnancy have been shown in preclinical studies to affect cell differentiation, synaptogenesis, and dendritic arborization (Monk et al. 2013, Prado & Dewey 2014).

Nowadays, the spread of industrialized agriculture has allowed for a net increase in the calories and macronutrients consumed by the US population, leading to an overall rise in average body mass, but these gains are not necessarily associated with adequate micronutrient or fatty acid in-take. Adequate micronutrient intake is a critical factor for

maternal mental health: Deficiencies in folate, vitamin B12, calcium, iron, selenium, zinc, and magnesium have been associated with symptoms of depression in pregnant women (Leung & Kaplan 2009, Singh et al. 2017). Distress can also affect dietary patterns: The comfort food hypothesis suggests that chronic stress can promote a coping strategy leading to higher macronutrient intake and a preference for foods containing more carbohydrates and saturated fats. Stress and depressive symptoms have been shown to alter eating patterns, resulting in increased selection of less-nutritious food, particularly food high in fat and sugar, and processed foods, and decreased selection of fruits and vegetables (reviewed in Baskin et al. 2015). Previous studies have suggested that a diet high in fats and sugar could affect one's biology, leading to the development of depression (Sánchez-Villegas et al. 2011, 2012; Vermeulen et al. 2017).

In addition to the risk of high caloric intake occurring concomitantly with deficiencies in essential nutrients, an unhealthy diet itself can affect brain development. In animals, maternal consumption of a high-fat diet during gestation has been associated with hyperactivity, anxiety-like behavior, depressive behavior, and cognitive delays in the offspring (Sullivan et al. 2015). In humans, maternal consumption of a high-fat diet during pregnancy has been associated with an increased incidence of behavioral problems, poorer regulatory capacity, and lower surgency (i.e., low interest and motivation) in infants and children (Gustafsson et al. 2015, Pina-Camacho et al. 2015, Steenweg-de Graaff et al. 2014). The availability of methyl donors, such as folate and choline, as well as cofactors, including zinc and vitamins B2, B6, and B12, is essential for typical DNA methylation and placental function (Niculescu & Zeisel 2002). Several studies in animals and humans have shown the effects of caloric restriction and micronutrient deficiency, such as choline deficiency, on placental DNA methylation of glucocorticoid-regulating genes (Belkacemi et al. 2011, Bertram et al. 2001, Jiang et al. 2012).

Other disease states.—Psychological stress, anxiety, and depression are risk factors for infection (Cohen et al. 1991) as well as for diseases, such as diabetes (Hackett & Steptoe 2017), and hypertensive disorders, such as preeclampsia (Zhang et al. 2013), which even at the preclinical level could be contributing to offspring's risk for psychopathology. Pregnant women with chronic disease often are highly anxious, in particular in relation to their pregnancy outcomes.

Several lines of evidence from human and preclinical models suggest that diabetes onset is influenced by psychological stress (reviewed in Hackett & Steptoe 2017). Also, a recent study showed that psychosocial stressors may be associated with the onset of gestational diabetes mellitus (GDM) (Horsch et al. 2016). Pregestational diabetes and GDM have been associated with altered cognitive outcomes in the offspring (Adane et al. 2016) and with an increased risk for ASD (Sacks et al. 2016, Xiang et al. 2015). In Israel, a population-based study conducted on all pregnant women who delivered between 1991 and 2014 and their children found a higher prevalence of neuropsychiatric hospitalization (e.g., for ASD, eating disorders) in children exposed to GDM in utero (Sacks et al. 2016). In the United States, another cohort study that included 322,323 children born between 1995 and 2009 showed that the offspring of pregnant women diagnosed with GDM at 26 weeks had a higher risk of developing ASD (Xiang et al. 2015).

The onset of hypertensive disorders during pregnancy has been associated with emotional stress and depressive disorders (reviewed in Zhang et al. 2013). Hypertensive disorders during pregnancy are associated with higher risks of offspring developing behavioral problems, ADHD, affective disorder, and schizophrenia (reviewed in Dachew et al. 2018). A recent study conducted in the United States found a higher risk of developing ASD and developmental delays in children born from pregnancies complicated by preeclampsia (Walker et al. 2015). Importantly, the number of pregnant women with chronic diseases who are able to carry their pregnancy to term has increased over the years. A Danish cohort study that included all women who gave birth between 1989 and 2013 found that the prevalence of childbirth in women with chronic diseases increased from 3.71% in 1989 to 15.76% in 2013 (Jølving et al. 2016).

CLINICAL IMPLICATIONS

Prenatal Psychotherapy for Mother and Child?

The identification of maternal distress as a factor in prenatal programming, with implications for future neurobehavioral development of the child, introduces a possible time point for providing preventative interventions targeting fetal and child adaptations that may signal risk, and this has additional appeal in that there are at least two patients, the mother and her offspring. Because brain development begins before birth, parenting begins before birth (Glover & Capron 2017). Specifically, interventions that improve pregnant women's well-being and affect regulation may also reach the developing child; improvement in mood during pregnancy is thought to diminish risks for postpartum depression and the associated effects on the child and to foster more positive representations of the child in utero that will carry over into the quality of the mother-child attachment system (Glover & Capron 2017). Increasingly, clinical researchers who study maternal perinatal mood disturbance are calling for a dyadic approach to treatment, one that encompasses both the mother and her child (or future child), given the profound bidirectional psychological and biological influences between them (Weissman 2018, Werner et al. 2016). An innovative, ongoing NIH randomized controlled trial ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier) aims to ask the key question about early interventions addressing prenatal parenting: Does reducing pregnant women's depression lead to modifications in the neurobehavioral mechanisms in the infant that are associated with risks for later psychopathology? Results from this trial will have direct implications for addressing pregnant women's behavioral health needs and also will function as an experimental test of the fetal programming hypothesis.

The Complicated Case of Psychotropic Medication Use During Pregnancy

In 2016, the US Preventive Services Task Force recommended screening for depression in the adult population, including in pregnant women (Siu et al. 2016). Prior to this policy directive, prescriptions of selective serotonin reuptake inhibitors (SSRIs) to pregnant women already had increased four- to eightfold during the past 30 years (Lugo-Candelas et al. 2018). Targeted interventions offered as adjuncts to obstetrical care, such as MOMCare (Grote et al. 2015) and Massachusetts Child Psychiatry Access Project for Moms (MCPAP for Moms) (Byatt et al. 2016), have expanded access to psychopharmacology, and relevant professional bodies have developed partnerships to devise decision guides for the use of

these medications during pregnancy (Yonkers et al. 2009), in part because epidemiological and clinical observational studies have identified alterations in child brain–behavior development associated with prenatal SSRI exposure (Oberlander & Vigod 2016). For example, prenatal SSRI exposure is associated with gray matter expansion in the amygdala and insula in sleeping newborns and greater connectivity between the two regions, possibly indicating a potential for heightened fear conditioning and risk for future anxiety disorders (Lugo-Candelas et al. 2018). Preclinical studies with rodents indicate that the central role of serotonin [5-hydroxytryptamine (5-HT)] during prenatal brain development—5-HT signaling affects cell proliferation, differentiation, neuronal migration, network formation, and synaptogenesis—may be altered by SSRI exposure (Lugo-Candelas et al. 2018). However, many human studies have been criticized for confounding by indication—that is, the difficulty of specifying children’s altered brain–behavior development as the result of SSRI exposure via changes in 5-HT signaling or the indication (e.g., maternal depression) that precipitated the SSRI use and its associated factors, or some of both (Oberlander & Vigod 2016). For example, we found that maternal untreated depression was associated with increased inverse functional connectivity between the amygdala and dorsal prefrontal cortex in sleeping, nonsedated young infants (Posner et al. 2016). In addition, consistent with a DOHaD developmental model, some data show fetal and infant adaptation to prenatal SSRI exposure, such as precocious receptive language development, that is not easily categorized as risky (Oberlander & Vigod 2016). Currently, each individual pregnant woman needs to consider the risks and benefits of using SSRIs. DOHaD data on prenatal maternal distress should not be referenced to support the use of SSRIs during pregnancy as no rigorous trial has compared untreated maternal prenatal depression to SSRI-treated depression with respect to infants’ outcomes.

CHALLENGES TO RESEARCH FINDINGS AND RELATED CONTROVERSIES

DOHaD studies focused on the effects of maternal distress are not without challenges, based on alternative hypotheses for interpreting results, methodological weaknesses, and new tools that have yet to be incorporated into research. Below, we discuss and aim to address these concerns.

Is the Postnatal Environment Adequately Controlled?

The majority of studies of prenatal distress control for potential confounds such as postpartum maternal depression and the quality of parenting (van den Bergh et al. 2017). This is especially important given the likelihood that distress during pregnancy is highly predictive of postpartum distress and future parenting (Glover & Capron 2017). Indeed, the best rodent models of PS cross-foster the pups during rearing because previously stressed dams parent differently (and/or their PS-exposed offspring elicit different caregiving) (Weinstock 2017), and these models still identify PS effects on offspring’s outcomes. With respect to feasibility and costs, it is terrifically challenging to assess, and thereby control for, the extent of postnatal influences on children’s development that might be foreshadowed by, and thus associated with, maternal prenatal distress. Mechanistic studies of proximal intermediate child phenotypes—especially fetal and newborn ones—that are consistent with long-term epidemiological studies and combined with experimental animal research

synergistically help to diminish this criticism. However, other solutions are needed to address this challenge, such as the use of innovative, less costly approaches to biobehavioral assessment (e.g., ecological momentary assessment via electronic monitoring of pregnant women and their future children).

How Not to Blame the Mother

It would be a grave perversion of science if research into prenatal maternal distress were interpreted as blaming women for their child's development, as was prominent in the 1950s when the concept of the refrigerator mother was provided as a so-called cause of autism. If, however, this research is used to emphasize that pregnant women and their future children are vulnerable populations who need to be protected accordingly from undue hardship and distress, potentially this too will add to judgement of women regarding their children's neurobehavioral outcomes, as well as paternalistically diminishing their freedoms as citizens. Relevant legislative issues are being raised and policy discussions are occurring; for example, there are bills before the US Congress supporting care for mothers and babies [H.R. 4695—Quality Care for Moms and Babies Act (2015–2016)] and paid leave [S.337—FAMILY Act (2017–2018)], which could reduce anticipatory distress during pregnancy, and an initiative at the Eunice Kennedy Shriver National Institute of Child Health and Human Development to protect pregnant women through research, not from it (NIH 2017). Nearly 50% of births in the United States are covered by Medicaid, the government program for low-income families without health insurance, thus changing the law so that recertification is not required at 60 days postpartum also would lessen pregnancy distress.

There is no doubt that women feel immense pressure regarding the mothering role (Howorth 2017); research into prenatal distress must be considered in context such that prenatal programming via maternal distress occurs as one of a multitude of factors influencing fetal and infant neural organization and brain–behavior development. The quality of the father's sperm also influences development (Dias & Ressler 2014), and fathers are a significant factor in women's well-being during pregnancy (Glover & Capron 2017).

Shared Genes of Risk

Future studies investigating the effects of prenatal distress on offspring's risk for psychopathology should assess gene by environment interactions for both the mother and her child. Children's behavioral outcomes may be more or less impacted by prenatal maternal distress based on interindividual maternal genetic variability, leading to either increased susceptibility or protective influences. In research on humans, it is difficult to disentangle the effects of prenatal exposure from the shared genes of risk. Some studies have investigated the effect of maternal prenatal distress while controlling for parental history of psychiatric symptoms as a proxy for genetic vulnerability and showed an independent effect of prenatal maternal distress on children's risk for psychopathology (e.g., MacKinnon et al. 2018). One study considered the effects of prenatal distress on offspring's risk for altered developmental outcomes in children conceived via in vitro fertilization compared with controls (Rice et al. 2010). Results indicated there was an independent effect of prenatal maternal distress on children's risk for antisocial behavior and anxiety (i.e., the risk was present in both related and unrelated children) but not for ADHD (i.e., it was seen uniquely

in children related to their mother) (Rice et al. 2010). Allelic variation in the offspring could also moderate the effects of maternal prenatal distress on offspring's risk of psychopathology. Oberlander et al. (2010) have found that prenatal maternal distress interacts with a child's 5-HTTLPR genotype—which codes for the serotonin transporter gene—in predicting offspring's behavioral dysregulation. Maternal anxiety during the third trimester increased the risk of anxiety or depression only in children with two short S alleles, and it increased the risk for aggression and externalizing behaviors only in children with two copies of the L allele (Oberlander et al. 2010). More work needs to be done that is similar to that by Oberlander et al. to identify the unique effects of exposure to prenatal maternal distress and the interacting and/or moderating roles of maternal and/or infant genes on children's outcomes. However, it is important to note that rodent models of PS, which aim to control for genetic strain, consistently show independent effects of PS exposure in offspring on brain-behavior outcomes (van den Bergh et al. 2017).

Who Shows Up for Research

When evaluating DOHaD findings, it is paramount to consider their generalizability and ecological validity. In human studies, this consideration often comes down to inclusion and examining which groups are represented in study samples. It is unfortunate that even after passing S.1, the National Institutes of Health Revitalization Act of 1993, the past two decades have not seen increases in minority participation that parallel their distributions in the US population (Burchard et al. 2015, Oh et al. 2015). For example, in 2015, Latinos and African Americans made up more than one-third of the US population, yet only 6% of participants in federally funded clinical trials were African American or Hispanic. This lack of diversity and representation in research samples is not only an ethical dilemma but also a scientific one, given that the effects of race and ethnicity on disease risk and treatment response are well documented. Particularly important to the present review is the fact that the communities that are underrepresented in research are often the ones disproportionately exposed to the environmental factors thought to pose a risk for development (e.g., psychosocial stressors). Furthermore, there may be race and ethnicity effects in the responses to environmental exposures, suggesting that the current body of literature may be severely limited in its generalizability.

Many Simultaneous Prenatal Exposures, Yet Studies Isolate One

As indicated, maternal distress may serve as a marker for another variable that is the true agent affecting offspring's outcome, for example, poor nutrition. A related important consideration is that the exposures in DOHaD research rarely are explored in unison; in fact, they are usually examined in isolation. It is necessary to determine the independent contributions of each exposure, and it also is imperative to design research to reflect reality: More likely than not mothers, and therefore their fetuses, are exposed to a number of factors simultaneously. Experiencing multiple exposures may result in either additive or interactive effects that, if unaccounted for, may contribute to mixed findings in the literature. This is particularly true for exposures that may result in similar outcomes or phenotypes. Further, it is important to acknowledge that exposures and mechanisms may exert an influence on each other, as we and others have observed to be the case for maternal nutrition and stress (Lindsay et al. 2019, Monk et al. 2013), and others have hypothesized for prenatal

inflammation and the microbiome (Kim et al. 2017). Until the field moves toward including assessments of multiple, simultaneous exposures, particularly for exposures that tend to co-occur frequently, DOHaD studies of the effects of maternal distress will lack ecological validity and rigor.

CONCLUSIONS

Decades of epidemiological, clinical translational, and preclinical animal research have converged, demonstrating that maternal prenatal distress affects fetal brain–behavior development and influences children’s neurobehavioral trajectory, often increasing their risk for psychopathology. A developmental psychopathology perspective, in particular the DOHaD model, frames this body of research as an exposure (maternal distress) at a critical period of central nervous system development; prenatal programming occurs as the fetus (and placenta) makes adaptations to this environmental influence. Studies probing the biological, mechanistic pathways through which maternal distress “gets under fetal skin” as an intermediate phenotype of altered child outcomes—dysregulation in the HPA axis, variation in newborns’ functional brain connectivity following MIA during pregnancy, increases in placental gene methylation—underscore the subtle, complex, iterative process that is psychobiological development and commences even before birth. The clinical implications of this work necessitate realism and also are momentous: Maternal prenatal distress is only one of many, many influences on children’s futures; distress during pregnancy is typically a modifiable factor, and interventions with distressed pregnant women can help women and may positively affect their children as well.

ACKNOWLEDGMENTS

We thank the team at the Perinatal Pathways Laboratory for helping with this review and all research from our group cited here, with a special thank you to Elizabeth Werner, PhD, for her tremendous contributions to the lab and to Sinclair O’Grady for help with citations and submission processes. We also acknowledge the support of the US National Institutes of Health (grants 1R01HD088105, UG3OD023328, 1UG3OD023316, T32MH016434-39) and the Wharton Fund. We apologize to those of our colleagues whose papers could not be cited in this review owing to space limitations.

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SUMMARY POINTS

1. The in utero period is a critical one for brain development given its phenomenal plasticity and thus vulnerability to influence, as most of the billions of neurons we have are produced by mid-gestation, and up to 40,000 new synapses are formed every second during the late third trimester, thereby establishing the human connectome.
2. The developmental origins of health and disease (DOHaD) model applied to neurodevelopmental outcomes demonstrates the impact of pregnant women's distress—defined broadly to include perceived stress, life events, depression, and anxiety—on fetal and infant brain-behavior development.
3. With 10–12% of pregnant women reaching criteria for depression and anxiety disorders, with the rate doubled in samples of women living in poverty, and with 30% overall experiencing significant life stress, maternal prenatal distress may be a third pathway for the familial inheritance of risk for psychiatric illness beyond shared genes and the quality of parental care.
4. Mechanistic studies of the biological processes mediating the transmission of maternal distress to the fetus, as well as those identifying intermediate biobehavioral phenotypes of the effects of maternal distress on the child—for example, reductions in placental gene methylation or alterations in offspring HPA axis regulation—support the DOHaD epidemiological and preclinical animal studies.
5. The DOHaD model applied to neurodevelopmental outcomes is in line with the recent ascendance of a developmental perspective in understanding and, ideally, preventing psychopathology, and it has dramatically increased interest in the prenatal period as a key time point relevant to neurobehavioral outcomes.
6. A dyadic approach to clinical care, one that encompasses both the mother and her future child, is gaining increasing traction because interventions with distressed pregnant women can help women and may positively affect their children as well.

FUTURE ISSUES

1. Aside from in vitro fertilization's success in facilitating healthy births, it provides a powerful opportunity to disentangle the effects of prenatal exposure to maternal distress from shared genetics (D'Onofrio et al. 2014), yet weaknesses include the difficulty of obtaining large samples, the generalizability of findings, and animal studies that suggest the manipulation of preimplantation embryos might have biological consequences.
2. Work on the positive maternal health attributes in DOHaD research is likely. The Growing Up in Singapore Towards Healthy Outcomes group showed that self-reported positive maternal mental health (e.g., a positive sense of self and mood) was uniquely related to children's cognitive, linguistic, and socioemotional performance up to the age of 2 years (Phua et al. 2017).
3. Better assessments of pregnant women's physical activity may lead to additional treatment interventions because increased activity may improve placental functioning, reduce intrauterine inflammation, mitigate disorders such as gestational diabetes and preeclampsia, attenuate prenatal maternal depression, and improve sleep (Álvarez-Bueno et al. 2018).
4. Emerging evidence suggests that prenatal supplementation of folic acid, omega-3 fatty acids, phosphatidylcholine, and vitamins A and D also could reduce the risk of children developing future psychopathology, such as schizophrenia and autism spectrum disorder.
5. The risks for certain psychopathologies may commence in the previous generation. The mechanisms underlying this intergenerational transmission are thought to be epigenetic in nature, potentially affecting the germ line, with far-reaching research, clinical, and societal implications, yet more remains to be understood (Scorza et al. 2018).
6. Environmental Influences on Child Health Outcomes (ECHO) is a research program launched by the US National Institutes of Health in 2016 to understand the effects of a broad range of early environmental factors, including maternal prenatal distress, on children's health and development. The data from approximately 50,000 children will be made publicly available and provide unprecedented opportunities for multidisciplinary teams to conduct novel explorations and robust analyses—including those involving simultaneous prenatal exposures—that advance scientific understanding of the social determinants of children's future health.

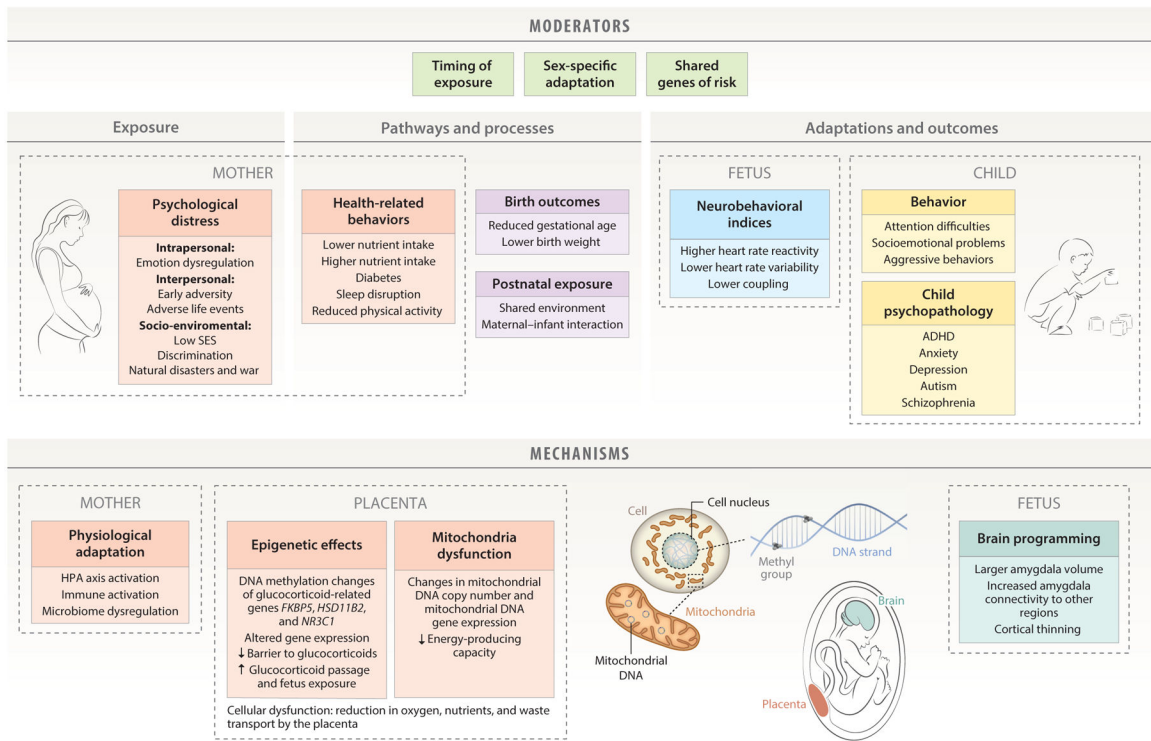


Figure 1. Mechanisms and pathways by which maternal distress affects fetal and child brain–behavior development and increases the risk for child psychopathology. Psychological distress during pregnancy and the maternal health behaviors associated with stress can negatively impact birth outcomes and shape the postnatal environment in which the child is raised. The effects of prenatal distress have been documented as early as the fetal stage and are related to increased risks for a host of psychopathologies. Potential pathways include maternal (HPA axis activation, immune activation, microbiome dysregulation), placental (epigenetic effects and mitochondria dysfunction), and fetal (brain programming). Growing evidence suggests that effects vary depending on the timing of stress exposure, the sex of the offspring, and shared genes of risk. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HPA, hypothalamic–pituitary–adrenal; SES, socioeconomic status.