Published in final edited form as:

Acta Obstet Gynecol Scand. 2011 December ; 90(12): 1307–1316. doi:10.1111/j.1600-0412.2011.01136.x.

Preconceptional stress and racial disparities in preterm birth: an overview

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Abstract

Objective—We reviewed the evidence for three theories of how preconceptional psychosocial stress could act as a contributing determinant of excess preterm birth risk among African American women: early life developmental plasticity and epi-genetic programming of adult neuroendocrine systems; blunting, weathering, or dysfunction of neuroendocrine and immune function in response to chronic stress activation through the life course; individuals' adoption of risky behaviors such as smoking as a response to stressful stimuli.

Methods—Basic science, clinical, and epidemiologic studies indexed in MEDLINE and Web of Science databases on preconceptional psychosocial stress, preterm birth and race were reviewed.

Results—Mixed evidence leans towards modest associations between preconceptional chronic stress and preterm birth (for example common odds ratios of 1.2–1.4), particularly in African American women, but it is unclear whether this association is causal or explains a substantial portion of the Black–White racial disparity in preterm birth. The stress-preterm birth association may be mediated by hypothalamic-pituitary-adrenal axis dysfunction and susceptibility to bacterial vaginosis, although these mechanisms are incompletely understood. Evidence for the role of epigenetic or early life programming as a determinant of racial disparities in preterm birth risk is more circumstantial.

Conclusions—Preconceptional stress, directly or in interaction with host genetic susceptibility or infection, remains an important hypothesized risk factor for understanding and reducing racial disparities in preterm birth. Future studies that integrate adequately sized epidemiologic samples with measures of stress, infection, and gene expression, will advance our knowledge and allow development of targeted interventions.

Keywords

Psychosocial stress; discrimination; African American; preterm; health disparities; infant health

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Introduction

Preterm birth is a persistent – and even growing – clinical and public health problem despite significant technological and biomedical advancement in obstetric and neonatal care over the past half century. The stubborn persistence in the USA of a large Black–White racial disparity in risk for preterm birth, i.e. a 60% excess risk for moderately preterm birth and 2.5 times the risk of very preterm birth in Black as compared with White women, adds additional urgency to the problem (1). Efforts to understand and reduce racial disparities in preterm birth are hindered by incomplete knowledge of the causes of preterm birth in humans. A general framework suggests that premature parturition results from triggering of one or more of the following pathways: activation of maternal/fetal/placental hypothalamic-pituitary-adrenal (HPA) axis; intrauterine infection or inflammation; decidual hemorrhage or ischemia; pathologic uterine distension (2). Once activated, these pathways initiate a common final pathway including release of prostaglandins and proteolytic enzymes which themselves trigger cervical ripening, rupture of membranes, and uterine contractions. Despite understanding of this general framework, limited progress has been made in identifying effective screening tools to identify women at risk for preterm delivery and interventions to prevent it. This may be due in part to the complexity of the biological pathways to preterm birth as well as the social, behavioral, and genetic factors that may interact to trigger a pathway in a given woman.

Another layer of complexity may be necessary to understand racial disparities in preterm birth. For instance, many important independent risk factors for preterm birth have been identified including low maternal education, low income, cigarette smoking, cocaine use, and chronic co-morbidities such as hypertension; however, statistical control for any of these, or all of them jointly, explains less than half of the Black–White gap in preterm birth risk (3). Genetic predisposition for preterm birth is often invoked as an explanation for the residual racial disparity. However, the absence thus far of simple genetic explanations suggests that, to the extent genetics plays a role in the disparity, it may well be via epigenetic changes, or complex gene-by-gene or gene-by-environment interactions. The problem of the racial disparity in preterm birth may best be understood as an end result of multiple interacting factors at the social, individual, and molecular levels (4).

One socially based but biologically mediated risk factor that has been posited as an explanation for the Black–White disparity in preterm birth is the exposure of individual women to psychosocial stressors (5). Although much research has focused on, and to some extent documented, associations between preterm birth and both pregnancy-related stress and acutely stressful experiences during pregnancy (6), we focus in this review on possible mechanisms and related evidence for the role of preconceptional psychosocial stress as a component contributor to subsequent preterm birth risk in Black and White women. Experiences of stress during pregnancy may be an additional important risk factor, but there is growing evidence that preconceptional patterns of health may better explain population differences and disparities in preterm birth risk (7). The two goals of this article are to provide an overview of the current social, epidemiologic, and biomedical literature with regard to mechanisms and evidence for preconceptional psychosocial stress as a determinant of preterm birth, and to specifically assess evidence for preconceptional stress as a

determinant of Black–White racial differences in preterm birth risk. Because little of the current literature on this subject adequately distinguishes between spontaneous and medically indicated preterm birth, we are unable to make that distinction in this overview.

Methods

To identify relevant research, systematic searches of MED-LINE and Web of Science biomedical and social science databases were conducted crossing the keywords ‘stress’, ‘psychosocial’ or ‘life course’ with the keywords ‘preterm birth’ or ‘prematurity’, and similar derivatives. Titles and abstracts for all potentially relevant papers were reviewed, and selected papers were followed up. References from relevant papers were also checked for previously missed papers.

Based on our early reading of this literature, and following prior work (7), we organized papers into three categories or pathways by which preconceptional stress might affect preterm birth risk: stress in a mother’s own intrauterine or early life environment, life course chronic or severe stressors, and behavioral risk factors as responses or coping mechanisms to perceived stress. We highlight a handful of recent novel papers which explicitly focus on stress measured in a period prior to conception of the index pregnancy, and with preterm birth as the outcome. However, the breadth of research on explicitly preconceptional stress is limited and we therefore also touch on research using other pregnancy outcomes, including low birthweight and intrauterine growth retardation.

Results

Psychosocial stress and prematurity: conceptual linkages

Cohen et al. (8) define stress as a process in which ‘environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological or biological changes that may place persons at risk for disease’. Three components of this definition are important in relation to health: (i) the host is exposed to objective environmental demands; (ii) the response of the host is variable with respect to adaptation or coping; and (iii) inadequate response results in biologic or psychological change. Stress can be further described along several dimensions including timing (early or later in the life course), severity (minor stressors vs. major stressors such as sexual assault, death of child or spouse) and length of exposure (acute vs. chronic stressors).

Three general and complementary theories of the mechanism by which preconceptional experiences of stress modify pregnancy outcomes are reviewed here. One theory, the developmental origins of health and disease, builds on the Barker hypothesis of early life programming of chronic disease (9), and suggests that exposures experienced *in utero* or during early childhood can have life-long consequences because of developmental plasticity. Thus, exposures to stress during critical developmental windows in a girl’s early life could program hypothalamic-pituitary-adrenal (HPA) axis function and reactivity in a manner that would make her prone to dysfunction in pregnancy. A second theory, sometimes termed the weathering hypothesis, is that physiological changes resulting from exposure to chronic stressors over a large portion of a woman’s life, such as caring for an ill family member,

living in poverty or repetitive experiences of discrimination, can cumulatively result in wear and tear on physiologic stress response systems such as the HPA axis, or permanently alter immune and vascular function, thus affecting pregnancy health (10). A third theory posits that psychological responses to stressors (acute or chronic) involve coping behaviors that may be deleterious to health, such as smoking and substance use/abuse, high-risk sexual behaviors leading to increased exposure to sexually transmitted infections, and non-adherence to medical treatments. Each of these behavioral choices could alter risk for preterm birth.

Recent studies which explicitly stated that stress was measured during a period prior to conception, and report preterm birth as an outcome are summarized in the Table 1. They and other relevant research are discussed in the following sections.

Intrauterine and early life programming, stress and preterm birth

One of the strongest risk factors for prematurity is a history of a prior preterm birth. In one study, women whose first birth was preterm had 3.8 (95%CI 3.7–3.9) times the odds of a preterm birth as those whose first birth was term (11). There is also a smaller but consistent association between a woman's own birth circumstances, where women who were themselves born preterm have higher risk [for example OR 1.5; 95%CI 1.4–1.8 (12)] of delivering a preterm infant. These observations could suggest genetic predisposition, although in the absence of measured genetic variants, all that is certain is that the etiologic factors accounting for recurrent preterm birth risk are stable rather than fleeting over the course of a woman's life. Non-heritable traits which could be stable in this manner include epigenetically induced alteration to gene expression, persistent aspects of the social or physical environment, and life-long learned behaviors.

Epigenetic change refers to mitotically stable alterations in gene expression without changes in underlying DNA sequence and result from processes such as nucleotide methylation or modification of the histones that package DNA in cells. Such changes can be induced by environmental stresses including *in utero* exposure to maternal hormones, malnutrition, or altered vascular function. In addition to developmental plasticity limited to particular periods of organogenesis *in utero*, epigenetic changes can extend to early childhood development for systems (such as the central nervous system) that continue to develop after birth.

Animal evidence suggests that investigator-manipulated exposure to stress-related chemicals such as cortisol and glucocorticoids *in utero*, as well as quality of maternal caretaking behavior postnatally, each result in life-long changes in HPA function in the offspring (13,14). In humans, female fetuses exposed prenatally to the Dutch Famine of 1944–45 delivered lower birthweight infants than did non-famine exposed siblings (15). Intrauterine famine exposure is also associated with altered vascular psychosocial stress reactivity and depression in adulthood (16). Trans-generational cohort studies link the social environment of an infant's maternal grandmother to the infant's own outcome (17,18). In one study of predominantly white women in the UK, women's own exposure to financial and social hardships in childhood was associated with 44% increased odds of delivering preterm (95%CI 1.08–1.92) (19). Similarly designed studies in the USA report that although the proportion of preterm birth attributable to maternal low birthweight is only about 2% for

Whites and Blacks, the population attributable percent for the exposure of maternal grandmother living in poverty is 10% for Blacks and only 2% for Whites (17).

The mere association of early life environment with subsequent stress-related disorders in adulthood and separately with birth outcomes in the next generation does not prove that they share a common cause. However, there is additional circumstantial evidence for a linking mechanism based on observations of the role of HPA axis function in women delivering preterm as compared to term. Corticotrophin releasing hormone (CRH), a mediator of the physiologic response to stressful stimuli in the non-pregnant state, plays a critical role in the length of gestation (20). In pregnancy, CRH stimulates adrenocorticotrophin hormone, stimulating cortisol, which acts in a positive feedback loop to further stimulate CRH. In prospective pregnancy cohorts, elevated levels of CRH and cortisol in early pregnancy, as well as a steeper trajectory of CRH increase during pregnancy, independently predict subsequent preterm birth (21,22). Thus it is possible that factors which alter basal HPA function, or CRH and cortisol reactivity to new stimuli in general, could lay the foundation for HPA dysfunction during pregnancy. A growing body of evidence from the psychiatric literature suggests that early life stressors such as prolonged separation from a parent, death of a parent, or child sexual and physical abuse, can lead to long-lasting changes in basal cortisol and CRH levels, as well as altered cortisol diurnal variation and reactivity to new stressful stimuli (23,24).

Chronic preconceptional stress and preterm birth

A handful of epidemiologic studies have examined the association between preterm birth and either chronic stress or severe life events such as the illness or death of a woman's partner or older child prior to conception. The results of such studies using a variety of study designs, populations, and analytic methods are mixed, some investigators finding no independent association (25,26) and others finding positive associations, with odds ratios ranging from 1.2 to 2.7 (27–29) for specific severe stressors in the year prior to conception.

Hans Selye in the 1930s first proposed that normally adaptive and protective physiological responses to stress could, if chronically activated, become harmful (30). While the cumulative burden of this allostatic load on other physiologic systems has been discussed for many disease processes, Geronimus was the first to apply this 'weathering' hypothesis to perinatal outcomes (10). Most populations demonstrate a J- or U-shaped curve for risk of low birthweight or preterm birth by maternal age. It is commonly assumed that the trough of this risk curve in young adulthood reflects a biologically optimum time for reproduction, and that the relatively elevated risk of preterm birth for the youngest and oldest mothers is due in part to non-optimal reproductive development or reserves. However, the shape of this maternal-age-risk curve has been observed to vary at the population level according to demographic characteristics such as race and socioeconomic status, with weathered Black and poor women demonstrating a shift to the left or younger years of the entire curve, a pattern referred to as premature aging (Figure 1).

A second epidemiologic trend suggesting that life course preconceptional exposures may be important is shown in the birth outcomes of immigrants to the USA. A recent meta-analysis of 24 studies comparing preterm birth risk for immigrants and native-born women found that

White and Asian women who were born in another country but deliver an infant in the USA have a risk of prematurity equal to or greater than that of native-born counterparts (31). In contrast, Black immigrants who deliver in the USA have a *lower* risk than US-born Blacks, and sub-Saharan African-born Black women have risk closer to that of US-born White women than to US-born Black women. Intergenerational studies of immigrants suggest that these trends are reversed for the daughters of first generation women. In second-generation White women the risk of preterm birth is lower, aligning with the daughters of US-born White women, whereas the second-generation Black women lose the relatively lower risk enjoyed by their mothers and instead demonstrate a risk closer to that of multi-generational African Americans (32).

These two patterns – the apparent premature aging of Black women with regard to preterm birth risk and the health-protective effect for Black women born outside the USA – suggest that determinants of preterm birth risk may accumulate across the life course and that exposures may differ for Black and White women in the USA. Such exposures could be epigenetic but could also be material in nature (such as access to health care or health promoting resources), behavioral (such as change in nutrition or substance use) or environmental (such as socioeconomic and residential environment).

Chronic stress has been hypothesized to influence preterm birth risk via three mechanisms: blunting of the normal CRH-cortisol feedback loop resulting in HPA dysfunction in pregnancy; altering cellular immunity and immune control of inflammatory response, which could predispose some women to infection during pregnancy or alter their immune response; and altering vascular tone and reactivity from chronic sympathetic activation, leading to placental insufficiency (4). Evidence for each mechanism will be reviewed in turn.

Despite the substantially higher risk of preterm birth in Black women, some studies report that CRH in Black women is, on average, lower in mid-pregnancy than for White women (33,34). However, these studies generally found that, within race strata, both the relative mid-pregnancy levels and the trajectory of CRH change between two points in pregnancy are predictive of preterm birth, and that this association may be stronger for Black than White women. One explanation for the apparent paradox of a lower mean CRH in Black women, yet a positive CRH–preterm birth risk association, is that exposure to chronic and prolonged stress blunts normal HPA function in a fashion commonly seen in individuals with post-traumatic stress disorder. Chronic stressors include experiences of poverty, homelessness, residing in dangerous neighborhoods, domestic violence, discrimination, and feeling frequent anger. In a nested case-control study mostly of White and Hispanic women, there was an interaction between self-reported chronic stress and mid-pregnancy CRH levels with regard to the association with preterm birth (35). Women with the highest chronic stress score had lower mid-pregnancy CRH levels, a finding in parallel with the White–Black patterns. There was no significant relation between CRH and preterm birth risk (OR 1.22; 95% CI 0.77–1.91) in women who denied any of seven specific sources of stress. In contrast, as the number of stressors increased, the strength of the CRH–preterm birth association increased, from an adjusted OR of 1.7 per log-unit CRH among women reporting one chronic stressor, to an OR of 2 per log-unit CRH among women with three or more chronic stressors (35).

A second, but interrelated, mechanism by which chronic stress could affect preterm birth risk is through immune modulation. Differences in immune response and function caused by chronicity of stressful stimuli are well described, with evidence that acute stress stimulates immune function, whereas chronic stress leads to suppressed cellular immunity and impaired suppression of pro-inflammatory cytokines (36). Maternal infection and inflammation are strongly associated with preterm birth, and the strength of association increases as gestational age decreases. Bacterial vaginosis (BV) has been implicated as a possible determinant of the Black–White racial disparity in preterm birth because it is associated with a doubling of preterm birth risk, and it is more prevalent in Black than in White women (37). Measures of life course chronic stress have been associated with both incidence and prevalence of bacterial vaginosis in pregnant and non-pregnant women (38). Culhane (39) reported that chronic stressors are associated with prevalent BV in pregnant Black and White women, and that adjustment for individual and contextual chronic stressors reduced the magnitude of the Black–White disparity in BV from an adjusted OR of 3.4 (95% CI 2.4–4.7) to 2.4 (95% CI 1.6–3.5).

Finally, chronic stress could lead to preterm birth via its association with vascular disease, which could cause increased prevalence of co-morbid risk factors in pregnancy such as hypertension, or could directly affect placental blood flow. Exposure to chronic stressors, such as repeated experiences of inter-personal discrimination, has been associated with elevated systolic and diastolic blood pressure, as well as heart rate reactivity (40). In a study of pregnant Black and White women in the military, mid-pregnancy cardiac stress testing demonstrated greater heart rate reactivity in Black women, and each 1-mm increase in diastolic blood pressure reactivity was associated with a marginally significant 1-day shortening of gestational length (41).

Stress, health risk behaviors, and preterm birth

A woman's behavioral or coping response in the face of perceived stress could also alter preterm birth risk. In a small, prospective cohort study of the effects of childhood sexual abuse, girls were referred by child protective services after substantiated abuse and matched by age, ethnicity, and neighborhood to non-abused girls, and followed over time with intermittent measure of health and behavior (42). By early adulthood the risk of preterm birth was twice as high in the abused group as the non-abused group, and although there was no evidence that this association was mediated by HPA dysfunction, there was an association with alcohol abuse, which itself is a risk factor for preterm birth with an apparent dose-response relation (43).

Tobacco use during pregnancy is also a risk factor for preterm birth. In a large British cohort, mother's own life course socioeconomic trajectory was predictive of both smoking just prior to conception and during pregnancy (44). If coping with stressful stimuli resulted in increased smoking it could affect preterm birth risk in stress-exposed groups, but this would not appear to directly mediate the racial disparity, as smoking is generally less prevalent in Black than in White pregnant women (45). However, in several studies, interactions and non-linear relations have been observed between markers of stress, smoking behavior, and risk for preterm birth in Black women, suggesting that this pathway may be socially and

biologically complex. A small study found that Black women who scored higher on a race-related stress survey were more likely to be smokers than were women with lower perceived discrimination (46). Another study tested whether a social environmental stressor, i.e. degree of metropolitan racial residential segregation, affected smoking prevalence during pregnancy among Black women (47). Comparing the degree of segregation and smoking prevalence across 216 large urban areas, the authors report a U-shaped association with the least and most segregated areas having the highest Black smoking prevalence compared to moderately segregated cities. It was proposed that in the least segregated areas, racial mixing results in a behavioral contagion process where Black women adopt smoking at similar rates as White women. In contrast, smoking may be higher in the most segregated areas as a response to chronic stress of concentrated poverty or experiences of discrimination. A separate study testing the weathering hypothesis of premature aging for women exposed to high poverty concentration and neighborhood neglect found that infant birthweight dropped more rapidly with advancing maternal age in the poorest compared to wealthiest neighborhoods, but that this trend was significantly accelerated among smoking mothers (48). This may suggest that smoking and chronic stress have a synergistic effect, possibly due to unmeasured confounding or perhaps biological interaction.

Stress and the racial disparity in preterm birth

Psychosocial stress is an increasingly accepted risk factor for preterm birth in humans (2,6) and improving study designs, available datasets, and tests of specific mechanisms continue to clarify this association. But for stress to explain the racial disparity in preterm birth, it must meet at least one of two additional criteria: (i) exposure to etiologically meaningful stressful stimuli must vary significantly by race; and/or (ii) the biologic response to etiologically relevant stress exposures must vary by race.

Evidence for persistent racial differences in exposure to stressful environments in the USA is not hard to find. For instance, in the 100 largest metropolitan areas of the USA, the average White child lives in a neighborhood with 7% poverty, whereas the average Black child lives in a neighborhood with 21% poverty (49). Living in neighborhoods with higher poverty, higher segregation or greater economic disinvestment are each consistently associated with preterm birth risk after adjusting for individual level socioeconomic status and health behaviors, a fact often attributed to the experiences of chronic stress (50,51).

One particular form of stress which may vary by race is the experience of interpersonal discrimination or racism. As with any stressful stimuli, the physiologic effect is a function of both the objective exposure to discrimination and the response or buffering capacity of the host. Self-reported experiences of interpersonal discrimination measured both during pregnancy and as an index of life time cumulative events, increase risk for preterm birth in Black women to OR 1.3 (95%CI 1.1–1.6) overall and odds ratios of 2.0 or greater for women without a high school education reporting varying types of perceived discrimination (52,53). As discussed above, because stressors such as perceived discrimination have also been associated with BV and vascular reactivity, these pathways may mediate the association with preterm birth.

In addition to racial differences in exposure to stress, some of the previously reviewed evidence suggests there are racial differences in the biological stress response. For instance the CRH blunting reported in Black as compared with White pregnant women may not be limited to pregnancy, but may simply reflect long term changes to stress reactivity in some Black women. A population-based sample of non-pregnant adolescents found similar racial differences in cortisol diurnal slope, with a flatter morning-evening change in cortisol for Black youth (54). There are racial differences in cytokine and protease expression in amniotic fluid of women delivering preterm suggesting differences in activation or response to immune and endocrine stimuli (55). What is unclear is whether these differences in phenotype result from underlying genetic variability, epigenetic changes that influence gene expression, physiologic consequences of chronic stress activation, or some complex interaction of each of these.

Discussion

The search for straightforward, independent risk factors that explain the racial disparity in preterm birth have thus far been inadequate. It is increasingly clear that the causes of preterm birth are complex, and that the causes of the racial difference in preterm birth risk are similarly complex. The body of evidence from epidemiology, psychology, clinical obstetrics and pediatrics, and the basic sciences supporting a causal link between experienced psychosocial stress and the racial disparity in preterm birth is intriguing but remains incomplete. Because of the historically rooted manner in which race and class remain intertwined in 21st century America, it is far from easy to separate one set of effects from another, and the risk of residual confounding is high. Much of the reviewed literature comes from population-based epidemiologic studies which capture some of the heterogeneity in environmental exposures, but often lack the data necessary to infer disease pathways and mechanisms. Other evidence from smaller, clinical or basic science study designs that test aspects of the stress hypothesis are able to describe elaborate biochemical processes, but often lack the size and inclusion of important social or environmental variables to complete the picture. The utility of the stress construct in understanding and reducing racial disparities in preterm birth may lie in better integration of testable hypotheses and data sources which simultaneously consider the social environment, life course social experience, behavior, the genome and epigenome, as well as biological function preconceptionally through delivery.

We find a moderate amount of evidence supporting the role of chronic preconceptional stress and stress-associated behaviors as risk factors for preterm birth. Evidence for the developmental origins of health hypothesis positing early life programming of subsequent preterm birth risk is more circumstantial. The implications for either of these pathways from stress to preterm birth are substantial, and include the elucidation of intervention strategies. Important opportunities for intervention include improving preconceptional screening and management of co-morbidities including hypertension and bacterial vaginosis as well as exploring the role for targeted prenatal screening and interventions for mental health disorders such as depression and post-traumatic stress disorder, which may be most strongly tied to biochemical patterns important in preterm birth.

Acknowledgments

Funding

No specific funding.

This article follows on from a four-part seminar series on causes of racial disparities in preterm birth held in the fall of 2009 at the Rollins School of Public Health, Emory University, Atlanta, GA. The series and this work are supported in part by the National Institute of Health Reproductive, Perinatal, and Pediatric Health Training grant T32 HD052460.

Abbreviations

CI	confidence interval
CRH	corticotrophin releasing hormone
HPA	hypothalamic-pituitary-adrenal axis
OR	odds ratio
PAR%	population attributable risk percent

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Figure 1.

Risk for very preterm birth (<32 weeks' gestation) by maternal age and race, USA, 2003–2006. Data source: National Center for Health Statistics. Arrows point to lowest risk point in age curve for Black (solid line) and White (dotted line) mothers. At all ages, Black mothers experience higher risk for very preterm birth than White mothers, but the nadir of risk for Black mothers is shifted to the left (younger ages) and the rate of increased age-specific risk after the nadir is steeper in Black than in White mothers.

Table 1

Selected studies of preconceptional stressors and preterm birth.

Author, Year	Population	Exposure	Findings
EARLY LIFE			
Collins et al., 2010 (17)	Illinois, USA transgenerational birth file (<i>n</i> =33 801)	Maternal low birthweight and economic environment as predictors of infant preterm birth	PAR% for maternal LBW on infant PTB risk: 1.8% for whites; 2% for blacks PAR% for maternal grandmother living in poverty on infant PTB risk: 2% for whites; 9.8% for blacks
Love et al., 2010 (18)	Illinois, USA transgenerational birth file (<i>n</i> =70 409)	Maternal grandmother's neighborhood SES as predictor of maternal age-PTB association (e.g. 'weathering' hypothesis)	Significantly accelerated age-LBW and age-SGA association for Black but not White infants whose maternal grandmothers resided in poor neighborhoods. No change in age-PTB association by maternal grandmother neighborhood.
Harville et al., 2010 (19)	National Child Development Study cohort, Great Britain (<i>n</i> =4 865)	Mother's own childhood experience of financial, family, structural hardship	Exposure to 4 or more hardships in childhood associated with maternal smoking in pregnancy OR 2.02 (95%CI 1.58–2.58) and infant PTB, OR 1.44 (95%CI, 1.08–1.92)
CHRONIC STRESS/SEVERE STRESSOR			
Guendelman et al., 2008 (35)	Case-control sample from Southern California, USA (<i>n</i> =364 PTB cases, 730 term controls)	Occupational, emotional, and social chronic stressors as predictors of mid-pregnancy CRH and PTB	Chronic stressors associated with lower CRH Among women with 3+ chronic stressors, increasing CRH associated with PTB (OR 2.01 per log (CRH), 95%CI 1.13–3.57)
Khashan et al., 2009 (29)	Danish Medical Birth Registry, 1979–2002 (<i>n</i> =1.35 million)	Severe life events defined as mother's exposure to illness or death of close relative in 6 months prior to conception	Maternal experience of preconceptional death or illness of relative associated with increased PTB risk (OR 1.16, 95%CI 1.07–1.27). Severe illness in older child associated with increased PTB risk (OR 1.23; 95%CI 1.02–1.49)
Kramer & Hogue, 2009 (26)	Prospective cohort in Montreal, Canada (<i>n</i> =5 337)	Chronic stressors including housing crowding, daily hassles, insufficient resources to meet daily needs and lack of social support	No chronic stressors associated with PTB although 'Lack of perceived social support' was borderline significant (OR 1.3, 95%CI 0.9–1.8)
Lu & Halfon, 2004 (25)	Pregnancy Risk Assessment Monitoring System (PRAMS), USA, 2000 (<i>n</i> =33 542)	Stressful life events such as job change, divorce, illness in close relative, interpersonal violence in the 12 months before delivery	No association of stressful life events with PTB
Nkansah-Amankra et al., 2010 (28)	PRAMS, North Carolina, USA, 2000–2003 (<i>n</i> =8 064)	Stressful life events in 12 months before delivery and neighborhood stressors	Emotional stress (OR 1.41; 95%CI 1.35, –1.48) and Traumatic stress (1.07; 95%CI 1.03–1.12) associated with PTB. Significant interaction with neighborhood characteristics so that stress-PTB association is strongest in poor and predominantly Black neighborhoods.
Precht et al., 2007 (27)	Danish Medical Birth Registry, 1980–1992 (<i>n</i> =22 953)	Death or severe illness of mother's partner or child in the year prior to conception	Hazard ratio for SGA very preterm infant (<32 weeks) was 2.71 (95%CI 1.64–4.48) for women exposed to stressful life event 6–11 months before conception.
BEHAVIORAL			
Fernander et al., 2010 (46)	African American women seeking prenatal care, Kentucky, USA (<i>n</i> =70)	Self report of race-related stress (individual, cultural, institutional) and discrimination as predictor of smoking status during pregnancy	Race-related stress in the individual and cultural domains associated with higher smoking prevalence (<i>p</i> < 0.05), but not for institutional domain.
Graham et al., 2010 (44)	Millennium Cohort Study, UK (<i>n</i> =11 857)	Mother's life course social class and disadvantage including childhood poverty, completed educational attainment, marital status as predictor of	Life course social disadvantage associated in dose-response manner with preconceptional smoking regardless of metric used (OR 1.3–3.5)

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Author, Year	Population	Exposure	Findings
Noll, 2007 (42)	Prospective cohort of women sexually abused as children ($n=84$) and neighborhood-matched comparison ($n=102$) recruited 1982 and followed forward, Washington DC, USA	preconceptional smoking and quitting during pregnancy Mother's exposure to childhood sexual abuse as predictor of perinatal HPA function, alcohol use, and PTB	Sexually abused women had higher risk for PTB (20 vs. 10%); difference was mediated by prenatal alcohol use but not by HPA axis function