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Review Article

Trauma and Posttraumatic Stress Disorder as Important Risk Factors for Gestational Metabolic Dysfunction

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Abstract

Gestational metabolic diseases adversely impact the health of pregnant persons and their offspring. Pregnant persons of color are impacted disproportionately by gestational metabolic disease, highlighting the need to identify additional risk factors contributing to racial-ethnic pregnancy-related health disparities. Trauma exposure and posttraumatic stress disorder (PTSD) are associated with increased risk for cardiometabolic disorders in nonpregnant persons, making them important factors to consider when identifying contributors to gestational metabolic morbidity and mortality health disparities. Here, we review current literature investigating trauma exposure and posttraumatic stress disorder as psychosocial risk factors for gestational metabolic disorders, inclusive of gestational diabetes, low birth weight and fetal growth restriction, gestational hypertension, and preeclampsia. We also discuss the physiological mechanisms by which trauma and PTSD may contribute to gestational metabolic disorders. Ultimately, understanding the biological underpinnings of how trauma and PTSD, which disproportionately impact people of color, influence risk for gestational metabolic dysfunction is critical to developing therapeutic interventions that reduce complications arising from gestational metabolic disease.

Keywords

- trauma
- PTSD
- stress
- metabolic disorders during pregnancy
- gestational diabetes mellitus
- hypertensive disorders of pregnancy
- fetal growth restriction

Key Points

- Gestational metabolic diseases disproportionately impact the health of pregnant persons of color.
- Trauma and PTSD are associated with increased risk for cardiometabolic disorders in nonpregnant per.
- Trauma and PTSD impact physiological cardiometabolic mechanisms implicated in gestational metabolic.

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Metabolic disorders during pregnancy, which include gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), and fetal growth restriction (FGR), are adverse health outcomes that jeopardize the wellbeing of both pregnant persons and their offspring during and beyond gestation. During gestation, physiological adaptations across multiple tissue and organ systems occur in unison to meet the energy demands of the growing fetus.[1] These adaptations create a metabolic challenge that increases risk for gestational metabolic disorders. Increased risk for gestational metabolic dysfunction is reflected in the prevalence of prenatal metabolic disorders, with baseline rates in the United States for GDM ranging from 5 to 10% and HDP and FGR around 3 to 10%.[2–5]

The burden of metabolic disorders during pregnancy is disproportionately distributed among racial-ethnic lines, as demonstrated by higher GDM rates among Asian and Hispanic/Latinx populations,[6] higher HDP rates among black and Hispanic/Latinx populations,[7] and higher FGR rates among black populations[1,8] relative to white populations. Additionally, non-white pregnant persons have a higher risk for adverse outcomes when diagnosed with gestational metabolic disorders. Preeclampsia, a subset of HDP, is the second leading cause of maternal mortality[6]; the risk for severe morbidity is 9.8 and 7.7% in non-Hispanic black and Hispanic/Latinx pregnant persons respectively, compared with 6.1% morbidity risk in white pregnant persons.[9] Gestational hypertension (GHTN) prevalence shows similar racial-ethnic inequities, with non-Hispanic black and Hispanic/Latinx pregnant persons at higher risk for pregnancy-associated stroke than white pregnant persons and nonpregnant persons.[2,3] Given the dangers of gestational metabolic dysfunction, it is essential to identify risk factors that alter metabolic physiology in pregnancy and understand how those risk factors contribute to racial-ethnic disparities in pregnancy-related health.

Risk factors for gestational metabolic disease include age, income, family history, preexisting metabolic disease like type 2 diabetes mellitus (T2DM), and high blood pressure.[4–7] However, when controlling for these risk factors, pregnant persons of color, in particular black pregnant persons, still experience increased rates of gestational metabolic disease as compared with non-Hispanic white pregnant persons, indicating that psychosocial factors may modify gestational metabolic health as well.[8] Trauma exposure and resulting posttraumatic stress disorder (PTSD) are two psychosocial risk factors that may contribute to gestational metabolic dysfunction and associated racial-ethnic health disparities. Traumatic stress exposure leads to set of maladaptive physiological responses that adversely impact overall health, including behavioral health.[10] PTSD is a psychiatric disorder that occurs after exposure to a traumatic event and adversely impacts individuals' mood and fear responses.[9] Critically, non-white nonpregnant individuals, particularly black and Latinx/Hispanic individuals, are exposed to higher rates of traumatic events and suffer more from PTSD.[11–14] This increased exposure to trauma and PTSD in non-white populations not only impacts mental health but may also adversely impact metabolic function. In particular, trauma exposure and PTSD are associated with increased risk for the development of T2DM,[13] hypertension[14] and cardiovascular disease in nonpregnant populations.[15] Exposure to trauma and PTSD negatively impact multiple biological systems, including the autonomic nervous system (ANS) and hypothalamic-pituitary adrenal axis (HPA) stress systems, whose dysregulation can lead to heightened systemic inflammation.[1,15,16] Dysregulation of these physiological systems maintains the body in a catabolic state of glucose production, predisposing individuals to increased risk of metabolic dysfunction.[16–18]

Despite the link between trauma, PTSD, and metabolic dysfunction in nonpregnant persons, it remains unclear how trauma and PTSD impact risk for metabolic dysfunction in pregnancy and associated pregnancy-related health disparities. Thus, in the current narrative review, we will summarize and synthesize significant findings to date that address the association between trauma and PTSD and gestational metabolic diseases including GDM, HDP, FGR, and low birth weight (LBW). To contextualize relevant findings, we first discuss underlying biological mechanisms by which trauma exposure and PTSD act as chronic stressors that lead to metabolic dysfunction in nonpregnant persons. Following, we assess and evaluate findings form the limited studies that address the relationship between metabolic dysfunction in pregnant persons and traumatic stress exposure and PTSD, while highlighting socioeconomic and racial-ethnic study demographics. Uncovering the biological mechanisms that underlie gestational metabolic risk is critical to developing preventive and interventional treatments for pregnant persons at high risk for gestational metabolic disease. Ultimately, understanding the role of trauma and PTSD in gestational metabolic dysfunction is a crucial component in better understanding the biological mechanisms that underlie racial-ethnic and socioeconomic pregnancy-related health disparities and associated infant health complications.

Biological Pathways Underlying Stress Effects on Metabolism Outside of the Context of Pregnancy

Overview of the Physiological Stress Response Systems

The stress response is a broad term that refers to any physiological change in response to a physical or psychological stimulus (stressor) that is perceived as a danger to an individual.[17] The stress response evolved to promote the survival of organisms and is composed of the co-activation of the fast-acting ANS, which activates the immune system to prepare for potential wounding, and the slower acting HPA axis. The ANS is divided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS), which work in a complimentary fashion alongside the HPA axis to regulate physiological and behavioral responses when danger is detected.[18] During exposure to an acute stressor, the SNS and HPA axis signal the release of epinephrine and cortisol from the adrenal glands, respectively. These hormones work in tandem to increase heart

rate, respiration rate, and blood vessel dilation to increase the availability of oxygen to accommodate the body's perceived emergency state.[19] HPA axis-induced release of cortisol initiates catabolic processes in liver, fat, and muscle tissue via activation of glucocorticoid receptors, therefore increasing glucose availability that is critical for providing the body and brain with an adequate energy supply in the face of an acute stressor.[20]

The ANS and HPA axis also stimulate and inhibit inflammatory processes, respectively, in response to acute stress.[21] More specifically, these two stress systems work in tandem: epinephrine quickly stimulates the immune system to increase blood levels of inflammatory cytokines,[22] while slower acting cortisol-driven negative-feedback mechanisms of the HPA axis inhibit the ANS-driven inflammatory response, preventing inflammatory cytokines from damaging important organ systems.[22,23] After the eminent threat of the acute stressor has subsided, both the ANS and HPA axis act to return homeostasis. Specifically, SNS activity is downregulated and that of the PSNS is upregulated.[24] Similarly, HPA-axis negative feedback inhibition of the HPA axis by glucocorticoids results in termination of the neuroendocrine stress response.[19,25] While exposure to acute stressors initiates this short-term adaptive stress response, exposure to prolonged and repeated stressors dysregulates ANS, HPA axis, and inflammatory functions, leading to dysfunction of critical bodily processes, including metabolism.[10] As common and debilitating chronic stressors, repeated exposure to trauma (e.g., traumatic stressors) and resulting PTSD are important risk factors to consider in the context of metabolic dysfunction.

ANS Dysregulation and Adverse Impacts on Metabolic Function

Exposure to traumatic stressors leads to continuous hyperactivation of the SNS, which hinders the normal counteraction of the PSNS and disturbs ANS homeostasis (►Fig. 1A).[26] Specific to metabolism, traumatic stress induces an increase in epinephrine and norepinephrine release by the ANS, leading to maintenance of high heart rate, blood pressure, and serum cortisol, as well as a reduction in heart rate variability (HRV), all of which are linked to the development of metabolic diseases such as diabetes and hypertension in the general population.[27–30] Similarly, ANS dysfunction has been repeatedly implicated as a likely underlying biomechanism linking PTSD and metabolic dysfunction.[31] Key PTSD symptoms such as re-experiencing, where an individual involuntarily relives the traumatic event via flashbacks and nightmares,[32] and hyperarousal, a cluster of symptoms including hypervigilance and heightened startle reaction, are associated with increased release of norepinephrine, low HRV, and high blood pressure,[33–35] indicating that ANS dysfunction may contribute to the high comorbidity between PTSD and metabolic dysfunction in nonpregnant individuals.[36,37]

HPA Axis Dysregulation and Adverse Impacts on Metabolic Function

Exposure to repeated traumatic stressors leads to dysregulation of the HPA axis and increased glucocorticoid release (►Fig. 1A).[19] Chronic exposure to elevated glucocorticoids deteriorates the negative feedback control of the HPA axis via down-regulation of glucocorticoid receptor expression in the

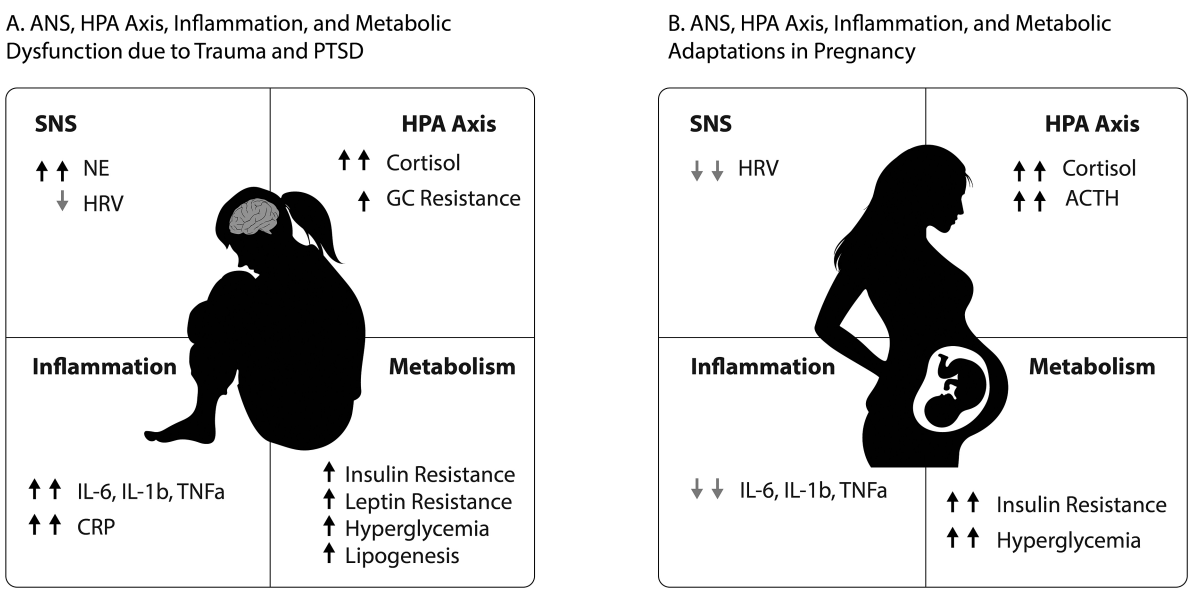

Fig. 1 Parallel impacts of trauma and PTSD (**A**) and pregnancy (**B**) on physiology. (A) Trauma exposure and PTSD lead to dysregulation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (ANS) axis. Downstream, dysregulation of the major stress axes leads to an increase in inflammatory markers and dysregulation in metabolic processes such as glucose and insulin production and sensitivity, leptin release and lipogenesis. (B) SNS and HPA axis adaptations during gestation. Normal pregnancy is accompanied by adaptive physiological shifts in both the SNS and HPA axis, including a reduction in HRV and an increase in cortisol and ACTH, respectively. To accommodate increasing fetal energy demands, gestation is also accompanied by hyperglycemia and insulin resistance. To prevent rejection of the growing fetus by the pregnant person's immune system, there is a shift toward an anti-inflammatory state during the second and third trimester of pregnancy. Illustration by Bona Kim; reproduced with permission of ©Emory University. HRV, heart rate variability; PTSD, posttraumatic stress disorder.

brain.[38] Disinhibition of glucocorticoid release then leads to a chronic catabolic state, where there is continuous increase of glucose production, degradation of protein and muscle mass, and antagonization of anabolic hormones.[39] Additionally, trauma exposure is also associated with decreased levels of neuropeptide Y (NPY), an orexigenic neuropeptide that also has anxiolytic properties.[40] Together, such neuroendocrine changes have detrimental effects on metabolism, namely leading to a decrease in lean body mass, an increase in visceral body fat, and the development of hyperglycemia and insulin resistance.[41–43] Left untreated, such metabolic changes can progress into metabolic disorders in nonpregnant populations.[44,45]

The development and maintenance of PTSD symptoms are due in part to altered HPA axis function.[46,47] Alterations in glucocorticoid function have been described in individuals with PTSD, including reduced glucocorticoid response to acute stressors,[48] elevated glucocorticoid receptor levels,[49] and an enhanced glucocorticoid negative feedback mechanism.[50] PTSD is also associated with low baseline levels of NPY.[51] Animal studies also suggest that increased sensitivity of the glucocorticoid receptor, as is found in PTSD, upregulates gene expression of genes implicated in metabolic pathways, including NPY and adiponectin 1, key regulators of appetite and insulin sensitivity, respectively.[52,53] Similar neuroendocrine changes have been described in obesity and metabolic syndrome in the general population, metabolic disorders that are highly comorbid with PTSD in trauma-exposed persons.[16,54] It remains unclear, however, whether HPA axis dysregulation may induce behavioral changes in appetite and physical activity in individuals with trauma and PTSD that contribute to metabolic dysfunction.

Increased Inflammation Resulting from ANS and HPA dysfunction and Impacts on Metabolic Function

ANS and HPA axis dysregulation leads to heightened systemic inflammation that has detrimental impacts on multiple physiological functions, including metabolism (►Fig. 1A).[55] Under chronic stress conditions, the HPA axis releases an excess of cortisol,[56] which enhances the expression of pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-18.[57] Concurrently, heightened norepinephrine release as a result traumatic stress exposure promotes the secretion of inflammatory factors including tumor necrosis factor α (TNFα), a major regulator of the inflammatory response, and IL-6, a pro-inflammatory cytokine.[58,59]

The ANS and HPA-axis dysregulation present in PTSD can also result in increased systemic inflammation.[60] For example, elevated serum catecholamines characteristic of PTSD are associated with an increase in pro-inflammatory mediators, primarily prostaglandins.[61] Individuals with PTSD show higher concentrations of C-reactive protein (CRP), IL-6),[62] IL-1b,[63] as well as greater gene expression and activity of nuclear factor-kappa betta (NF-kB), a master transcriptional activator of pro-inflammatory markers that is regulated by glucocorticoid receptor activity.[64,65] Additionally, polymorphisms in inflammatory genes, such as *CRP*, are associated with increased risk for augmented systemic inflammation,[66] as well as PTSD and psychophysiological hyperarousal in trauma-exposed individuals.[67] This excess pro-inflammatory activity in PTSD is coincident with increased levels of inflammation in metabolic disease including T2DM.[68]

Overall, existing data suggest that traumatic events and PTSD act as chronic stressors to impact metabolism in nonpregnant individuals via ANS and HPA-axis dysregulation and heightened systemic inflammation. Augmented levels of IL-6, IL-1β, and TNFα contribute to insulin resistance and hyperglycemia in people with T2DM,[69,70] while IL-18 is closely associated with metabolic syndrome.[71] This suggests that trauma exposure and resulting PTSD may be two psychosocial risk factors that may contribute to racial-ethnic health disparities in gestational metabolic dysfunction. In the following section, we will review what is currently known regarding the relationships between trauma, PTSD, and gestational metabolic dysfunction in pregnant individuals.

Stress and Metabolic Dysfunction in Pregnancy

Pregnancy is a period of metabolic adaptations directed toward meeting dynamic maternal–fetal energy requirements (►Fig. 1B).[35,72] Metabolic adaptations in pregnancy are divided into anabolic and catabolic stages, the first which involves maternal accumulation of fat and nutrient stores during the beginning two trimesters of pregnancy, followed by a breakdown of lipid reserves and transferring of nutrients to the rapidly growing fetus during the third trimester.[72–74] Normal pregnancy shifts the activity of the major stress systems, leading to reduction in HRV via the SNS and increase in cortisol and ACTH secretion by the HPA-axis.[75–77] To meet dynamic energy demands of both the growing fetus and pregnant person, gestation induces hyperglycemia and insulin resistance.[78,79] Lastly, during the last two trimesters of pregnancy, the pregnant person's immune system shifts toward an anti-inflammatory state to prevent rejection of the fetus.[80,81] While these metabolic shifts are essential to the survival of the maternal–fetal unit, adaptations may surpass normal pregnancy parameters, leading to gestational metabolic dysfunction and in more severe cases, gestational metabolic disorders.[82] Among factors that can contribute to gestational metabolic dysfunction, trauma and PTSD warrant further exploration.

Relationships between Trauma, PTSD, and Gestational Diabetes Mellitus

GDM is a subtype of diabetes seen in pregnant people without preexisting diabetes characterized by exaggerated disinhibition of glucose production.[83] In normal pregnancy, there is a transfer of glucose from pregnant person to fetus via simple and facilitated diffusion through the placenta. This process occurs in stages, beginning with pancreatic β-cell hyperplasia during early pregnancy to increase insulin release and maintain glucose tolerance at a normal or slightly

improved level, as compared with an individual's nonpregnant state.[84] During the second half of gestation, to increase glucose supply for the growing fetus there is a decrease in maternal insulin sensitivity.[85] To counter insulin resistance inherent to pregnancy, the pregnant person's body upregulates insulin production, a process believed to occur through the expansion of pancreatic β-cells.[86] In GDM, however, such compensatory mechanism is insufficient, leading to the pregnant person being unable to upregulate insulin production to counter gestational insulin resistance, resulting in hyperglycemia.[87]

Similar to hyperglycemia in nonpregnant populations, trauma and PTSD are associated with GDM (►Table 1). A current PTSD diagnosis is associated with an increased risk of GDM in a large, racially diverse sample of pregnant veterans.[88] Associations between early life trauma and GDM, however, are equivocal such that one study suggests an almost 30 to 40% increased risk for GDM among a white population with severe childhood physical abuse,[89] and on the contrary, another suggested this association only with the presence of prepregnancy depression in a similar demographic group.[90] However, only one of these studies[90] controlled for previous GDM and diet, two key risk factors for the development of GDM.

The associations between trauma or PTSD and GDM are further supported by studies that have established a relationship between nontraumatic chronic stressors and GDM. For example, increases in perceived psychosocial stress from early to mid-pregnancy is associated with a 2.6-fold increased odds of GDM and an increase in glucose level in a majority low-income Hispanic sample.[91] Similarly, the odds of GDM are 13-fold higher among individuals with high antenatal perceived stress compared with individuals with low antenatal stress in a sample of women from Karnataka, India.[92] Moreover, in a racially diverse sample, perceived discrimination is associated with increased risk of developing GDM.[93] Experiencing greater than five stressful events (including financial and job issues, interpersonal problems, moving, etc.) within 12 months before birth is associated with GDM in a primarily white and college-educated sample.[94] However, a study with similar demographics found no association between chronic stress 12 months before birth and GDM.[95]

Relationships between Trauma, PTSD and Low Birth Weight and Fetal Growth Restriction

LBW is defined as infant birthweight of less than 2,000 g. Infants with LBW are at an increased risk of chronic illnesses later in life including diabetes and hypertension.[96] In cases when LBW falls below the 10th percentile for gestational age, infants are diagnosed with FGR. FGR impacts 5 to 10% of pregnancies in which the fetus fails to reach its growth potential in utero and affects essential bodily functions in offspring including breathing, immunity, and cognition, making it a particularly dangerous pregnancy complication.[97] The metabolic origins of LBW and FGR are complicated, with studies implicating reduced supply of nutrients,[98] higher maternal–fetal glucose concentrations,[99] and reduced amino acid delivery[100] in the development of LBW and FGR. Seeking to uncover psychosocial risk factors, a handful of studies have explored the connection between trauma, PTSD, and risk for LBW and FGR.

Existing literature suggests that trauma and PTSD are associated with LBW but not FGR (►Table 2). Racial trauma, specifically experiencing or witnessing racism during childhood, leads to an increase in diastolic blood pressure during the last two trimesters of pregnancy, which is associated with LBW in a sample of black American women.[101] Similarly, high maternal lifetime traumatic stress (e.g., natural disasters, childhood maltreatment, interpersonal violence, sexual assault) resulting in increased prenatal hair cortisol is associated with infant LBW but not FGR in male offspring in a study within a primarily low-income Hispanic and black sample.[102] PTSD diagnosis is associated with LBW but not FGR in a racially diverse sample of Hurricane Katrina survivors.[103] Similarly, in a large sample of displaced Pakistani women, PTSD is independently associated with LBW.[104] PTSD resulting from intimate partner violence has also been associated with LBW in a racially diverse and majority low-income study cohort.[105] In contrast, a study conducted in a Latinx population with variable trauma type exposures found no association with PTSD and LBW, but did find a relationship between PTSD diagnosis and preterm delivery.[106] Equivocal findings in these two studies may be due to use of different PTSD measures, a long-form scale adapted from the University of Michigan Composite International Diagnostic review[105] and the PTSD Checklist-Civilian Version,[106] respectively.

The associations between trauma and PTSD and LBW are further supported by studies that have established a relationship between nontraumatic chronic stressors and GDM. For example, maternal perceived stress during the second and third trimester is associated with LBW and preterm delivery, but not FGR, in a Brazilian Latinx low-income sample.[107] Additionally, perceived medical discrimination is associated with increased risk for LBW in a cohort of Aboriginal Australian women.[108]

Relationships between Trauma, PTSD and Gestational Hypertension and Preeclampsia

GHTN is defined as persistent blood pressure readings higher than 140 mmHg systolic or 90 mmHg diastolic pressure in a woman who was normotensive prior to 20-weeks gestational age and in the absence of signs of end-organ damage.[109] GHTN causes cardiovascular insufficiency and, if left untreated, is often a precursor to the development of preeclampsia (PRE-E). PRE-E is a gestational cardiovascular disease defined as persistent severe hypertension with signs of end-organ damage following 20 weeks gestational age.[110–113] PRE-E is a severe life-threatening condition that increases risk for secondary health complications including placental abruption, stroke, and seizures (eclampsia).[114]

Recent studies have explored associations between trauma and PTSD and GHTN and PRE-E (►Table 3). PTSD is associated with both GHTN and PRE-E, while trauma is not associated with HDP. More specifically, experiencing four or

Table 1 Relationship between trauma, PTSD, chronic stress, and GDM

GDM	Reference	Stress/trauma subtype	Association with GDM	Sample size (*N*)	Racial-ethnic demographics	Income	Education
Trauma	Mason et al, 2016	Early life abuse	↑	45,550	NW: 46%	Not reported	SC +: 100%
	Schoenaker et al, 2019	Adverse childhood experiences	—	6,317	Not reported	Not reported	<HS: 21.4% SC: 21.5% C: 57.1%
PTSD	Shaw et al, 2017	PTSD in pregnant veterans	↑	15,986	W, NH: 64.2% B, NH: 23% O: 11%	Not reported	Not reported
Chronic stress	Hosler et al, 2011	>5 stressful events 12 months before birth	↑	2,690	W, NH: 73.4% B, NH: 9.1% H: 12.1% A: 3.1% O: 2.2%	Not reported	<HS: 15.3% HS: 22.4% SC +: 62.3%
	Records et al, 2015	Any chronic stressor 12 months before birth	—	3,655	W, NH: 85.5% H: 1.2%	Not reported	<HS: 10.9% HS: 19.3% SC: 39.4 SC +: 30.4
	Silveira et al, 2014	Increase in stress during pregnancy	↑	1,115	H: 100%	Less than or equal to 15k: 28.6% 15k–30k: 14.4%; greater than or equal to 30k: 6.8%	<HS: 45.9% HS: 31.3% SC +: 18.8%
	Mishra et al, 2020	Antenatal stress	↑	373	A: 100%	No info	<HS: 49.2% HS +: 23.7%
	MacGregor et al, 2020	Perceived discrimination	↑	595	W, NH: 61.8% B, NH: 16.6% H: 15.6% O: 5.8%	Less than or equal to 15k: 14.6% >15k–50k: 34.79 >100K: 22%	Less than or equal to HS: 32.2% SC: 24.2% C/C +: 43.3%

Abbreviations: GDM, gestational diabetes mellitus; PTSD, posttraumatic stress disorder.
Note: Race and ethnicity: W, NH: white non-Hispanic; B, NH: black non-Hispanic; H: Hispanic; A: Asian; I: indigenous; O: other; MR: multiracial; NW: non-white.
Education: <HS: less than high school; HS: high school; SC: some college; SC +: some college or more; C: college; G: graduate school; T: training program/certification.
↑: positive association found; —: no association found.

Table 2 Relationship between trauma, PTSD, chronic stress, and LBW or FGR

LBW and FGR	Reference	Stress/trauma subtype	Association with LBW	Association with FGR	Sample size (*N*)	Racial-ethnic demographics	Income	Education
Trauma	Hilmert et al, 2014	Childhood racial trauma	↑		39	B, NH: 100%	2,350 (167) reported as mean (SD)	>HS: 35.9% SC: 46.2% C: 15.4% G: 2.6%
	Flom et al, 2018	Lifetime traumatic stress	↑	—	314	W, NH: 33% B, NH: 26% H: 41%	Majority lower income	Less than or equal to 12: 63% Greater than 12: 37% reported in years
PTSD	Rosen et al, 2007	PTSD due to intimate partner violence	↑		148	B, NH: 54.1%	73% low income	35.4% >HS
	Gelaye et al, 2020	PTSD due to variable trauma	—		4,408	H: 77.8%	Not reported	<6: 2.9%; 7–12: 49.9%; >12: 47.2%
	Xiong et al, 2008	PTSD due to natural disasters	↑		219	W, NH: 53.8% B, NH: 41.6% O:14.6%	<20k: 24.9% 20k–60k: 39% >60k: 36.1%	Not reported
	Rashid et al, 2020	PTSD in war-displaced women	↑		450	A: 100%	<10k Pakistani rupee: 72%	<5: 59% (reported in years)
Chronic stress	Rondó et al, 2003	Psychosocial stress during 2nd and 3rd trimester	↑	—	865	H: 100%	0–1: 24% 1–2: 34.7% 2–3%: 20% >3: 21.3% - reported as per capita income	<4: 8.9% 4–8: 57.0% >8: 34.1% reported in years
	Brown et al, 2019	Perceived medical discrimination	↑		344	I: 100%	Not reported	>HS: 47.5% T: 46.0% C: 6.5%

Abbreviations: FGR, fetal growth restriction; LBW, low birth weight; PTSD, posttraumatic stress disorder.
Note: Race and ethnicity: W, NH: white non-Hispanic; B, NH: black non-Hispanic; H: Hispanic; A: Asian; I: indigenous; O: other; MR: multiracial; NW: non-white.
Education: <HS: less than high school; HS: high school; SC: some college; SC +: some college or more; C: college; G: graduate school; T: training program/certification.
↑: positive association found; —: no association found.

Table 3 Relationships between trauma, PTSD, chronic stress, and GHTN or PRE-E

GHTN and PRE-E	Reference	Stress/trauma subtype	Association with GHTN	Association with PRE-E	Sample size (*N*)	Racial-ethnic demographics	Income	Education
Trauma	Shaw et al, 2017	Traumatic exposure in war veterans		↑	14,047	W, NH: 10,262 B, NH: 3,673 O: 519	Not reported	Not reported
	Stanhope et al, 2020	Adverse childhood experiences	—		2,319	H: 100%	Not reported	<HS: 31.6% HS: 22.3% >HS: 36.4%
PTSD	Gilliam et al, 2022	Inter-partner violence (IPV) and PTSD symptoms during pregnancy	↑		137	B, NH: 69.9% W, NH: 18.4 MR: 8.1% H: 7.4% O: 0.7%	Majority low income	Not reported
	Shaw et al, 2017	PTSD and associated symptoms		↑	14,047	W, NH: 10,262 B, NH: 3,673 O: 519	Not reported	Not reported
Chronic stress	Leeners et al, 2007	Emotional stress	↑		1,605	W: 100%	Not reported	< Elementary school: 0.62%, Extended elementary school: 12.6% HS: 36.9. >HS: 49.9
	Vollebregt et al, 2008	Psychosocial stress	—	—	12,377	W, NH: 2,461 B, NH: 157 Turkish/ Moroccan: 347 O: 712	Not reported	0–5: 557, 6–10: 1,445, >10: 1,651 Reported in years of education
	Klonoff-Cohen et al, 1996	Job stress		↑	218	W, NH: 58% B, NH: 42%	Not reported	12: 40.8% 12+: 65.6% Reported in years of education
	Schneider et al, 2011	Psychosocial Stress		↑	647,392	Not reported	Not reported	Not reported
	Marcoux et al, 1999	Job stress during first 20 weeks of pregnancy	↑	↑	730	Not reported	Not reported	Less than or equal to 12: 50% 13–14: 18.9% Greater than or equal to 15: 31.1% Reported in years of education
	Caplan et al, 2021	Lifetime stress	↑	↑	744	W, NH: 59.1% B, NH:16.3% H: 18.7%	Not reported	<HS: 26% C+: 39.5%

Abbreviations: GHTN, gestational hypertension; PRE-E, precursor to the development of preeclampsia; PTSD, posttraumatic stress disorder.
Note: Race and ethnicity: W,NH: white non-Hispanic; B, NH: black non-Hispanic; H: Hispanic; A: Asian; I: indigenous; O: other; MR: multiracial; NW: non-white.
Education: <HS: less than high school; HS: high school; SC: some college; SC+: some college or more; C: college; G: graduate school; T: training program/certification.
↑: positive association found; —: no association found.

more traumatic experiences during childhood (e.g., abuse, parental separation, witnessing abuse, living with a substance abuser, household member imprisonment) was not associated with the development of GHTN or PRE-E in a cohort of Latinx pregnant women.[115] However, a PTSD diagnosis is associated with an increased risk of both GHTN and PRE-E in a large, racially diverse sample of pregnant veterans.[88] Similarly, a diagnosis of PTSD stemming from experiencing inter-partner violence is associated with the development of GHTN and PRE-E in a majority black study sample.[88,116]

While literature assessing the role of trauma or PTSD in the development of GHTN and PRE-E is limited, other studies have established a relationship between nontraumatic chronic stressors and GHTN or PRE-E. Lifetime stress, for example, increased the risk of developing GHTN or PRE-E in a majority white multi-site sample of pregnant women.[117] In parallel, lifetime chronic stress secondary to racial discrimination in a sample of black pregnant women was associated with GHTN.[101] Experiencing lifetime stressors (e.g., financial, emotional, relationship stress) was associated with an increased prevalence of HDP.[118] Furthermore, having an occupation with high mental stress was associated with an increased risk of developing PRE-E in a sample of Canadian women,[119] and job-related stress during pregnancy increased the risk for PRE-E in a black and white sample.[120] Social burden, defined as low social status and high psychosocial stress, was associated with PRE-E development in a cohort of pregnant German women.[121] Moreover, experiencing emotional stressors (including social, psychological, financial, family, and medical stressors) during pregnancy was associated with a 1.6-fold increased risk for developing a hypertensive disease in pregnancy in a white study cohort.[122] Conversely, a study conducted in the Netherlands in a primarily white sample determined that psychological stress (including work stress, depression, anxiety, and pregnancy-related anxiety) in the first trimester had no significant influence on the incidence of PRE-E in nulliparous women.[123]

Conclusions and Future Directions

In summary, the limited existing literature supports the premise that trauma and PTSD may be important factors that impact metabolic function within the context of pregnancy, as trauma exposure and PTSD are associated with increased risk of gestational metabolic dysfunction (►**Tables 1–23**). However, further work is needed to characterize the specific biological mechanisms that underlie how trauma and PTSD can contribute to the development of metabolic disorders of pregnancy. Specifically, no known studies have investigated associations between gestational metabolic disorders and biological markers of chronic stress or trauma (e.g., cortisol, HRV) or physiological measures of PTSD severity (e.g., hyperarousal), despite evidence of a relationship between such biological markers and metabolic disorders in nonpregnant persons (►**Fig. 1**).[124,125]

Importantly, many of the existing studies failed to consider key confounders in the relationship between trauma or PTSD and gestational metabolic disease in pregnancy. For instance, despite genetic predisposition being one of the biggest risk factors for gestational metabolic disease,[126,127] several of the included studies did not consider family history as a confounding variable.[4,77,88,101,102,104,116] Moreover, not all studies controlled for preexisting metabolic disease[88,105,106] and previous gestational metabolic disease.[102,105,106,116] Specific to GDM, diet and having a sedentary lifestyle,[128,129] are some of the biggest risk factors of GDM; however, only one of the three included studies controlled for these factors in their analyses.[90] For FGR and LBW, food insufficiency, which causes undernutrition,[130] and substance abuse, which limits uterine and placental blood flow necessary for fetal growth,[131] were each controlled for in only two out of the six included studies.[103,105,106] Finally, few of the existing studies considered how behavioral changes following trauma or onset of PTSD, including changes in sleep, physical activity, and eating behaviors, impact metabolism during pregnancy.[128,129]

The equivocal nature of some studies assessing risk for HDP due to PTSD may be due to inconsistent measures of PTSD used across studies. Studies to date have used the Mini International Neuropsychiatric interview[105] and the Posttraumatic Stress Disorder Checklist,[106] which are self-report measures, and the International Classification of Disease, Ninth Revision (ICD-9),[88] a clinician-administered diagnosis of PTSD. Self-report measures have been found to result in higher severity scores as compared with scores from clinician-administered measures. Additionally, the cutoff score for PTSD diagnosis using the same self-report measure is inconsistent across study groups.[132] Conversely, clinician-administered PTSD measures like the ICD-9 require access to mental health care. This is an important caveat to consider, as previous studies have found that socioeconomically disadvantaged and minoritized women are underdiagnosed for PTSD.[133] The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a psychometrically valid and standardized alternative to measures used in studies to date that has shown excellent reliability for over 20 years.[134] Future studies would benefit from using the most rigorous instruments to quantify PTSD symptoms, traumatic events, and chronic stressors like racial discrimination.

In the current review, we included various trauma types when assessing the relationship between trauma and gestational metabolic disease. However, different trauma types may have distinct impacts on the ANS and HPA-axis as well as on metabolism in and outside the context of pregnancy. For instance, childhood maltreatment, has been consistently shown to have deleterious effects on cardiometabolic health in nonpregnant people.[135–137] Childhood sexual abuse, in particular, has been associated with metabolic risk factors including low HRV and higher body mass index,[138] highlighting the need for future studies to consider how different types of trauma impact gestational metabolic function and risk for HPD.

Another important limitation of existing studies assessing the relationships between trauma, PTSD, and metabolic disorders in pregnancy is the lack of representation of racial-ethnic minorities (see all tables). Given the disproportionate impact of gestational metabolic disorders on people of color, in particular black pregnant persons,[8] studies that aim to identify risk factors for gestational metabolic dysfunction would benefit greatly from having representative study samples. As a result of interpersonal, systemic, and institutional racism, non-white persons, especially black persons, are exposed to greater levels of chronic stress, traumatic experiences, and are more likely to be diagnosed with PTSD, suggesting that these exposures may be risk factors for gestational metabolic disease.[11–14,139] Due to maternal health inequities, there is a critical need to understand the biological mechanisms underlying the relationship between chronic stress, trauma, PTSD, and gestational metabolic disease. This research could aid with early identification of pregnant individuals at high risk for gestational metabolic disease, allowing for preventive and early treatment to improve maternal health inequities and associated disease in their offspring.

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Conflict of Interest

None declared.

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