HHS Public Access

Author manuscript

Dev Psychobiol. Author manuscript; available in PMC 2019 January 22.

Published in final edited form as:

Dev Psychobiol. 2018 November ; 60(7): 753–764. doi:10.1002/dev.21773.

Extending the developmental origins of disease model: Impact of preconception stress exposure on offspring neurodevelopment

Kate Keenan, Ph.D.,
Department of Psychiatry and Behavioral Neuroscience, University of Chicago

Alison E. Hipwell, Ph.D.,
Department of Psychiatry, University of Pittsburgh

Quetzal A. Class, Ph.D., and
Department of Obstetrics and Gynecology, University of Illinois at Chicago

Kimberley Mbayiwa, M.A.
Department of Psychiatry and Behavioral Neuroscience, University of Chicago

Abstract

The concept of the developmental origins of health and disease via prenatal programming has informed many etiologic models of health and development. Extensive experimental research in non-human animal models has revealed the impact of *in utero* exposure to stress on fetal development and neurodevelopment later in life. Stress exposure, however, is unlikely to occur *de novo* following conception, and pregnancy health is not independent of the health of the system prior to conception. For these reasons, the preconception period is emerging as an important new focus for research on adverse birth outcomes and offspring neurodevelopment. In this review we summarize the existing evidence for the role of preconception stress exposure on pregnancy health and offspring neurodevelopment across species and discuss the implications of this model for addressing health disparities in obstetrics and offspring outcomes.

Keywords

preconception; prenatal; stress; offspring; neurodevelopment

Developmental origins of health and disease

Fetal programming is a model for understanding the development of health and disease focused on prenatal conditions that impact the vulnerability of individuals to multiple pathologies (Barker 1995; 2003). Maternal exposure to environmental stressors during the prenatal period is one such condition that has been consistently linked with suboptimal

Address correspondence to: Kate Keenan, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 South Maryland Avenue, Chicago IL, 60637, [kekeenan@uchicago.edu], 773-702-4449.

The authors have no conflicts of interest to report.

developmental outcomes in the offspring. For example, evidence from animal studies demonstrates that maternal stress during pregnancy can permanently compromise offspring neurodevelopment (Chapillon et al., 2002; Weinstock, 2005) as evidenced by disturbances in executive function (Keenan & Hipwell, 2015; Schneider et al., 2002), impaired learning and disruption in neurogenesis (Chapillon et al., 2002; Coe, Lulbach & Schneider, 2002) and heightened anxiety-like behaviors (Schneider et al., 2002). The strength of the causal claim that maternal stress has a direct impact on offspring development is based on rigorous controlled experiments in animals, including distinguishing prenatal from postnatal effects using methods such as cross-fostering or nursery rearing.

In contrast to models tested in animals, research on the effect of prenatal stress on human offspring is more heterogenous both in terms of operational definitions of stress and in the consistency of the results. In humans, prenatal stress has been conceptualized as bereavement, financial hardship, maternal anxiety and depression, infection, poor nutrition, and exposure to natural disasters or terrorist attacks, each of which may co-occur and may be relatively chronic across development. Despite the heterogeneity in methodologies and operational definitions of prenatal stress, the pattern of findings in this body of research largely mirrors the findings from studies of animals, with some exceptions (see reviews by Kim, Bale & Epperson, 2017 and Talge et al., 2007). Several non-experimental, but prospective, studies of humans have also shown that maternal stress during pregnancy is associated with adverse birth outcomes (Ruth et al., 2012; Kent et al., 2013; Giscombe & Lobel, 2005), shorter gestational length, low birth weight, and preterm birth (Dole et al., 2003; Dominguez et al., 2005; Holzman et al., 2001; Class et al., 2011; Dayan, et al., 2006; Glover, 2015; Wadhwa et al., 2011; Rice et al., 2010). Prenatal stress also is associated with impairments in multiple systems related to offspring neurodevelopment, including alterations in the reactivity of the offspring's hypothalamic-pituitary-adrenal (HPA) axis (Keenan, Gunthorpe & Grace, 2007; O'Connor et al., 2005; Davis et al., 2011; Entringer et al., 2009), executive functioning (*e.g.*, attention, learning, language problems) (O'Connor, Heron, & Glover, 2002; Buss et al., 2012; Laplante et al., 2008; Bergman et al., 2010), and neural structure and development (Korosi et al., 2012). Furthermore, maternal stress during pregnancy has been associated with an increased risk for neurodevelopmental disorders, including attention deficit/hyperactivity disorder (Linnet et al., 2003; Rodriguez & Bohlin, 2005). These neurodevelopmental deficits and disorders are known to increase risk for later health problems and general impairments (Kelly et al., 2013; Colman, et al., 2014; Sibley et al., 2014; Hankin et al., 2010), underscoring the critical importance of optimizing the health of the fetal environment.

From a developmental and life-course perspective, stress exposure is unlikely to occur *de novo* following conception. Similarly, pregnancy health is not independent of the health of the system prior to conception. For these reasons, the preconception period is emerging as an important new focus for research on adverse birth outcomes and offspring neurodevelopment (Grandjean et al., 2015), as well as a model for understanding and ultimately preventing health disparities during pregnancy and in child health outcomes (Vaivada et al., 2017). We review the existing evidence for the role of preconception stress exposure on pregnancy health and offspring neurodevelopment across species and outline a program of research to

further probe the role of preconception stress exposure within the developmental origins of disease model.

Extending the developmental origins of disease model

Evidence suggests that one primary mechanism by which stress exposure confers risk for offspring neurodevelopment is via maternal neuroendocrine functioning, including the HPA axis. Support for this mechanism comes from decades of research linking prenatal maternal stress and adverse offspring outcomes with dysregulation of maternal gluccocorticoids (GCs) and placental stress regulation on the rapidly developing fetal nervous system. Briefly, the normal response to stress has the effect of maintaining physiological homeostasis, which typically results in adrenal activation and the release of cortisol. However, repeated or chronic increases in stress exposure, and hence chronically increased plasma cortisol, can lead to responses that have pathological and illness-inducing consequences for the offspring: maternal GCs are transported across the placenta, entering the fetal circulation leading to alterations in fetal stress architecture (Weinstock, 2005).

Additionally, the maternal HPA axis system is impacted by the growth and development of the placenta, (O'Donnell, O'Connor & Glover, 2009). In contrast to the inhibitory control of cortisol on the expression of CRH in a non-pregnant state, maternal cortisol activates the promoter region in the placenta and stimulates further CRH synthesis during pregnancy (King, Smith, & Nicholson, 2001). Maternal GCs also induce placental CRH production that stimulates the fetal HPA axis, leading to increased levels of fetal cortisol (Beijers, Buitelaar, & de Weerth, 2014). Typically, the placental enzyme 11-β hydroxysteroid dehydrogenase-type 2 (11-β-HSD2) converts maternal cortisol to inactive cortisone, thereby decreasing the level of GCs in the placenta. Prenatal stress exposure, however, results in the down-regulation of the 11-β-HSD2 enzyme, which in turn exposes the fetus to higher levels of maternal GCs (O'Donnell, et al., 2012).

Substantial work has led to the identification of numerous candidate genes associated with individual differences in stress regulation. The glucocorticoid receptor (GR) gene, for example, is a well-researched gene; several single nucleotide polymorphisms (SNPs) have been functionally characterized including. Experimental manipulations of the sensitivity of GR have been associated with impaired functioning in the negative feedback of the HPA-axis and depression in animals (Pariante, 2004). In humans, the *BclI* GG genotype is associated with the high levels of cortisol in response to a controlled laboratory stressor (Kumsta et al., 2007). Variations in the FK506-binding protein 5 (FKBP5) gene also are associated with the regulation of the HPA axis, particularly in the recovery following termination of the stressor. Ising and colleagues (2008) found that three SNPs of the FKBP5 gene were associated with cortisol response to a social stressor. Thus, genotype likely accounts for some variability in sensitivity to stress exposure prior to conception as well as changes in HPA axis functioning over the course of pregnancy.

There is increasing evidence that epigenetic effects are likely to play a major role in the molecular mechanisms underlying the long-lasting effect of stress exposure on adult health. Indeed, there is a growing body of evidence that the epigenome is responsive to

environmental exposures including the social environment both across development in animals and in humans. A potential mechanism by which prenatal stress impacts offspring outcome is via epigenetic changes in placental 11β-HSD2. In rodent models, maternal stress during pregnancy has been shown to decrease placental 11β-HSD2 mRNA levels (Mairesse et al., 2007; Welberg, Seckl & Holems, 2000), thus impairing the conversion of maternal glucocorticoids to less active forms. In humans, maternal depression and anxiety during pregnancy has been associated with increased maternal NR3C1 methylation, and greater methylation of placental NR3C1 and 11β-HSD2, as well as indications of offspring neurodevelopmental problems (Hompes et al., 2013; Jensen Peña, Monk & Champagne, 2012; O'Donnell et al., 2012; Togher, et al., 2017).

A life-course perspective (Elder & Rockwell, 1979) naturally extends the prenatal stress model to the integrity of the system *prior to conception*. Numerous studies have shown links between stress exposure and compromised health earlier in development. For example, psychosocial stress exposure (e.g., poverty, neighborhood crime) during childhood and adolescence is associated with higher ambulatory blood pressure (Beatty & Matthews, 2009) and higher levels of C-reactive protein (CRP) (Broyles et al., 2012; Fuligni et al., 2009; Lande et al., 2008), both of which signal risk for later disease. Exposure to stress in childhood and adolescence is also associated with cortisol reactivity to a controlled stressor (Jaffee et al., 2015), higher concentrations of hair cortisol (Simmons et al., 2016), greater inflammatory activity including Tumor Necrosis Factor (TNF)-alpha (Hartwell et al., 2013), as well as altered Interleukin-6 (IL-6) immune response to a bacterial stimulus in the laboratory (Miller, Rohleder & Cole, 2009).

Adolescence may be a point in development during which stress exposure is especially impactful on health. Data from cross-sectional studies suggest that there are significant changes in the functioning of the HPA axis during late adolescence as measured by diurnal cortisol and cortisol reactivity (Gunnar et al., 2009; Oskis et al., 2009; Sumter et al., 2010). There also appear to be changes in functioning of brain regions involved in the regulation of the HPA axis during late adolescence (McCormick et al., 2010). In a study of rodent behavior, (Jankord et al., 2011), the effects of chronic, variable stress were exaggerated in animals exposed in late adolescence compared to those exposed in early adolescence and adulthood, and the late adolescent exposed animals were the only group for which stress was associated with an increase in basal corticosterone. Evidence for the impact of early stress exposure of epigenetic changes that impact HPA-axis functioning is emerging. Childhood adversity, such as parental loss and maltreatment, has been associated with increased methylation and alterations in HPA axis response to a controlled stressor (Tyrka et al., 2012). In one of only a handful of studies testing the impact of preconception stress exposure on perinatal gene expression, preadolescent female mice who were exposed to chronic variable stress differed from controls in their HPA axis response to stress during pregnancy, but not postpartum, and in expression of a number of genes in the paraventricular nucleus of the hypothalamus (Morrison et al., 2016). These findings suggest that adolescence may be a developmental period during which the HPA-axis may be highly sensitive to environmental factors, and that exposures during this period may shape the responsiveness of the system in the future. Stress exposure, therefore, is associated with health indices across development, and dimensions of exposure such as developmental timing, chronicity and acuity are likely

important factors. There has been relatively little research, however, linking work on stress exposure over the course of development on later pregnancy health and offspring development. Among the existing studies, the period immediately preceding conception has been the focus. We review that literature in the following section.

Non-human models of preconception stress exposure on offspring neurodevelopment

Animal models provide compelling evidence for preconception stress effects on offspring neurodevelopment. Exposure to highly translatable stressors (*e.g.*, overcrowding, temperature, and pain stress), results in altered behavior, neurobiology and brain morphology; effects which have been shown to persist into adulthood. Results from these studies are summarized in Table 1. Shachar-Dadon and colleagues (2009) exposed female rats to unpredictable and variable stress (e.g., swim test, isolation, water and food deprivation) for either a week or two weeks prior to mating and compared the offspring of those two groups (n = 83 and 25, respectively) to offspring of unexposed females (n= 86). Five probes were used to examine behavior of the offspring in adulthood: navigation of an elevated maze, shock avoidance learning, acoustic startle response, open field test, and social interaction test; with offspring from each litter distributed across each test. Stress exposure experienced within one week of, but not two weeks prior to, conception resulted in increased anxiety and activity and decreased social interaction in the offspring. There were also significant interactions between stress exposure and sex of the offspring on later development: preconception stress exposure resulted in greater shock avoidance among male offspring whereas the opposite effect was observed for females. In contrast, male offspring of dams exposed to preconception stress showed less startle than control males, whereas the female offspring stress showed greater startle than control females. In a follow-up to the study described above, Bock and colleagues (2016) examined dendrite morphology in the medial prefrontal cortex (mPFC) in a subsample of the offspring. These analyses revealed an effect for preconception stress experienced two weeks prior to conception: dendrites in the left mPFC were more complex in male and female offspring and the spines longer in the male offspring of the stress exposed dams. Within the same sample, therefore, effects of preconception stress varied as a function of timing, sex of the offspring, and phenotype, as well as the characterization of altered offspring behavior as heightened or dampened.

Li and colleagues (2010a) reported statistically significant differences in behavior and neurochemistry between adult male offspring of maternal rats exposed to 21 days of chronic unpredictable stress prior to conception (n = 8) to male offspring of control dams (n=8). Regarding impact on behavior, exposed offspring had decreased spatial memory, and lower sucrose consumption, which may indicate altered reward sensitivity. In terms of neurochemistry, exposed offspring had higher levels of norepinephrine (NE) in the hippocampus, lower levels of serotonin (5-HT) in the hypothalamus, and less protein expression of phosphorylated Cyclic AMP responsive element binding protein (P-CREB), which also may indicate dysregulated serotonergic and noradrenergic neurotransmitter systems.

Neurochemistry and behavior also were altered as a function of chronic, unpredictable, and variable preconception stress administered for a period of three weeks immediately prior to conception (Huang et al., 2010). In this study, behavior of maternal rats was observed prior to and after stress exposure. Weight loss and decreases in sucrose intake and motor activity during the open field test, all of which are animal analogues of depression phenotypes, were observed in the stress exposed rats. Adult male and female offspring of stress exposed rats had longer escape latencies during the Morris water maze task and higher serum corticosterone levels following the task. Expression of brain-derived neurotrophic factor and N-methyl-D-aspartate receptor in the hippocampus, both of which are critical to synaptic plasticity, was decreased in the stress exposed offspring compared to the controls. In this study, preconception stress impacted several systems – maternal behavior and offspring learning, and offspring HPA axis activity, and neural integrity.

Effects of preconception stress exposure on neuroendocrine functioning have been observed in *both* the first (F1) and second (F2) generation offspring. Zaidan and colleagues (2013; 2015) exposed female rats to one week of chronic, unpredictable stress two weeks prior to conception. First, expression of corticotropin releasing factor (CRF) type 1 and 2 receptors in the brain, which mediate the initial activation of the HPA axis response to stress, were increased in neonatal and adult brains, compared to brains of control offspring. In addition, corticosterone levels were increased in the F1 females. Corticosterone levels were also altered as a function of preconception stress exposure in the second generation: males showed higher levels, whereas females showed lower levels, than offspring of controls.

Human models of preconception stress and offspring health

A small but growing evidence base in human studies provides preliminary support for the impact of preconception stress exposure on birth outcomes. Many of these studies are based on maternal *retrospective* report of stress exposure (see Table 2 for a summary). For example, in a Swedish population-based cohort, preconception stress, operationalized as maternal bereavement of a first-degree relative within 6 months of conception, was associated with elevated risk of adverse birth outcomes (*e.g.*, preterm birth, low birth weight, small for gestational age), as well as increased risk for infant mortality (Class et al., 2013). These findings have been replicated and extended to predict childhood mortality in a Danish population-based sample (Class et al., 2015), in which bereavement experienced *prior to conception, but not post-conception*, increased the risk of neonatal and infant mortality.

Data from representative U.S. samples also support the association between retrospective recall of preconception stress exposure and offspring outcome, as well as the unique effects of preconception exposure, controlling for post-conception exposure. In a study of nearly 1,000 participants, women who reported stressful life events (e.g., death of a family member) prior to conception were 40% more likely to deliver a child of very low birth weight, controlling for pregnancy complications; stressful life events experienced during pregnancy were not associated with birth weight (Witt et al., 2014a). The magnitude of this association was greatest among offspring of women residing in low-income neighborhoods (Witt et al., 2014a).

One important study to this emerging field in humans is The National Child Development Study, a cohort study of children born in Britain during one week of March 1958. Over 18,000 participants were enrolled and then followed up at ages 7, 11, 23, 33, and 41 (Atherton et al., 2008). Stressors were assessed by parental report and interviewer observation in the home and included financial, parenting, family, and community stressors. At ages 33 and 41 years, female participants (n≈5,000) were asked about pregnancy outcomes, including gestational age and birth weight. The results revealed that exposure to stressors during childhood was associated with higher rates of preterm birth and low offspring birth weight. These results held even after controlling for stress exposure and smoking during pregnancy (Harville et al., 2010).

Investigation of associations between preconception stress and indices of later *neurodevelopment* are scarce. First, in a cohort of women from the Southampton Women's Survey (SWS), who were recruited between 20–34 years of age and followed through their subsequent pregnancies, associations between maternal preconception psychological stress (e.g., symptoms of depression and anxiety) and infant sleep were tested. Based on a sample of 874 mother-infant pairs, preconception psychological distress was prospectively associated with compromised sleep in offspring, including middle of the night awakening, at 6 and 12 months even when controlling for postnatal symptoms of distress (Baird et al., 2009). In a nationwide population-based cohort study, including all 1,015,912 singletons born in Denmark from 1987 to 2001, associations between bereavement stress and ADHD were tested: 29,094 children were born to women who lost a close relative during pregnancy or up to 1 year before pregnancy. Maternal bereavement stress in the 6 months prior to pregnancy was shown to increase the risk for attention-deficit hyperactivity disorder (ADHD) in male offspring by almost fifty percent (Li et al., 2010b).

Although relatively few studies have been conducted in human samples, there is growing evidence of an association between preconception stress exposure and birth outcomes, using both retrospective and prospective data. Extant data from animal studies converge to highlight the potential critical influence of preconception stress exposure on offspring neurodevelopment in ways that may affect learning, memory, and stress reactivity.

Developmental timing and chronicity of preconception stress exposure

The timing of preconception stress exposure may differentially influence offspring outcomes. Although the period immediately prior to pregnancy may present the most vulnerable period for uterine priming, successful implantation of the zygote and healthy early placental development, more distal environmental exposures leading up to that point may be as important in shaping maternal biological, physiological, and psychological responses to stress. Additionally, a life-course maternal "health capital" perspective that considers all gains and losses in biological, psychological, and physical health over the lifetime is likely to provide the fullest picture of the impact of environmental exposures.

For females, adolescence is a likely sensitive period with regard to preconception stress exposure. In fact, a number of prevention scientists have argued that preconception care should begin in puberty (Witt et al., 2014; Dean et al., 2013). This is based, in part, on

evidence from neurodevelopmental studies that have revealed significant changes in brain morphology and function during adolescence (Casey, Getz & Galvan, 2008; Zehr et al., 2006). The pruning of brain regions involved in emotion regulation and higher cognitive functioning is hypothesized to render these regions particularly vulnerable to the experience of stressors (McCormick et al., 2010). Changes in adrenal hormones also occur during adolescence. Among girls, these changes result in slower recovery to baseline of cortisol in response to a stressor with more advanced maturation (Stroud et al., 2004). The effects of age on stress response are also evident in animal models: pubertal female rats have prolonged corticosterone release in response to restraint stress compared to adult females (Romeo, Lee & McEwen, 2005). This potential adolescent programming of the HPA axis may have implications for later functioning. For example, female, but not male, rats who were exposed to stress during adolescence showed altered behavioral response to stress in adulthood (McCormick et al., 2005). In humans, individual differences in HPA-axis functioning in adolescence are associated with self-reported exposure to stressors, and these individual differences appear to be relatively stable (Doane et al., 2015). Thus, late adolescence may be a particularly vulnerable period for sensitization of the HPA axis to environmental stress resulting in stable individual differences in reactivity and regulation that continue into adulthood.

We are aware of only one study in which the developmental timing of preconception stress on offspring development has been tested. In the aforementioned prospective cohort study of nearly 5,000 women (Harville et al., 2010), exposures most strongly influenced the birth outcomes if they occurred in adolescence: the highest risk for both low birth weight and preterm birth was among females who experienced multiple hardships in adolescence only, although exposure at any time during childhood/adolescence raised the risk of poor birth outcomes. These results are consistent with the conceptualization of adolescence as a critical period with regard to the development and sensitivity of biological systems involved in later reproductive health. However, a much clearer understanding of the developmental effects of stress exposure is needed given that life stressors are known to cluster and interact, leading to chronic and accumulating patterns across development (Evans, Li & Whipple, 2013). Furthermore, a wealth of data has shown that exposure to sustained, repeated or multiple stressors is associated with more severe and chronic impairment and distress in individuals (Clancy et al., 2006; Cloitre et al., 2001; Dohrenwend et al., 2006; Gerard & Buehler, 2004; Larson et al., 2008; Margolin et al., 2010; Mistry et al., 2010) than is exposure to single, discrete forms of stress. Gaining an understanding of the *developmental* effects of stress exposure on health, including prenatal health, is fundamental to informing the timing and type of prevention efforts.

Relevance of preconception stress exposure to understanding health disparities

As stated earlier, a developmental and life-course perspective would posit that because stress exposure is unlikely to occur *de novo* following conception, pregnancy health is not independent of the health of the system prior to conception. In the U.S., higher levels of acute and chronic stress are found among families living in low-income environments than

among families living in other income environments. Neighborhood disorder, lack of safety and exposure to violence are all significantly higher in areas with lower per capita income (Evans, 2003; Ewart & Shuchdat, 2002). African Americans live in poverty at a disproportionately high rate; more than a quarter of African Americans live in poverty (DeNavas-Walt & Proctor, 2014).

Both minority race and living in a low resourced environment appear to impact both the diurnal rhythm and feedback loop of the stress response system, and the interface between HPA-axis and other systems critical for maintaining health such as immune functioning beginning in adolescence and continuing into adulthood. Discrimination and unfair treatment as a result of minority status (e.g., race, poverty) are associated with health risks in adolescence, including higher ambulatory blood pressure (Beatty & Matthews, 2009) and higher levels of CRP (Lande et al., 2008). Higher levels of cortisol in the afternoon and evening have been reported among African Americans and individuals living in lower SES environments than among European Americans and individuals living in higher SES environments (Chen & Paterson, 2006). African American women also are more likely to demonstrate a significant increase in cortisol in response to a psychosocial stressor than are European American women (Fowles & Gabrielson, 2005). Furthermore, data from studies using exposure to a controlled stressor provide evidence for racial differences in inflammatory response (i.e., interleukin-6) to stress, with African American pregnant and non-pregnant women show higher responses than European American women (Christian et al., 2013). In a study in which both cortisol and pro-inflammatory cytokines were measured during pregnancy, minority race and low-income status was characterized by high levels of cortisol without a compensatory decrease in cytokines, suggesting impaired feedback between the neuroendocrine and immune systems (Corwin et al., 2013).

In the U.S., African American women living in urban low-income environments are more likely to experience pregnancy complications than other women (Giscombé & Lobel, 2005; Kent et al., 2013). A primary cause of maternal and child health disparities for African Americans in the U.S. is likely due to compromised health from earlier stress exposure. If this is the case, then successfully improving health of the offspring via prenatal interventions will be challenging, as the maternal systems for maintaining health have already been impacted for the current generation. The application of the developmental origins of health and disease model to health disparities may serve to identify targets that will disrupt intergenerational cycles of poverty and impairment.

Conclusion and future directions

There is strong evidence for negative effects of maternal prenatal stress on the developing fetus; effects that continue to impact development throughout childhood. There is developing evidence that the observed association between prenatal stress and offspring neurodevelopment may be largely due to stress exposures that occur prior to conception. Consistent with a kindling or stress sensitization model, we posit that the development of the stress architecture during childhood and adolescence is in part based on environmental inputs, and that observed differences in stress regulation during pregnancy are largely due to variability in those earlier inputs. This hypothesis is testable via several interrelated

approaches. First, more research is needed to understand the developmental timing of stress exposure on pregnancy health and offspring neurodevelopment, including models that compare chronicity and type of stressor (e.g., social, safety, health). Second, animal models will be critical for characterizing the unique effects of preconception stress exposure on pregnancy health and postnatal caregiving and offspring development. For example, cross-fostering is needed to determine the relative contribution of preconception stress on fetal development as opposed to postnatal caregiving effects on offspring neurodevelopment. Third, examining prevention effects will provide further information on the relative impact of preconception stress on offspring development. An example is using an enriched environment to attenuate earlier stress exposure. Cutuli and colleagues (2017) demonstrated that exposure to an enriched environment prior to reproduction had neuroprotective effects on the offspring even after exposure to a stressor; adolescent offspring of enriched dams had a more modulated immune response and more climbing behavior in response to the forced swim test, and greater expression of gluccocorticoid receptors in the amygdala, which was comparable to adolescent offspring of dams who were not stress exposed. Testing the timing and dose of an enriched environment on the attenuation of the effects of preconception stress exposure on offspring neurodevelopment is necessary for pursuing a preventive intervention program in humans.

In parallel to hypothesis-testing in animal models, prospective studies of humans from childhood through pregnancy are required to provide further evidence and to characterize the stress phenotype in terms of type, timing, and chronicity. Much of the current research in humans is limited by retrospective, self-reports of exposures and or emotional distress. Bias in recall and individual differences in perceptions and definitions of stress exposure may obscure true effects between preconception stress exposure and pregnancy health. Alternatively, observed associations based on recall and individual differences in perceptions may be in fact due to third variables such as genetic factors that account for variance in both maternal recall of stress exposure and infant outcomes. The likelihood of the co-occurrence stressors in humans (e.g., parental bereavement, financial hardship, poor nutrition) provides an additional challenge. In addition, although most models of social stress exposure (e.g., economic, housing, community stress) in humans assume chronicity of exposure or equivalence of effects across development, there is often substantial variability in timing and chronicity within and across domains of stressors (e.g., Keenan et al., unpublished manuscript). Capturing these dimensions will be important for testing the specificity of timing of exposure on offspring development, especially for stress exposure that occurs both pre- and post-conception. Key elements to future programs of research in humans, therefore, include prospective, repeated assessments of a range of stress exposure in childhood and adolescence and objective biomarkers of stress sensitivity and stress related health conditions in controlled settings. Characterizing stress phenotypes at multiple levels (e.g., behavioral, immune, endocrine), as well as severity, timing, and chronicity, will be important for articulating measurable targets of preventive interventions.

The results from the proposed research agenda will fill a critical gap in knowledge about the developmental origins of disease. To date, the model has been limited by right-hand censoring, with the possibility that effects attributed to exposures during pregnancy are in fact causally linked to environmental exposures occurring prior to conception and the

resulting alterations in biological systems critical in supporting healthy fetal development. Filling these gaps could lead to the design and deployment of public health initiatives that communicate the importance of reduction of stress and improved stress regulation during childhood, adolescence and early adulthood to support later maternal and offspring health. Consequently, the proposed research is uniquely poised to elucidate the type and timing of biobehavioral targets for early preventive interventions.

Acknowledgments

Preparation of this paper was supported by NIH grant UG3 OD023244.

References

Atherton K, Fuller E, Shepherd P, Strachan DP, Power C (2008). Loss and representativeness in a biomedical survey at age 45 years: 1958 British birth cohort. Journal of Epidemiology and Community Health, 62, 216–223. [PubMed: 18272736]

Baird J, Hill CM, Kendrick T, Inskip HM, Group SS. (2009). Infant sleep disturbance is associated with preconceptional psychological distress: findings from the Southampton Women's Survey. Sleep, 32, 566–568. [PubMed: 19413152]

Barker DJ. (1995). Intrauterine programming of adult disease. Molecular Medicine Today, 1, 418–423. [PubMed: 9415190]

Barker DJ. (2003). Editorial: the developmental origins of adult disease. European Journal of Epidemiology, 18, 733–736. [PubMed: 12974544]

Beatty DL, Matthews KA. (2009). Unfair treatment and trait anger in relation to nighttime ambulatory blood pressure in African American and white adolescents. Psychosomatic Medicine, 71, 813. [PubMed: 19661190]

Beijers R, Buitelaar JK, de Weerth C. (2014). Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. European Child & Adolescent Psychiatry, 23, 943–956. [PubMed: 24875898]

Berghella V, Buchanan E, Pereira L, Baxter JK. (2010). Preconception care. Obstetrical & Gynecological Survey, 65, 119–131. [PubMed: 20100361]

Bergman K, Sarkar P, Glover V, O'Connor TG (2010). Maternal prenatal cortisol and infant cognitive development: Moderation by infant–mother attachment. Biological Psychiatry, 67, 1026–1032. [PubMed: 20188350]

Blaxter M (2010). Health (key concepts). Cambridge: Polity Press.

Bock J, Poeschel J, Schindler J, et al. (2016). Transgenerational sex-specific impact of preconception stress on the development of dendritic spines and dendritic length in the medial prefrontal cortex. Brain Structure and Function, 221, 855–863. [PubMed: 25395153]

Boksa P (2010). Effects of prenatal infection on brain development and behavior: a review of findings from animal models. Brain, Behavior, and Immunity, 24, 881–897.

Broyles ST, Staiano AE, Drazba KT, Gupta AK, Sothern M, Katzmarzyk PT.(2012). Elevated C-reactive protein in children from risky neighborhoods: evidence for a stress pathway linking neighborhoods and inflammation in children. PloS One, 7, e45419. [PubMed: 23049799]

Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. (2012). Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proceedings of the National Academy of Sciences, 109, E1312–E1319.

Casey B, Getz S, Galvan A. (2008). The adolescent brain. Developmental Review, 28, 62–77. [PubMed: 18688292]

Chapillon P, Patin V, Roy V, Vincent A, Caston J. (2002). Effects of pre-and postnatal stimulation on developmental, emotional, and cognitive aspects in rodents: A review. Developmental Psychobiology, 41, 373–387. [PubMed: 12430161]

Chen E, Paterson LQ. (2006). Neighborhood, family, and subjective socioeconomic status: How do they relate to adolescent health? Health Psychology, 25, 704–14. [PubMed: 17100499]

Christian LM, Glaser R, Porter K, Iams JD. (2013). Stress-induced inflammatory responses in women: Effects of race and pregnancy. Psychosomatic Medicine, 75, 658–69. [PubMed: 23873713]

Clancy CP, Graybeal A, Tompson WP, et al. (2006). Lifetime trauma exposure in veterans with military-related posttraumatic stress disorder: association with current symptomatology. Journal of Clinical Psychiatry, 67, 1346–1353. [PubMed: 17017820]

Class QA, Mortensen PB, Henriksen TB, Dalman C, D'Onofrio BM, Khashan AS. (2015). Preconception Maternal Bereavement and Infant and Childhood Mortality: A Danish Population-Based Study. Psychosomatic Medicine, 77, 863–9 [PubMed: 26374948]

Class QA, Khashan AS, Lichtenstein P, Långström N, D'Onofrio BM. (2013). Maternal stress and infant mortality the importance of the preconception period. Psychological Science, 24, 1309–1316. [PubMed: 23653129]

Cloitre M, Cohen LR, Edelman RE, Han H. (2001). Posttraumatic stress disorder and extent of trauma exposure as correlates of medical problems and perceived health among women with childhood abuse. Women & Health, 34, 1–17.

Coe CL, Lulbach GR, Schneider ML. (2002). Prenatal disturbance alters the size of the corpus callosum in young monkeys. Developmental Psychobiology, 41, 178–185. [PubMed: 12209659]

Colman I, Jones P, Kuh D, et al. (2014). Early development, stress and depression across the life course: pathways to depression in a national British birth cohort. Psychological Medicine, 44, 2845–2854. [PubMed: 25066933]

Corwin EJ, Guo Y, Pajer K, Lowe N, McCarthy D, Schmiege S, Weber M, Pace T, Stafford B. (2013). Immune dysregulation and glucocorticoid resistance in minority and low-income pregnant women. Psychoneuroendocrinology, 38, 1786–1796. [PubMed: 23541234]

Coussons-Read ME, Okun ML, Schmitt MP, Giese S. (2005). Prenatal stress alters cytokine levels in a manner that may endanger human pregnancy. Psychosomatic Medicine, 67, 625–631. [PubMed: 16046378]

Cutuli D, Berretta E, Pasqualini G, De Bartolo P, Caporali P, Laricchiuta D, Sampedro-Piquero P, Gelfo F, Pesoli M, Foti F, Begega A, Petrosini L. (2017). influence of pre-reproductive maternal enrichment on coping response to stress and expression of c-FOS and glucocorticoid receptors in adolescent offspring. Frontiers in Behavioral Neuroscience,11, 73. [PubMed: 28536510]

Davis EP, Glynn LM, Waffarn F, Sandman CA. (2011). Prenatal maternal stress programs infant stress regulation. Journal of Child Psychology and Psychiatry, 52, 119–129. [PubMed: 20854366]

Dayan J, Creveuil C, Marks MN, et al. (2006). Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. Psychosomatic Medicine, 68, 938–946. [PubMed: 17079701]

Dean SV, Imam AM, Lassi ZS, Bhutta ZA. (2013). Importance of intervening in the preconception period to impact pregnancy outcomes In: Bhatia J, Bhutta ZA, Kalhan SC, eds. Maternal and child nutrition: The first 1,000 days; 74th Nestle Nutrition Institute Workshop. Vol 74: Karger: 63–73.

DeNavas-Walt C, Proctor BD. (2014). U.S. Census Bureau Current Population Reports, P60–249, Income and poverty in the United States: U.S. Government Printing Office, Washington, DC.

Doane LD, Chen FR, Sladek MR, Van Lenten SA, Granger DA. (2015). Latent trait cortisol (LTC) levels: reliability, validity, and stability. Psychoneuroendocrinology, 55, 21–35. [PubMed: 25705799]

Dohrenwend BP, Turner JB, Turse NA, Adams BG, Koenen KC, Marshall R. (2006). The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. Science, 313, 979–982. [PubMed: 16917066]

Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. (2003). Maternal stress and preterm birth. American Journal of Epidemiology, 157, 14–24. [PubMed: 12505886]

Dominguez TP, Schetter CD, Mancuso R, Rini CM, Hobel C. (2005). Stress in African American pregnancies: testing the roles of various stress concepts in prediction of birth outcomes. Annals of Behavioral Medicine, 29, 12–21. [PubMed: 15677296]

Elder GH, Rockwell RC. (1979). The life-course and human development: An ecological perspective. International Journal of Behavioral Development, 2, 1–21.

Entringer S, Kumsta R, Hellhammer DH, Wadhwa PD, Wüst S. (2009). Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. Hormones and Behavior, 55, 292–298. [PubMed: 19084531]

Evans GW, Li D, Whipple SS. (2013). Cumulative risk and child development. Psychological Bulletin, 139, 1342. [PubMed: 23566018]

Ewart CK, Suchday S. (2002). Discovering how urban poverty and violence affect health: Development and validation of a neighborhood stress index. Health Psychology, 21, 254–262. [PubMed: 12027031]

Fowles ER, Gabrielson ML. (2005). First trimester predictors of diet and birth outcomes in low-income pregnant women. Journal of Community Health and Nursing, 22, 117–130.

Fuligni AJ, Telzer EH, Bower J, Cole SW, Kiang L, Irwin MR. (2009). A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. Psychosomatic Medicine, 71, 329. [PubMed: 19196810]

Gerard JM, Buehler C. (2004). Cumulative environmental risk and youth problem behavior. Journal of Marriage and Family, 66, 702–720.

Giscombe CL, Lobel M. (2005). Explaining disproportionately high rates of adverse birth outcomes among African Americans: The impact of stress, racism, and related factors in pregnancy. Psychological Bulletin, 131, 662–683. [PubMed: 16187853]

Glover V (2015). Prenatal stress and its effects on the fetus and the child: possible underlying biological mechanisms Perinatal Programming of Neurodevelopment: Springer:269–283.

Grandjean P, Barouki R, Bellinger DC, et al. (2015). Life-long implications of developmental exposure to environmental stressors: new perspectives. Endocrinology, 156, 3408–3415. [PubMed: 26241067]

Hankin BL, Badanes LS, Abela JR, Watamura SE. (2010). Hypothalamic–pituitary–adrenal axis dysregulation in dysphoric children and adolescents: Cortisol reactivity to psychosocial stress from preschool through middle adolescence. Biological Psychiatry, 68, 484–490. [PubMed: 20497900]

Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology. 2012;37(1):137–162. [PubMed: 21918508]

Hartwell KJ, Moran-Santa Maria MM, Twal WO, et al. Association of elevated cytokines with childhood adversity in a sample of healthy adults. Journal of Psychiatric Research. 2013;47(5): 604–610. [PubMed: 23415658]

Harville EW, Boynton-Jarrett R, Power C, Hyppönen E. Childhood hardship, maternal smoking, and birth outcomes: a prospective cohort study. Archives of Pediatrics & Adolescent Medicine. 2010;164(6):533–539. [PubMed: 20530303]

Henry C, Kabbaj M, Simon H, Moal M, Maccari S. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. Journal of Neuroendocrinology. 1994;6(3): 341–345. [PubMed: 7920600]

Hogue CJ, Bremner JD. Stress model for research into preterm delivery among black women. American Journal of Obstetrics & Gynecology. 2005;192(5 Suppl):S47–55. [PubMed: 15891712]

Holzman C, Jetton J, Siler-Khodr T, Fisher R, Rip T. Second trimester corticotropin-releasing hormone levels in relation to preterm delivery and ethnicity. Obstetrics & Gynecology. 2001;97(5):657–663. [PubMed: 11339911]

Hompes T, Izzi B, Gellens E, Morreels M, Fieuws S, Pexsters A, et al. (2013). Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the glucocorticoid receptor gene (NR3C1) promoter region in cord blood. Journal of Psychiatric Reserch, 47, 880–891.

Huang Y, Shi X, Xu H, et al. Chronic unpredictable stress before pregnancy reduce the expression of brain-derived neurotrophic factor and N-methyl-D-aspartate receptor in hippocampus of offspring rats associated with impairment of memory. Neurochemical Research. 2010;35:1038–1049. [PubMed: 20309729]

Jensen Peña C, Monk C, Champagne FA. (2012). Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PLoS One, 7, e39791 [PubMed: 22761903]

Keenan K, Gunthorpe D, Grace D. (2007). Parsing the relations between SES and stress reactivity: Examining individual differences in neonatal stress response. Infant Behavior and Development, 30, 134–145. [PubMed: 17292786]

Keenan K, Hipwell AE. (2015). Modulation of prenatal stress via docosahexaenoic acid supplementation: implications for child mental health. Nutrition Reviews, 73, 166–174. [PubMed: 26024539]

Keenan K, Fu H, Tung I, Berona J, Carpio K, Krafty R, Hipwell A (unpulbished manuscript). Capturing the dynamic nature of stress expsoure in the Pittsburgh Girls Study.

Kelly PA, Viding E, Wallace GL, et al. (2013). Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? Biological Psychiatry, 74, 845–852. [PubMed: 23954109]

Kent ST, McClure LA, Zaitchik BF, Gohlke JM. (2013). Area-level risk factors for adverse birth outcomes: trends in urban and rural settings. BMC Pregnancy & Childbirth, 13, 129. [PubMed: 23759062]

Kim DR, Bale TL, Epperson CN. (2015). Prenatal programming of mental illness: current understanding of relationship and mechanisms. Current Psychiatry Reports, 17, 5. [PubMed: 25617041]

King BR, Smith R, Nicholson RC. (2001). The regulation of human corticotrophin-releasing hormone gene expression in the placenta. Peptides, 22, 1941–1947. [PubMed: 11754985]

Korosi A, Naninck E, Oomen C, et al. (2012). Early-life stress mediated modulation of adult neurogenesis and behavior. Behavioural Brain Research, 227, 400–409. [PubMed: 21821065]

Lande MB, Pearson TA, Vermilion RP, Auinger P, Fernandez ID.(2008). Elevated blood pressure, race/ethnicity, and C-reactive protein levels in children and adolescents. Pediatrics, 122, 1252–1257. [PubMed: 19047242]

Laplante DP, Brunet A, Schmitz N, Ciampi A, King S. (2008). Project Ice Storm: prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. Journal of the American Academy of Child & Adolescent Psychiatry, 47, 1063–1072. [PubMed: 18665002]

Larson K, Russ SA, Crall JJ, Halfon N. Influence of multiple social risks on children's health. Pediatrics. 2008;121(2):337–344. [PubMed: 18245425]

Li H Zhang L, Fang Z, Lin l, Wu C, Hunag Q (2010a). Behavioral and neurobiological studies on the male progeny of maternal rats exposed to chronic unpredictable stress before pregnancy. Neuroscience Letters, 469, 278–282. [PubMed: 20018228]

Li J, Olsen J, Vestergaard M, Obel C. (2010b). Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark. European Child & Adolescent Psychiatry, 19, 747–753. [PubMed: 20495989]

Linnet KM, Dalsgaard S, Obel C, et al. (2003). Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. American Journal of Psychiatry, 160, 1028–1040. [PubMed: 12777257]

Lynch C, Sundaram R, Maisog J, Sweeney A, Louis GB. (2014). Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study—the LIFE study. Human Reproduction, 29, 1067–1075. [PubMed: 24664130]

Mairesse J, Lesage J, Breton C, Bréant B, Hahn T, Darnaudéry M, Dickson SL, Seckl J, Blondeau B, Vieau D, Maccari S, Viltart O. (2007). Maternal stress alters endocrine function of the feto-placental unit in rats. American Journall of Physiology, Endocrinology, and Metabolism, 292, E1526–33

Margolin G, Vickerman KA, Oliver PH, Gordis EB. (2010). Violence exposure in multiple interpersonal domains: Cumulative and differential effects. Journal of Adolescent Health, 47, 198–205. [PubMed: 20638013]

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

McCormick CM, Robarts D, Kopeikina K, Kelsey JE. (2005). Long-lasting, sex-and age-specific effects of social stressors on corticosterone responses to restraint and on locomotor responses to psychostimulants in rats. Hormones and Behavior, 48, 64–74. [PubMed: 15919386]

Miller G, Rohleder N, Cole SW. (2009). Chronic interpersonal stress predicts activation of pro-and anti-inflammatory signaling pathways six months later. Psychosomatic Medicine, 71, 57. [PubMed: 19073750]

Mistry RS, Benner AD, Biesanz JC, Clark SL, Howes C. (2010). Family and social risk, and parental investments during the early childhood years as predictors of low-income children's school readiness outcomes. Early Childhood Research Quarterly, 25, 432–449.

Morrison KE, Epperson CN, Sammel MD, Ewing G, Podcasy JS, Hantsoo L, Kim DR, Bale TL. (2016). Preadolescent adversity programs a disrupted maternal stress reactivity in humans and mice. Biological Psychiatry, 15, 693–701.

O'Connor TG, Heron J, Glover V. (2002). Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. Journal of the American Academy of Child & Adolescent Psychiatry, 41, 1470–1477. [PubMed: 12447034]

O'Connor TG, Ben-Shlomo Y, Heron J, Golding J, Adams D, Glover V. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. Biological Psychiatry, 58, 211–217. [PubMed: 16084841]

O'Donnell K, O'Connor T, Glover V. (2009). Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Developmental Neuroscience, 31, 285–292. [PubMed: 19546565]

O'Donnell KJ, Jensen AB, Freeman L, Khalife N, O'Connor TG, Glover V. (2012). Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology, 37, 818–826. [PubMed: 22001010]

Reynolds RM, Labad J, Buss C, Ghaemmaghami P, Räikkönen K. (2013). Transmitting biological effects of stress in utero: implications for mother and offspring. Psychoneuroendocrinology, 38, 1843–9 [PubMed: 23810315]

Rice F, Harold GT, Boivin J, Van den Bree M, Hay DF, Thapar A. (2010). The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. Psychological Medicine, 40, 335–345. [PubMed: 19476689]

Robinson M, Oddy WH, Li J, Kendall GE, de Klerk NH, Silburn SR, Zubrick SR, Newnham JP, Stanley FJ, Mattes E. (2008). Pre- and postnatal influences on preschool mental health: a large-scale cohort study. Journal of Child Psychology and Psychiatry, 49, 1118–28. [PubMed: 19017026]

Rodriguez A, Bohlin G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? Journal of Child Psychology and Psychiatry, 46, 246–254. [PubMed: 15755301]

Romeo RD, Lee SJ, McEwen BS. (2005). Differential stress reactivity in intact and ovariectomized prepubertal and adult female rats. Neuroendocrinology, 80, 387–393.

Ruth CA, Roos N, Hildes-Ripstein E, Brownell M. (2012). The influence of gestational age and socioeconomic status on neonatal outcomes in late preterm and early term gestation: a population based study. BMC Pregnancy & Childbirth, 12, 62. [PubMed: 22748037]

Schneider ML, Moore CF, Kraemer GW, Roberts AD, De Jesus OT. (2002). The impact of prenatal stress, fetal alcohol exposure, or both on development: perspectives from a primate model. Psychoneuroendocrinology, 27, 285–298. [PubMed: 11750784]

Shachar-Dadon A, Schulkin J, Leshem M. (2006). Adversity before conception will affect adult progeny in rats. Developmental Psychology, 45, 9.

Sibley MH, Pelham WE, Jr, Molina BS, et al. (2014). The role of early childhood ADHD and subsequent CD in the initiation and escalation of adolescent cigarette, alcohol, and marijuana use. Journal of Abnormal Psychology, 123, 362. [PubMed: 24886010]

Stroud LR, Papandonatos GD, Williamson DE, Dahl RE. (2004). Sex differences in the effects of pubertal development on responses to a corticotropin-releasing hormone challenge: The Pittsburgh Psychobiologic Studies. Annals of the New York Academy of Sciences, 1021, 348–351. [PubMed: 15251908]

Talge NM, Neal C, Glover V, Early stress translational research and prevention science network. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? Journal of Child Psychology and Psychiatry, 48, 245–261. [PubMed: 17355398]

Togher KL, Treacy E, O'Keeffe GW, Kenny LC. (2017). Maternal distress in late pregnancy alters obstetric outcomes and the expression of genes important for placental glucocorticoid signalling. Psychiatry Research, 255, 17–26. [PubMed: 28511050]

Tyrka AR, Price LH, Marsit C, Walters OC, Carpenter LL. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: preliminary findings in healthy adults. PLoS One, 7, e30148. [PubMed: 22295073]

Vaivada T, Gaffey MF, Das JK, Bhutta ZA.(2017). Evidence-based interventions for improvement of maternal and child nutrition in low-income settings: what's new? Current Opinion in Clinical Nutrition Metabolic Care, 20, 204–210 [PubMed: 28207425]

Wadhwa PD, Glynn L, Hobel CJ, Garite TJ, Porto M, Chicz-DeMet A, Wiglesworth AK, Sandman CA. (2002). Behavioral perinatology: biobehavioral processes in human fetal development. Regulatory Peptides, 108,149–57. [PubMed: 12220739]

Wadhwa PD, Entringer S, Buss C, Lu MC. (2011). The contribution of maternal stress to preterm birth: issues and considerations. Clinics in Perinatology, 38, 351–384. [PubMed: 21890014]

Weinstock M (2005). The potential influence of maternal stress hormones on development and mental health of the offspring. Brain, Behavior, and Immunity, 19, 296–308.

Welberg LA, Seckl JR, Holmes MC. (2000). Inhibition of 11beta-hydroxysteroid dehydrogenase, the foeto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring. European Journal of Neuroscience 12, 1047–54 [PubMed: 10762336]

Winning A, Glymour MM, McCormick MC, Gilsanz P, Kubzansky LD. (2015). Psychological distress across the life course and cardiometabolic risk: findings from the 1958 british birth cohort study. Journal of the American College of Cardiology, 66, 1577–1586. [PubMed: 26429083]

Witt WP, Cheng ER, Wisk LE, et al. (2014a). Maternal stressful life events prior to conception and the impact on infant birth weight in the United States. American Journal of Public Health, 104, S81–S89. [PubMed: 24354829]

Witt WP, Litzelman K, Cheng ER, Wakeel F, Barker ES. (2014b). Measuring stress before and during pregnancy: a review of population-based studies of obstetric outcomes. Maternal and Child Health Journal, 18, 52–63. [PubMed: 23447085]

Wood CE, Walker CD. (2015). Fetal and Neonatal HPA Axis. Comprehensive Physiology, 15, 33–62.

Zaidan H, Gaisler-Salomon I. (2015). Prereproductive stress in adolescent female rats affects behavior and corticosterone levels in second-generation offspring. Psychoneuroendocrinology, 58, 120–9. [PubMed: 25973567]

Zaidan H, Leshem M, Gaisler-Salomon I. (2013). Prereproductive stress to female rats alters corticotropin releasing factor type 1 expression in ova and behavior and brain corticotropin releasing factor type 1 expression in offspring. Biological Psychiatry, 74, 680–687. [PubMed: 23726318]

Zehr JL, Todd BJ, Schulz KM, McCarthy MM, Sisk CL. (2006). Dendritic pruning of the medial amygdala during pubertal development of the male Syrian hamster. Journal of Neurobiology, 66, 578–590. [PubMed: 16555234]

Table 1.

Animal models providing evidence for preconception stress effects on offspring neurodevelopment.

Reference	Model/design	Dependent Measure	Results
Bock et al (2016)	Compared offspring of female rats assigned to an unstressed control group (n = 11) to two experimental groups that were stressed one week before mating (n= 15) or 2 weeks before mating (n= 9).	Spine number/density and dendritic length/ complexity in offspring at postnatal day 65.	There was a significant increase in spine number in the left hemisphere of the medial prefrontal cortex (mPFC) of male and female offspring of dams who were stressed 2 weeks before mating versus the control group ($p = 0.011$). Male offspring of dams who were stressed 2 weeks before mating also had longer dendrites ($p = 0.02$) compared to the control group. There were no other significant group differences.
Shachar et al. (2009)	Compared adult offspring (n = 146) of dams assigned to an unstressed control group (n = 86) to two experimental groups: one that mated immediately following 7 days of stress exposure (n = 83) and one that mated 2 weeks after the stress exposure (n = 25).	Activity (lines crossed on runway), tone and shock response (avoidance, escape or escape failure), startle response, prosocial behavior, asocial behavior.	Offspring of preconception stress dams were more active, in terms of lines crossed in the elevated maze plus, versus those in the control group ($p < .001$). There were also group effects in prosocial behavior ($p < 0.05$), and asocial behavior ($p < 0.001$). There were no other group differences.
Huang et al (2010)	Compared 2-month old offspring of adult female rats assigned to an unstressed control group($n = 8$) versus a chronic, unpredictably stressed (CUS) group ($n = 12$).	Escape latency in the Morris water maze task, serum corticosterone (COR) levels, expression of brain-derived neurotrophic factor (BDNF), and N-methyl-D-aspartate (NMDA) 2A (NR2A) and 2B (NR2B) receptors in the hippocampus.	Escape latency of the offspring of dams who were stressed preconception was significantly longer than that of the control group ($p < 0.01$). There was a significant increase in the COR levels of the offspring of preconception stress dams versus the control group ($p < 0.01$). Decreased expression of BDNF and NR2B in the hippocampus in offspring of preconception stress dams versus offspring of the control group ($p < 0.05$).
Li et al., (2010	Compared adult offspring of female rats assigned to an unstressed control group ($n = 8$) versus a 21-day chronic, unpredictable stress (CUS) group (n=8)	Dam behavior pre- and post-administration of CUS; offspring behavior in the Morris Water Maze test; 5-HT in the hypothalamus, NE levels in the hippocampus, P-CREB in the hippocampus	Exposed offspring had decreased spatial memory, lower sucrose consumption, higher levels of norepinephrine (NE) in the hippocampus, lower levels of serotonin (5-HT) in the hypothalamus, and less protein expression of phosphorylated Cyclic AMP responsive element binding protein (P-CREB).
Zaidan et al (2013; 2015)	Compared brains of male (n= 6) and female (n=5) F1 offspring of rats exposed to 1 week of chronic, unpredictable stress two weeks prior to conception to male (n=5) and female (n= 7) controls; and corticosterone in F2 (7 males and 5 females) and controls (7 males and 7 females)	expression of CRF1 receptors in the brain in first generation (F1), and corticosterone levels in F1 and second generation (F2) offspring compared to offspring of controls	Expression of corticotropin releasing factor (CRF) 1 and 2 receptors were increased in neonatal and adult brains, comparedto brains of control offspring. Corticosterone levels were increased in the F1 females, and F2 males anddecreased in F2 females compare to offspring of controls

Table 2.

Human models providing evidence for preconception stress effects on offspring health and neurodevelopment.

Reference	Sample	Model/design	Dependent Measure	Results
Class et al. (2013)	3,055,361 Swedish population based sample of offspring born between 1973 and 2008	Tested the association between preconception (6 months before conception) and prenatal (across pregnancy) bereavement stress, on birth outcomes and infant mortality.	Preterm birth (PTB), defined as < 37 weeks gestation; small for gestational age (SGA) defined by birth weight less than 2 standard deviations below the mean for GA; infant mortality (8,398 cases) from medical records.	Preconception stress increased risk for PTB (AOR=1.19; 95% CI=1.12–1.26) and SGA (AOR=1.14; 95% CI=1.05–1.23); Preconception stress increased risk for infant morality controlling for PTB and SGA (AOR=1.37; 95% CI=1.11–1.70. Prenatal stress was not associated with birth outcomes or infant mortality
Class et al. (2015)	1,865,454 Danish population-based sample of offspring born 1979 to 2009	Tested the association between preconception (6 months before conception), prenatal (across pregnancy) bereavement stress, on infant mortality.	Neonatal (0–28 days), infant (29–364 days), and early childhood (1–5 years) mortality from medical records	Preconception stress was associated with neonatal (AOR = 1.87, 95% confidence interval = 1.53–2.30) and infant mortality (AOR = 1.52, 95% confidence interval = 1.15–2.02). Bereavement during the prenatal period was not associated with offspring mortality
Baird et al. (2009)	874,874 mother and offspring pairs from the Southampton Women's Survey (SWS) followed through pregnancy and 12 months of age.	Tested the association between maternal psychological distress before conception and offspring sleep disturbance during infancy.	Number of times babies woke on average between the hours of midnight and 6:00am each night during a 2-week period at 6 and 12 months of age	At 6 and 12 months, offspring whose mothers experienced preconception psychological distress had an increased risk of waking compared to offspring of women not reporting preconception stress.
Harville et al. (2010)	Sample of 4,865 women who were enrolled as children in the prospective National Child Development Study in Great Britain in 1958, and who later had at least 1 singleton birth	Tested the association between prospectively collected data on childhood stress exposure (e.g., including financial hardship, family dysfunction, violence/mental health issues, and family structure) and low birth weight and preterm birth.	Low birth weight (LBW) defined as below 2500 grams; preterm birth (PTB), defined as more than 3 weeks prior to due date. Participants were also asked if they smoked before or during the pregnancy.	Childhood stressors were associated with risk of LBW (OR = 1.51, 95% CI 1.10–2.06) and PTB (OR = 1.44, 95% CI 1.08–1.92)., controlling for smoking status and adult social class.
Li et al. (2009; 2010)	Registry study of 1,015,912 singletons born in Denmark from 1987 to 2001.	Tested the association between preconception maternal bereavement and offspring risk for attention-deficit/hyperactivity disorder (ADHD), and cerebral palsy.	ADHD hospitalization or administration of ADHD medication after 3 years of age; Diagnosis of cerebral palsy.	Maternal bereavement due to death of a child or spouse during preconception was associated with increased risk of ADHD (HR 1.44, 95% CI 1.00 – 2.16) in male offspring; maternal bereavement during the periods of 7 to 12 months before pregnancy 2.29 (95% CI, 1.54 – 3.43) and 6 to 0 months before pregnancy 1.93 (95% CI, 1.34 −2.78) was associated with risk of cerebral palsy.

Note: AOR = adjusted odds ratio; CI = confidence interval.