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Prenatal stress-immune programming of sex differences in comorbidity of depression and obesity/metabolic syndrome

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Introduction

Major depressive disorder (MDD) is the number one cause of disability worldwide, with women having twice the risk of men. Furthermore, depression is comorbid with other chronic medical conditions, including obesity and metabolic syndrome (MetS), with higher prevalence of the comorbidity among women. MDD is more severe among comorbid obese than nonobese depressed individuals, with poorer weight loss outcomes and increased risk for cardiovascular disease (CVD). The comorbidity of MDD and obesity/MetS contributes substantially to increased medical expenditures, reaching about $245 billion in the United States alone and is associated with premature death.

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Selected abbreviations and acronyms

- **ANS**: autonomic nervous system
- **AT**: angiotensin II type 1
- **CVD**: cardiovascular disease
- **GC**: glucocorticoid
- **HPA**: hypothalamic-pituitary-adrenal
- **HPG**: hypothalamic-pituitary-gonadal
- **IL**: interleukin
- **MDD**: major depressive disorder
- **MetS**: metabolic syndrome
- **PVN**: paraventricular nucleus
- **RAS**: renin-angiotensin system

A number of studies demonstrated fetal risk factors for MDD\textsuperscript{4,6} and obesity/MetS\textsuperscript{7}, with final common pathways involving disruption of maternal-fetal hypothalamic-pituitary-adrenal (HPA)-axis development (ie, “prenatal stress” models of chronic disease). The conceptualization of prenatal stress includes obstetric conditions (eg, preeclampsia, fetal growth restriction), maternal overnutrition or undernutrition, and other environmental and psychological exposures that cause maternal secretion of glucocorticoids and subsequent immune dysregulation. The pathways through which these stressors impact fetal growth and brain development are not well understood, but probably involve genetic and epigenetic mechanisms mediated by hormones, growth factors, and/or markers of immune function that cross the placenta.

We argue that prenatal stress disruptions occurring during key gestational periods have sex-dependent effects on brain development within highly sexually dimorphic regions that regulate mood, stress, metabolic function, the autonomic nervous system (ANS), and others. Brain regions implicated in mood, ANS, metabolism, and CVD function include the hypothalamic paraventricular nucleus (PVN), central/medial amygdala, hippocampus, periaqueductal gray, medial and orbital prefrontal cortices, and anterior cingulate cortex. These brain regions are morphologically and functionally sexually dimorphic\textsuperscript{8-12} (Figure 1). Thus, as shown in clinical and preclinical studies, prenatal maternal stress (ie, excess glucocorticoid expression and associated immune disruption) that occurs during the sexual differentiation of the fetal brain will produce lifelong, shared risk for sex differences in MDD-MetS by altering the development of common pathways. Previous critical reviews by our team argued this case for MDD-CVD\textsuperscript{13,14}

We believe there are shared biologic substrates at the anatomical, molecular, and/or genetic levels that produce comorbid risk for these disorders that have fetal origins and are sex-dependent (Figure 2).  

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Epidemiology

In 2012, MDD became the leading cause of morbidity and mortality worldwide, surpassing ischemic heart dis-
ease, with almost 20% prevalence in women. Similarly, rates of adult obesity increased dramatically between 1999 and 2004 and reached 41% in 2015.3 More women suffer from comorbidities with MDD than men, with women being 62% more likely to have multiple conditions. Although men have higher rates of comorbid CVD-MetS, women have higher rates of depression, anxiety disorders, and pain comorbid with CVD and MetS. Thus, understanding the sex-dependent mechanisms that underlie these associations is important for the development of novel therapeutics to address the call for precision medicine.

Obesity (body mass index $\geq 30.0$), when comorbid with MDD,15 is associated with greater severity16 and worse outcomes among those taking antidepressants17 and/or during weight loss treatment. The literature suggests that the comorbidity of MDD-obesity/MetS may be stronger among, and perhaps limited to, women.18 The rate of obesity is higher for women than men, and among women, those with MDD are more likely than nondepressed women to develop obesity.19 Given the public health crisis regarding obesity-related health conditions and expenditures, it is important to understand sex differences in pathways leading to obesity-related health diseases.

CVD (which is associated with obesity/MetS) is a major cause of mortality worldwide, with higher prevalence in men (40.5%) than women (35.5%).20 although CVD is the number one cause of death among women in the United States. Furthermore, as with MetS, women have an almost twofold higher prevalence than men of comorbid MDD-CVD, which is predicted to be the number one cause of disability worldwide by 2020.13,14 MDD also leads to a higher death rate among women with CVD.

MetS is a cluster of metabolic dysfunction comprising central obesity, dyslipidemia, impaired glucose metabolism, and hypertension.21 Approximately 30% of the US population exhibits MetS,22 which confers a twofold increased risk for CVD.20 Although the prevalence of MetS is similar (around 32%) among men and women (in contrast to CVD prevalence), its individual components vary by sex, with higher proportions of hypertriglyceridemia, hypertension, low high-density lipid levels, and hyperglycemia in men and higher proportions of central adiposity in women.23 Thus, understanding the impact of sex on MetS may provide etiologic clues as to the nature of the comorbidity of MDD and CVD, and it may be one reason why there is a higher death rate from CVD among women, even though CVD prevalence is lower than in men.

**Role of HPA and HPG steroid hormones**

Dysregulation of HPA and HP-gonadal (HPG) axes has been independently implicated in the pathogenesis of both MDD and obesity/MetS. Cushing syndrome, characterized by excess cortisol (glucocorticoid; GC), has a higher prevalence among women and is associated with cardiometabolic complications, including obesity, impaired glucose tolerance, and hypertension.24 The HPA overactivity observed among obese compared with lean patients is associated with abdominal obesity, MetS, and high blood pressure.25 Obese women have higher corticotropin-releasing hormone (CRH)-stimulated cortisol levels than men,25 even though men have higher levels of basal cortisol than women.

Studies linking the association of stress and GC response with the development of obesity/MetS in humans are limited because of a lack of longitudinal data and difficulty in assessing subtle changes in local tissue...
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via autocrine and paracrine mechanisms. GCs promote adipocyte differentiation and proliferation where visceral adipocytes have high GC receptor distribution. There are some genetic polymorphisms in glucocorticoid receptors associated with alterations in GCs, obesity, and comorbid obesity-MDD, although their roles are unclear. Proposed mechanisms linking HPA activity and obesity/MetS include alterations in GC metabolism in adipose tissue depots and interactions of cortisol with high-fat diet and key appetite-regulating hormones, such as leptin and ghrelin (see below).

In response to an energy deficit, cortisol rises and facilitates food intake and fat deposition. Among obese women, cortisol is decreased or similar to healthy-weight women, increased after food intake or in response to social stress, and decreased after weight loss. Mechanisms explaining these findings include direct central nervous system action in tissues with high GC receptor concentration, in regions that are sexually dimorphic and regulate mood. Therefore, we suggest that disruptions in the development of these regions will produce multiple systemic endocrine and metabolic effects.

The PVN, the key relay station for HPA activity, develops differently in male and female brains, and is the most highly vascularized central nervous system region, and is important for regulating homeostatic, neuroendocrine, and behavioral functions associated with MDD. Furthermore, the PVN is an essential component of brain circuitries important for feeding and energy balance and can regulate the ANS, which is critical for healthy cardiovascular responses. Thus, understanding the role of the PVN may be critical for understanding the impact of HPA activity on sex differences in the comorbidities among MDD, MetS, and CVD.

Gonadal steroids are also associated with MetS and CVD. Abnormalities in estradiol levels among obese women compared with healthy-weight women may be decreased, elevated, or show no differences. Estrogens affect body weight and food intake, which vary with reproductive age. Premenopausal women demonstrated decreased food intake during the follicular phase, and during postmenopause, estrogen levels are reduced and circulate proportionally to body fat. Estrogen receptors are found in food reward regions and act to suppress appetite and increase energy expenditure. Hyperandrogenic conditions in women (hirsutism and polycystic ovary syndrome) are associated with CVD, insulin resistance, visceral fat accumulation, and MetS, but low circulating testosterone in men is associated with obesity, type 2 diabetes, and MetS. Thus, dysregulation of gonadal steroid levels is associated with cardiometabolic phenotypes in women and men. The presence of comorbid MDD and insulin resistance was underscored by recent findings from a large population study (n=12,231) using the Northern Finland Birth Cohort from 1966, which demonstrated the emergence of comorbid MDD and insulin resistance in women only after menopause, but in men, onset occurred at an earlier age.

There is a very long history of studies of HPA dysregulation associated with MDD, in particular, heightened cortisol levels, that may become blunted among those with long-term, recurrent MDD. However, these studies will not be reviewed here, given extensive reviews elsewhere. In brief, depressive symptoms can occur in the face of endogenously elevated cortisol (Cushing syndrome) or of exogenously administered corticosteroids. Patients treated with corticosteroids can develop MDD. Human studies demonstrate consistent HPA-axis dysregulation associated with MDD, including elevated plasma and cerebral spinal fluid cortisol levels and 24-hour urinary cortisol levels, high cerebral spinal fluid CRH levels, blunted responses to CRH administration, and lack of negative feedback suppression by dexamethasone.

HPG deficits in MDD include lower estradiol levels and adjunctive estradiol has been found effective in treating MDD among women. This observation has been reviewed elsewhere so will not be reviewed here. In brief, women’s reproductive variability and aging are related to mood fluctuations and MDD. In women, MDD incidence increases with puberty, late luteal phase, and after childbirth and after menopause. Population studies demonstrated that ovarian dysfunction precedes MDD onset. Aside from estradiol abnormalities, deficits have been found in luteinizing hormone and pituitary function.

The comorbidity between MDD, HPA-HPG-axis dysregulation, and MetS risk is not surprising from the perspective of the brain circuitry involved. MDD involves hypothalamic nuclei central/medial amygdala, hippocampus, anterior cingulate cortex, and medial and orbitofrontal cortices—regions that are dense in glucocorticoid and sex steroid hormone receptors.
that can relay information that regulates metabolic and cardiac function through the ANS. Reduced gray-matter volume has been noted within several of these regions in MDD patients, including the anterior cingulate, orbitofrontal cortex, prefrontal cortex, insula, putamen, caudate nucleus, and hippocampus and adjacent temporal lobes as demonstrated in recent large meta-analyses focused on volumetric and cortical thickness indices. More nuanced analyses have revealed effects of medication on the amygdala, in which decreases in amygdala volume are associated with some specificity to nonmedicated status. In the hippocampus, volumetric variation has been associated with clinical state, with reduced hippocampal volume evident in first-episode depression, currently depressed but not remitted patients, recurrent MDD, or prolonged (>1 year) illness duration. These findings suggest a critical link between lowered mood state and hippocampal structural integrity that is potentially related to abnormal HPA-axis feedback on glucocorticoid receptors in the hippocampus. Differences in results from studies identifying brain abnormalities in MDD are, in part, a function of methodological variability across studies, such as MDD chronicity (eg, acute versus chronic disability), sex and age of subjects, sample sizes, and/or measurement of brain regions. However, there is consistent evidence that deficits in these brain regions originate during fetal development and have lifelong consequences for sex differences in the risk for MDD-MetS comorbidity, dependent on brain region and age of assessments.

Appetite-regulating hormones

One pathway through which mood and metabolic function co-occur may be related to the overlap of brain regions that regulate mood, HPA, HPG, and ANS. These areas are dense with receptors for ghrelin and leptin, two peptides that are involved in hunger and satiety. Ghrelin is a potent orexigenic peptide, with levels rising sharply before meals and falling to nadir within an hour after eating. Ghrelin receptors are located in the substantia nigra, ventral tegmental area, raphe nuclei, hypothalamic nuclei (PVN, arcuate, and ventromedial), and hippocampus; direct ghrelinergic projections connect the PVN to amygdala. Intravenous ghrelin administration heightens neural activation in these brain regions in response to food images. Ghrelin levels are decreased in obesity, and plasma ghrelin levels negatively correlate with percent body fat during fasting, whereas increases in ghrelin occur after weight loss. Circulating ghrelin levels are higher among women than men, and in postmenopausal obese women, they are inversely related to estradiol. Reported ghrelin levels among healthy-weight persons and MDD status are inconsistent across studies. Among healthy-weight individuals with MDD, ghrelin has been reported as elevated, decreased, or similar to that in individuals without MDD. Inconsistencies in MDD studies may be due to the lack of control for sex, given that women have higher levels of circulating ghrelin than men.

In contrast, leptin suppresses appetite by effects at similar hypothalamic sites, and it stimulates energy expenditure. Leptin circulates in proportion to fat mass, signaling energy availability and satiety, and is generally higher among women than men, beginning in puberty, even after accounting for differences in body fat distribution and menopause. Leptin receptors are located within many brain regions, some of which are sexually dimorphic and overlap areas involved in mood and stress regulation. Though circulating leptin follows a pulsatile release pattern, decreases in leptin occur with fasting and basal plasma leptin levels are elevated in obesity.

Recent evidence links inflammatory adipokines and ghrelin–growth hormone (GH) axis with obesity and MDD. Adiponectin is an anti-inflammatory peptide secreted by adipocytes and plays a role in fetal growth and endothelial function. Women exhibit higher adiponectin levels than men, and reports suggest a sex-dependent role of adiponectin as a biomarker for CVD and diabetes risk. Low adiponectin levels are associated with depressive-like behaviors, and genetic haploinsufficiency of adiponectin (Adipo−/+−) causes depression-like behavior and impaired HPA-axis feedback, which are reversed by intracerebroventricular adiponectin administration.

Collectively, although disruption of peptides involved in appetite regulation is well documented in obesity, mixed findings in MDD suggest attention to sex and variability in weight may explain inconsistencies across studies. Given the overlap of a number of regulatory peptides in key brain regions (eg, hypothalamus, mesolimbic circuitry) and their roles in the pathophysiology of sex differences in MDD-obesity/MetS, systematic designs stratifying subject groups by
MDD and obesity status by sex would allow for delineation of shared and unshared pathways contributing to understanding brain abnormalities associated with metabolic and mood dysregulation and sex differences therein.

**Fetal origins: mapping developmental pathways to comorbidity**

There is emerging evidence that alterations in HPA axis and stress adaptation in response to suboptimal conditions in utero produce disturbances in fetal metabolism and development of obesity and MDD in adulthood. Sex differences in MDD alone and in comorbid MDD-CVD have been reviewed elsewhere. Epidemiological evidence shows increased incidence of obesity and diabetes as a result of severe maternal malnutrition, possibly secondary to effects on early fetal programming of the HPA axis. Obstetric complications, such as preeclampsia and low birth weight, have been found to be significant risk factors for MDD and cardiometabolic outcomes. Nonetheless, beyond few population-level investigations, sex differences in fetal programming of comorbid MDD-MetS has not been well examined, owing largely to a paucity of longitudinal datasets that are able to address these critical fetal developmental models that have already been established for animals.

Excessive maternal glucocorticoid responses to stress are also associated with maternal inflammatory responses. Altered levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, and IL-10 in maternal sera during gestation are associated with preeclampsia and fetal growth restriction and adult risk for CVD and MDD. These cytokines are also associated with maternal HPA dysregulation. TNF-α, IL-1β, and IL-6 are the primary coactivators of HPA response, and their receptors are located in PVN, hippocampus, and pituitary. We recently reported that maternal prenatal immune dysregulation has an impact on sex differences in the adult offspring MDD risk. In fact, elevated IL-1, IL-6, and TNF-α have been associated with CVD risk and MetS.

Few human studies have directly linked maternal markers of immune function during gestation with MetS risk among adult offspring by sex. However, preclinical studies are leading the way in mapping out pathways implicated in the fetal stress-immune programming of sex differences in the comorbidity of mood and anxiety-related behaviors and cardiometabolic dysfunction (Figure 1).

**Preclinical evidence**

In rodents, prenatal synthetic glucocorticoid (sGC) exposure or inhibition of 11β hydroxysteroid dehydrogenase (11β-HSD; a placental enzyme that metabolizes GCs and acts as barrier to maternal GCs) can cause long-term adult changes in cardiometabolic function and neuroendocrine responses to stress and anxiety-depressive-like behaviors. As in humans, the neuropeptide neurons in the PVN are key in regulating the HPA axis. Similarly, the ANS is controlled in part by preautonomic neurons located within the rat PVN that project to preganglionic autonomic neurons located in the brainstem and spinal column.

The timing of prenatal stressors will have very different effects on physiological systems because various tissues and brain regions develop and mature at different times of gestation. Moreover, the ability to extrapolate the effects of environmental perturbations in experimental animals to humans is complicated by differences in gestation length and maturation rate.

**Cardiovascular system and metabolism**

Exposure to prenatal stressors, including sGC administration, dietary restriction, and inflammation, can program changes in cardiovascular function in male and female rodent offspring, with increased vascular sensitivity to norepinephrine, neuropeptide Y, and electrical field stimulation; increased peripheral resistance and reduced cardiac output, and hypertension or hypotension altering stress responses. In females alone, prenatal stressors resulted in enhanced endothelin responsiveness and impaired parasympathetic function (although males were not tested in the latter). Adult offspring of prenatally stressed dams were more susceptible to elevations in blood pressure in response to high salt diet, angiotensin II, and restraint. As in humans, prenatal GC exposures in rodents are coupled with inflammatory responses, known to be associated with hypertension and heart disease. Prenatal exposure to IL-6 causes hypertension and enhanced cardiovascular responses to stress, with a greater effect in females.
Epigenetic changes are associated with cardiovascular programming from prenatal stress. Prenatal GCs reduced global DNA methylation in the kidney, adrenal glands, and cerebellum in adult offspring. There is some evidence for increased methylation related to an altered renin-angiotensin system (RAS; a major regulator of long-term control of blood pressure), where prenatal sGC altered the expression of angiotensin receptors, renal angiotensin II production, and plasma renin activity. However, the direction of the RAS activity in male versus female offspring varied with the nature or timing of prenatal stress. Enhanced RAS activity was observed after prenatal exposure to sGCs, demonstrating that acute angiotensin II type 1 (AT1) receptor blockade lowered blood pressure—partially normalizing parasympathetic dysfunction—and fully normalized blood pressure variability in adult male sheep (females not tested). A maternal low-protein diet caused corticosterone-dependent increases in angiotensin 1b receptor gene (AT1b) expression coupled with reduced methylation of the AT1b promoter. Importantly, in addition to changes in angiotensin receptor expression, inhibition of corticosterone production in utero prevented hypertension in these offspring. Prenatal stress also altered central RAS activity. Central infusion of the AT1 receptor antagonist losartan reduced blood pressure and heart rate in sGC-treated versus control male sheep (females not tested). Prenatal sGC exposure also increased AT1 expression in brainstem of adult offspring and increased angiotensin II levels relative to the protective Ang(1-7) peptide levels in the dorsal medulla. Together, these studies suggest that prenatal stress alters the RAS by programming the expression of angiotensin receptors during gestation.

Animal studies also demonstrated that late-gestation stressors predisposed offspring to MetS in adulthood. Moreover, late-gestation exposure to sGC increased liver enzymes involved in gluconeogenesis in adult male, but not female, offspring and altered production of insulin by reducing pancreatic β-cells and their capacity to secrete insulin. Prenatal GCs also increased circulating triglycerides and storage of fat in the liver and decreased fatty acid uptake in visceral adipose tissue. Most of these studies were restricted to adult male offspring; however, we previously demonstrated that high-fat-diet-induced hepatosteatosis was more profound in female offspring of dexamethasone-treated dams, and this was coupled with sex-specific changes in circulating insulin-like growth factor 1 (IGF-1). Taken together, these studies highlight the role of prenatal GC exposure, whether from prenatal stress or treatment with sGC, on the impact of glucose homeostasis programming and risk for adult MetS.

In fact, prenatal stress programming of MetS may be initiated very early in gestation and have sex-selective effects expressed as different metabolic phenotypes in males and females. An example of this was found in studies of O-linked βN-acetyl glucosamine (O-GlcNAc) transferase (OGT). This enzyme, expressed by the placenta, senses changes in maternal energy homeostasis and regulates epigenetic marks on chromatin. Early gestational stress reduces placental OGT, giving rise to changes in offspring endocrine and hypothalamic mitochondrial function and body weight. Reductions in placental OGT were only found in male placentas, suggesting a pathway whereby early changes in placental OGT regulated sex-selective epigenetic modification of genes important for adult metabolism.

Gestational stress can also foster MetS by organizing hypothalamic nuclei that control energy homeostasis. Leptin is important for the development of both orexigenic and anorexigenic projections from the arcuate nucleus and acts during development to regulate autonomic centers controlling peripheral tissues in adulthood. A surge of circulating leptin occurs in development and peaks about postnatal day (PD) 9 to 12 in male and female rats. Gestational malnutrition advanced the leptin surge, leading to hypothalamic leptin insensitivity in adult male offspring (females not tested), and delaying the postnatal leptin surge led to diet-induced obesity in female rats (males not tested). Similarly, intrauterine growth restriction caused hyperleptinemia followed by leptin resistance by PD21 in female, but not male, rats, whereas a leptin antagonist increased food intake in adult male, but not female, offspring. Together, these studies suggest sex-dependent roles for the postnatal surge of leptin in the development of hypothalamic regulation of energy balance in adulthood.

### Adult behavior and neuroendocrine function

Prenatal stressors in rodents also program the HPA axis, causing increased stress responsiveness, and this is mimicked by prenatal exposure to glucocorticoids. The impact of late-gestation prenatal stress on...
adult stress responsivity is more profound in adult female offspring, where prenatal stressors increase basal adrenocorticotropic hormone (ACTH) and corticosterone levels and the peak and duration of responses to adult stressors, indicative of reductions in GC negative feedback. Supporting this, Tobe and colleagues detected increased apoptosis in the fetal female, but not male, PVN after long-term maternal stress, and this correlated with changes in neuroendocrine function and anxiolytic behaviors. Moreover, late-gestation sGCs resulted in increased anxiety and depressive-like behaviors in adult female, but not male, offspring, suggesting potential sex-dependent pathways to sex differences in mood and anxiety disorders.

A recent study provided evidence of potential sex-dependent targets for the long-term effects of prenatal stress and sGCs. In females, upregulation of 5α-reductase and 3β-HSD in adults that were prenatally stressed was effective in reversing programming effects on the HPA-axis response to IL-1β administration. Thus, timing of environmental perturbations is critical for the sex-dependent alterations in the development of HPA-axis responses in adulthood, suggesting the potential for sex-specific critical periods for the actions of perinatal GCs. Nonetheless, the system appears to retain sufficient plasticity to allow deficits to be overcome by later manipulations. Given that sex-dependent changes can occur after prenatal perturbations, future studies need to determine the importance of central versus peripheral changes in the RAS, HPA axis, and metabolic markers involved and how they impact sex-dependent long-term changes in cardiovascular, metabolic, and behavioral-associated diseases.

**Conclusion**

In summary, clinical and preclinical studies demonstrate the impact of prenatal stress-immune programming of sex differences in adult risk for mood and anxiety and ANS, metabolic, and cardiac dysfunctions. The sex-dependent impact is timing specific during gestation and brain-region specific, resulting in multiple systemic sex-dependent effects on HPA-HPG axes and on metabolic and cardiac functions, leading to sex differences in the comorbidity of MDD-obesity/MetS. Translational studies are critical to map out the specificity of these developmental pathways among men and women. The developmental nature and preclinical evidence for some reversibility of effects suggests optimism for early intervention with sex-dependent novel therapeutics.

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