THE RELATIONSHIP OF GENE EXPRESSION, STRESS, DEPRESSION, AND THE SOCIAL DETERMINANTS OF HEALTH DURING PREGNANCY

by

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This dissertation was prepared under the direction of the candidate's dissertation advisor, Dr. Ruth Tappen, of Christine E. Lynn College of Nursing, and has been approved by all members of the supervisory committee. It was submitted to the faculty of the Christine E. Lynn College of Nursing and was accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

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The purpose of this study was to explore differences in perceived stress, glucocorticoid receptor (GR), and the expression of histone acetylation (HAT) of the corticotropin-releasing hormone (CRH) gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. Black women are 2–3 times more likely to experience preterm birth (PTB) and maternal mortality than White women (Hoyert, 2022; Martin et al., 2019). Researchers have reported chronic stress associated with factors such as experiencing discrimination, financial hardship, and abuse may induce dysregulation of the stress hormones (Kramer et al., 2013; Shapiro-Mendoza et al., 2016). Likewise, the stress hormones glucocorticoid and CRH dysregulation have been linked to early labor, preeclampsia, and maternal death (Kramer et al., 2013; Shapiro-Mendoza et al., 2016; Yu et al., 2013). Additionally, social status, gender, education, and income are recognized as social determinants of health.

This study used an observational, cross-sectional design to analyze the differences in perceived stress, depression, GR, and HAT of the CRH gene between a group of Black and White pregnant women in their 2nd trimester of pregnancy. This study analyzed perceived stress, depression, and peripheral blood monocytes cells (PMBC) using secondary, deidentified data from pregnant women. The Perceived Stress Scale was used to measure stress, the profile in Mood Depression Scale measured depression, a chromatin immunoprecipitation (ChIP) to quantitative Polymerase chain reaction (qPCR) analysis was used to measure GR and HAT of the CRH gene. The data were analyzed using correlation and analysis of covariance (ANCOVA) to examine relationships and the differences between groups.

The sample population consisted of 105 women in their 2nd trimester aged 18–44 (i.e., 73 White and 32 Black). Pearson's correlation showed a strong relationship between HAT of the CRH gene and GR (Pearson's $r = .65$, $p < .01$) and between stress and depression (Pearson's $r = .64$, $p < .01$). The ANCOVA results found no significant difference between the groups in levels of perceived stress, depression, and the expression of GR while controlling for age. The ANCOVA results showed a significant difference in HAT of the CRH gene while controlling for age, $F(1, 88) = 8.26$, $p = .005$, $\eta^2 = .086$, and in HAT of the CRH gene between groups while controlling for GR and age, $F(1, 91) = 5.6$, $p = .02$, $\eta p^2 = .058$.

The significant finding of a difference between the groups In HAT of the CRH gene while controlling for GR and age suggested epigenomic adaptive changes related to the construct antecedent of stress in the social environment. The construct of the antecedent of stress in the social environment refers to the lack of resources available to

some population groups. This lack of resources includes secure employment, safe neighborhoods, access to nutritious foods, and education, which encompass the social determinants of health. Further research on this topic is recommended.

DEDICATION

I dedicate this dissertation to the noble notion of health equity and all individuals seeking to explore the health inequities that exist in various populations. May we continue striving to create a more just society where the optimal health of all population groups is achievable.

THE RELATIONSHIP OF GENE EXPRESSION, STRESS, DEPRESSION, AND THE SOCIAL DETERMINANT OF HEALTH DURING PREGNANCY

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

The social environment in which people live and work enormously influences their health and well-being. The World Health Organization (WHO) termed this phenomenon as social determinants of health. The WHO defined the social determinants of health "as the conditions under which people are born, live, work, age, and the sociopolitical structure in place" (PAHO, n.d.). WHO produced a seminal policy report in which they described health inequity as differences in health that were unnecessary, avoidable, unfair, and unjust (Whitehead, 1992). Recently, WHO updated the definition of health inequities to "systematic differences in the health status of different population groups, which are unfair and could be reduced by the right mix of government policies" (WHO, 2018a). Braveman (2006) noted the terms health disparities or inequalities were the more frequently used terms used in the United States to describe health inequity. Furthermore, Braveman defined health disparities/inequalities as the systematic, avoidable differences in health between people who are of different social positions (e.g., racial/ethnic, socioeconomic, gender, disability status, and sexual orientation), where those individuals who are more socially privileged experience better health than those individuals who are less privileged.

Health disparities are considered unfair and unjust because the less privileged group is further deprived of health (Braveman, 2006). The National Academy of Medicine reported the development of health inequity is connected to social and economic systems embedded in society (Institute of Medicine, 2003). Some researchers

have suggested the systematic differences in health based on race/ethnicity, socioeconomic status, gender, and geography have continued in the United States (Penman-Aguilar et al., 2016). This difference in health relative to social position has become an ethical issue because it favors a privileged group over a less privileged group.

People who live and work in stressful social environments have a greater propensity to develop differences in health that are considered unfair or unjust (Whitehead, 1992). Poor health stemming from social environmental factors such as low wages, lack of fresh produce, and lack of recreational facilities, restricts a person's choices of living and working, therefore producing health differences that are considered unjust (Whitehead, 1992).

Healthy People 2030 (n.d.) acknowledged factors of social determinants of health contribute to health inequities or disparities. The social determinants of health include factors such as economic stability, access to education, access to healthcare, and stable housing. The Healthy People organization was created to improve health in the United States by advancing health promotion and disease prevention strategies. An overarching goal of Healthy People 2030 is creating social and physical environments that promote health and well-being. In accordance with this goal, Healthy People 2030 has incorporated objectives related to improving health and reducing health disparities. The Healthy People 2030 organization has identified the factors of reduction of maternal mortality, infant mortality, and preterm births (PTB) as leading indicators of health for the United States.

It has been well established the social environment in which people live and work has immense influences on their health and well-being (Braveman, 2006; Healthy People

2030, n.d.; Penman-Aguilar et al., 2016; Whitehead, 1992). When people lack the resources to meet the society's demands, they may become frustrated and develop a lack of self-confidence and social functioning (Lazarus, 1999). Conditions such as lack of education, low income, ethnicity, and abuse influence a person's ability to meet societal demands. People living in adverse social conditions with a lack of resources to meet their basic daily needs may lack the capacity to cope effectively. Lazarus (1999) described the frustrations of meeting the requirements of daily life as chronic stress. The human body's responses to chronic stress are not only psychological. The human body responds to stress in physiological and epigenetic ways to maintain adaptation and stability. The physiological responses to chronic stress have been extensively documented. McEwen (2017a) referred to the cumulative effect of chronic stress on the body and its pathophysiological consequences over time as allostatic load. The progressive impact of chronic stress on the body can lead to vulnerability culminating in illness.

When hormones that respond to chronic stress become dysregulated, they may increase inflammation (Silverman & Sternberg, 2012). Researchers have reported psychosocial stress cause activation of the hypothalamic-pituitary-adrenal (HPA) axis to secrete corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoid (cortisol) to promote adaptation and maintain homeostasis in the human body (Silverman & Sternberg, 2012). Researchers have associated psychosocial stress with diseases such as obesity, diabetes, cardiovascular disorders, hypertension, depression, and kidney disease (An et al., 2016; Cain et al., 2019; Kuzawa & Sweet, 2009; Sahle et al., 2020).

In a study exploring race and socioeconomic status, researchers reported African American women who experienced high levels of racial and gender discrimination had lower mental health and well-being (Perry et al., 2013). These investigators reported women on the lower end of the socioeconomic scale were more likely to have experienced racial and gender discrimination and suffer from financial hardship (Perry et al., 2013). Other researchers suggested social factors related to race/ethnicity and low socioeconomic status may contribute to chronic stress inducing maternal susceptibility to increased inflammatory activities during pregnancy (Shapiro-Mendoza et al., 2016).

Hoyert (2022) reported the maternal mortality rate was 2.9 times higher for non-Hispanic Black women than non-Hispanic White women in 2020. MacDorman et al. (2021) reported eclampsia/preeclampsia was the leading cause of maternal mortality for non-Hispanic Black women. Other researchers suggested the higher maternal mortality among Black women was related to factors such as implicit bias and racial and gender inequalities (Amankwaa et al., 2018).

Black women experience significantly higher rates of PTBs (14.39%) when compared to White women (9.26%) in the United States (Martin, 2019). Worldwide, 1 in 10 babies are born prematurely annually (WHO, 2018b). In 2019, 10.2% of live births in the United States were premature (Martin, 2021). PTBs are associated with multiple disabilities, such as cerebral palsy, developmental delay, hearing impairment, vision problems, respiratory dysfunction, and feeding difficulties. Early childhood psychological disorders such as social anxiety disorder, attention-deficit/hyperactivity disorder, and conduct disorder are also associated with PTB (Martini et al., 2010;

Shapiro-Mendoza et al., 2016). The estimated annual healthcare cost for PTBs in the United States alone was 16.9 billion dollars (March of Dimes, 2015).

Statement of the Problem

Researchers refer to the difference in maternal health outcomes between non-Hispanic Black and non-Hispanic White women as a health disparity in the United States (Kramer et al., 2011). Martin (2019) found PTBs were twice as high among Black women compared to non-Hispanic White women. Additionally, other investigators reported maternal mortality was 2.5–2.9 times higher in Black women than in White women (MacDorman et al., 2021; Singh, 2021). Researchers have reported an association between chronic stress and PTB among Black women (Braveman et al., 2017; Manuck et al., 2015). Other researchers have linked stress related hormones (i.e., CRH and cortisol) to both PTB and eclampsia (Harville et al., 2009; Mohamed et al., 2018; Yu et al., 2013).

When the HPA axis gets stimulated during stressful situations it secretes CRH, which leads the adrenal glands to secrete cortisol to promote adaptation. Some researchers have suggested chronic stress causes overstimulation of the HPA axis, which results in dysregulation of CRH and cortisol (Bekhbat et al., 2017; Silverman & Sternberg, 2012). Additionally, CRH is the hormone that prepares the myometrium for labor. Increased circulating cortisol may result in increased placental CRH levels. This dysregulation of placental CRH may induce early labor (Harville et al., 2009; Smith, 2007).

Exploring the cellular processes of stress hormones during gestation could provide valuable information about their impact on pregnant women experiencing social adversities. Researchers reported factors such as experiencing racial discrimination,

financial strain, abuse, and lack of emotional support were associated with hormonal dysregulation, proinflammatory cytokines, and PTBs (Corwin et al., 2013; Gillespie et al., 2017; Giurgescu et al., 2013). Likewise, some researchers have investigated epigenomic transcription factors in relation to pregnancy. Ross et al. (2019) reported women exposed to high levels of stressful life events had more proinflammatory cytokines, suggesting posttranscription factors were upregulating their expressions during pregnancy. Similarly, Di Stefano et al. (2015) reported differences in the levels of posttranscription factors associated with the CRH gene between midterm and term placentas. These researchers concluded cortisol activated posttranscription factors that upregulated CRH and influenced the initiation of labor. Ruiz et al. (2016) found evidence CRH was a predictor of PTB.

A body of research has examined the influence of increased levels of the stress hormone cortisol on pregnancy and an association between increased cortisol, CRH, early labor, and conditions leading to PTB and maternal death (Di Stefano et al., 2015; Mesner et al., 2019; Mohamed et al., 2018; Ruiz et al., 2016; Yu et al., 2013). A better understanding of the relationship between posttranscription factors, glucocorticoid receptors (GRs), and the upregulation of CRH during pregnancy could assist in providing more knowledge about the role of psychosocial stress in maternal health.

Purpose of the Study

The purpose of this study was to evaluate differences in perceived stress, depression, GRs, and the expression of histone acetylation of CRH gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. This

study analyzed secondary data from a deidentified data set from a repository of a pregnant women (M. Groer, personal communication, 2016).

Significance

Non-Hispanic Black women have increased incidence of PTB and maternal mortality. Analyzing the difference between non-Hispanic Black and non-Hispanic White women's psychosocial stress, depression, and epigenomic factors during pregnancy will provide more evidence for the need to have more strategies to identify women at risk for poor health outcomes during pregnancy and the postpartum period. The knowledge gained from this study could assist in improving population health by bringing a deeper understanding to this health disparity. The results of this study could contribute to developing strategies for improving nursing care and changing healthcare policies.

Globally, PTB is the leading cause of death in children under the age of 5 years. Approximately 1 million children die each year due to complications of PTB (WHO, 2018b). In 2015, the infant mortality rate in the United States was the highest among countries with comparable gross domestic products (Kamal & Gonzales, 2015). This high mortality rate was partially due to the infants born preterm. In the United States, 36% of infant mortality was linked to PTBs (Matthews et al., 2015). In 2018, the PTB rate rose significantly for Black women but not for White women (Martin et al., 2019), and between 2019 and 2020, PTBs decreased 1% for White women and increased .06% for non-Hispanic Black women (Martin et al., 2022).

PTB describes infants born before 37 weeks of gestation. Additionally, there were subcategories of PTB that included extreme preterm (i.e., less than 28 weeks), very preterm (i.e., 28–32 weeks), and moderate to late preterm (i.e., 32–37 weeks; WHO,

2018b). Infants born very preterm were in more danger of complications and even death. The last 4 weeks in utero are critical for the development of a healthy baby, as this time is a period for the growth of the brain, lungs, and liver (Shapiro-Mendoza et al., 2016). Infants born preterm are prone to develop physical disabilities and early childhood psychological disorders (Martini et al., 2010; Shapiro-Mendoza et al., 2016).

The WHO (2017) estimated in 2017, 295,000 maternal deaths occurred worldwide, which calculated to a maternal mortality ratio of 211 deaths per 100,000 live births. WHO defined maternal mortality ratio as the number of maternal deaths per 100,000 live births in the same period. WHO (2017) defined maternal mortality as "number of maternal deaths divided by person years lived by women of reproductive age in a population" (p. 8).

The U.S. maternal mortality ratio increased from 14 per 100,00 in 2014 to 17.4 per 100,000 in 2018 (Declercq & Zephyrin, 2020). In the United States, the maternal mortality ratio has been declining for non-Hispanic White women. However, alarmingly, the maternal mortality ratio has increased among non-Hispanic Black women. In 2018, non-Hispanic Black women had a 2.5 higher maternal mortality ratio (37.1/100,000) than non-Hispanic White women (14.7) and 3 times higher ratio than Hispanic women (11.8). Increased educational levels usually improve health outcomes in most population groups; but college educated Black women had a 1.6 higher pregnancy related mortality ratio compared to less than high school educated White women (Petersen et al., 2019). The most frequent causes of maternal death included hemorrhage, hypertension, cardiovascular disorders, cardiomyopathy, embolisms, and infections (Declercq & Zephyrin, 2020).

The findings of this study enhance the understanding of the mechanisms of chronic stress and their influence on pregnancy. The findings contribute to deeper understanding of the cellular changes associated with maternal morbidity during pregnancy. Furthermore, the results from this study could provide another factor to explain the impact of social determinants of health on health inequities. This information could inform public health policy and highlight the necessity for more resources to improve education, access to fair housing, healthy food, healthcare, and provisions of personnel to treat persons suffering from stress-related illnesses. For example, there may be a need for nurses and social workers to screen and treat pregnant women for stress-related conditions to reduce the incidence of chronic stress and depression in society.

Research Question

The overarching research question in this study was: Is there a difference in perceived stress, depression, glucocorticoid receptors (GR), and histone acetylation of the CRH gene between non-Hispanic Black compared to non-Hispanic White women in their 2nd trimester of pregnancy? The following specific hypotheses guided this research:

Hypothesis 1

Non-Hispanic Black women will have a significantly higher level of perceived stress, than non-Hispanic White in their 2nd trimester of pregnancy, when controlling for age as measured by the Perceived Stress Scale.

Hypothesis 2

Non-Hispanic Black women will have a significantly higher level of depression, than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by the Profile in Mood Depression Scale.

Hypothesis 3

Non-Hispanic Black women will have a significantly higher expression of GR then non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by chromatin immunoprecipitation (ChIP) to quantitative Polymerase chain reaction (qPCR).

Hypothesis 4

Non-Hispanic Black women will have a significantly higher expression of histone acetylation of the CRH gene, than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by ChIP to qPCR analysis.

Hypothesis 5

Non-Hispanic Black women will have a significantly higher expression histone acetylation of the CRH gene, than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age and the quantity of GR as measured by ChIP to qPCR analysis.

Theoretical Framework

This research study was conceptualized through the lens of the nursing as caring, the chronic stress emotions, and probabilistic epigenesis theories. The combination of concepts from these three theories provided the theoretical lens for the chronic stress epigenomic adaption model from a nursing perspective. Chronic stress epigenomic adaption could be defined as an individual's personal resources, coupled with their appraisal of their social situation, which lead to chronic stress, epigenomic changes, and culminate in adaptive biopsychosocial outcomes. Personal resources represented the

social determinant of health, which assists in mediating these biopsychosocial adaptive outcomes (Gottlieb, 2007; Peters, 2006).

Nursing Philosophy and Caring Science

The American Nursing Association (ANA, 2015) describes nursing as the art and science of a profession that evolved to address society's needs by ensuring people received the best healthcare regardless of who they were or where they live. Newman et al. (1991) explained the focus of a professional discipline was determined by "an area of study defined by the profession's shared social and service commitment" (p. 5).

Caring has been identified a central concept in the discipline of nursing (Boykin & Schoenhofer, 1990; Leininger, 2012; Watson, 2008). The concept of caring appears in several key definitions of nursing. Newman et al. (2008) defined nursing as "the study of human health and healing through caring" (p. 50). Swanson (1991) described caring as central to nursing practice and scholarship and defined caring as a nurturing way of relating to others. Leininger (2012) asserted, "Caring was one of the oldest and most universal expectations for human development and survival" (p. 57).

Likewise, Watson (2008) depicted "caring as the moral–philosophical–theoretical–foundational starting point for nursing education, patient care, research, and even administrative practices" (p. 16). The essence of Watson's theory revolved around 10 caring caritas processes that assisted with wholeness and healing. The caritas processes are as follows:

> 1. Practicing loving-kindness and equanimity for self and others. 2. Being authentically present and honoring the subjective world of self/other. 3. Cultivating one's spiritual practices; deepening self-awareness. 4. Developing and

> sustaining a helping-trusting caring relationship. 5. Being present to, and supportive of, the expression of positive and negative feelings. 6. Creative use of self and all ways of knowing/being/doing as part of the caring process. 7. Engaging in genuine teaching–learning experiences within the context of caring relationship. 8. Creating a healing environment at all levels 9. Respectfully assisting with basic needs, holding an intentional, caring consciousness of working with others. 10. Opening and attending to spiritual, mysterious, unknown existential dimensions of life–death suffering. (Watson, 2008, p. 116)

Chinn and Kramer (2018) suggested nursing knowledge development resides in the patterns of knowing. Carper (1978) originally introduced four fundamental patterns of knowing. These patterns of knowing include empirical, personal, aesthetic, and ethical patterns. White (1995) added "sociopolitical knowing" as the fifth fundamental pattern of knowing representing the sociopolitical and economic context in which health and illness are enacted, and nursing practice occurs. White (1995) asserted sociopolitical knowing as "essential to an understanding of all others" (p. 83). Chinn and Kramer (2018) called sociopolitical patter of knowing , emancipatory knowing. Chinn and Kramer (2018) explained that emancipatory knowing was the "human capacity to be aware of and to critically reflect upon the social, cultural, and political status quo and to figure out how and why it came to be that way" and "calls forth action in ways that reduce or eliminate inequality and injustice" (p. 5). They contended emancipatory knowing was interconnected with the other four patterns of knowing and it emphasized social justice.

Nursing researchers and theorists have identified the concept of caring as central to the professional discipline of nursing through the study of these patterns of knowing

(Chinn & Kramer, 2018). Kagan et al. (2014) described the human–environment relationships, including physical, socioeconomic, and political, as central to caring and health. Thus, conceptualizing and analyzing health phenomena in the context of the social determinants of health falls in the domain of nursing. Emancipatory knowing, as a dimension of caring, "is essential to health, well-being, and human flourishing" (Kagan et al., 2014, p. 9). Thurman and Pfitzinger-Lippe (2017) argued nurses should explore the sociopolitical factors that interfered with the health and well-being of population groups and individuals and address the social structure that keeps it in place. Social justice refers to acknowledging conditions of unfairness in society and the notion everyone deserves their highest level of health. The sociopolitical way of knowing should motivate nurses to recognize racial discrimination and other social determinants of health and develop strategies for achieving social justice for all population groups.

Nursing as Caring

Boykin and Schoenhofer (2010) formulated the nursing as caring theory, in which they identified caring as a central concept of nursing. They acknowledged caring as the aim and intention of nursing. The nursing as caring theory provided the grand theory level of abstraction for this research study. Boykin and Schoenhofer (2010) asserted the purpose of nursing is nurturing persons living and growing in caring. These authors conceptualized caring as an essential characteristic of all persons. There are six assumptions in the nursing as caring theory:

1) Persons are caring by being human.
2) Persons are whole and complete.
3) Persons lived caring moment to moment.

4) Personhood is a way of living caring.
5) Personhood is enhanced by a nurturing relationship, and
6) Nursing was both a discipline and a profession. (Boykin & Schoenhofer, 2010, p. 372)

Boykin and Schoenhofer (2010) posited nursing occurred in the context of a nursing situation where there is a call and response to the call for nurturance, and the intention of the nurse is to live caring person to person. The nurse responds to a call with the intention to express caring through nurturance to enhance the wholeness of persons in a nursing situation. The nurse brings to a nursing situation the multiple patterns of knowing. Through the multiple patterns of knowing, the nurse comes to understand "what matters most" to persons.

In the context of the nursing situation, authentic caring relationships develop between the nurse and person. Through the sociopolitical pattern of knowing, the nurse becomes aware of factors of the social determinants of health that interfere with the highest health outcomes. In the caring between the nurse and person, the nurse acknowledges and affirms the needs of the person. The nurse response expresses nurturance to enhance the whole of persons in the situation. Hence, the concept of the nursing as caring theory offers nurturing to enhance personhood in a caring relationship (Boykin & Schoenhofer, 2015). In this type of nursing situation, the nurse could advocate for policies that address the social determinants of health and promote health equity of the population. The nurse could advocate for polices such as higher living wages, depression screening for all pregnant women, or decreasing the number of unnecessary caesarian sections.

Probabilistic Epigenesis

The nursing as caring concept of enhancing caring relationships can be linked to other theories examining the human–environment–health relationship, such as the probabilistic epigenesis theory. The probabilistic epigenesis framework posits psychobiological development is influenced bidirectionally by the interaction of environmental (i.e., physical, social, and cultural), behavioral, neural, and genomic activities (Gottlieb, 2007). Gottlieb (2007) suggested there was a reciprocal relationship between human beings and their environment, which influence their growth, development, and the manifestation of health. Gottlieb also asserted the psychosocial environment and physiology interact reciprocally to influence gene expressions. He theorized epigenesis was reciprocally bidirectional and probabilistic instead of unidirectionally and predetermined. The fundamental principle of cellular biology is first, there is DNA, which RNA transcribes (i.e., copies), then RNA translates the DNA copy into protein. However, the bidirectional view of biology suggested reciprocal influences between genetics, psychosocial, and physiological functioning.

Bidirectionality implies although DNA is copied by RNA to make protein, other behaviors or life events could come between genetic activities and influence human growth, development, and health outcomes. The fact that genes require activation implies there are other intracellular proteins interacting with DNA and RNA. Therefore, an individual's environmental experience contributes to the activation of these epigenomic processes. The activation of genetic expressions depends on environmental experiences, as much as RNA is essential to copy and translate a strand of DNA. Gene activities are dependent upon signals from the internal and external environments (Gottlieb, 2007).

Gottlieb (2002) studied duckling imprinting which he experimented on the embryonic auditory system to evaluate the response of ducklings to the maternal calls of their species after hatching. This researcher observed that devocalizing the ducklings resulted in the ducklings not showing selective response to their mother's calling. The control group of ducklings that were allowed to hear their embryonic vocalizations responded to calls from their mothers. As a result of this experiment, Gottlieb (2002) concluded species-specific responses depended on the organism and sensory stimulation. After decades of research, Gottlieb (2002) formulated the theory of probabilistic epigenesis.

The term probabilistic refers to the bidirectional nature and the reciprocal influence between genetic activities and healthy development. An individual's environmental experience contributes to the activation of the epigenomic processes. For example, if a child grows up socially isolated, they will not learn how to talk (Curtiss, 1974). Likewise, if an infant does not receive adequate human contact, they may die or not grow, develop, or thrive (Spitz, 1945). The social environment influences physiological and behavioral development. The activation of genetic expressions depends on environmental experiences, as much as RNA is essential to copy and translate a strand of DNA. Gene activity depends upon signals from the internal and external environments (Gottlieb, 2007).

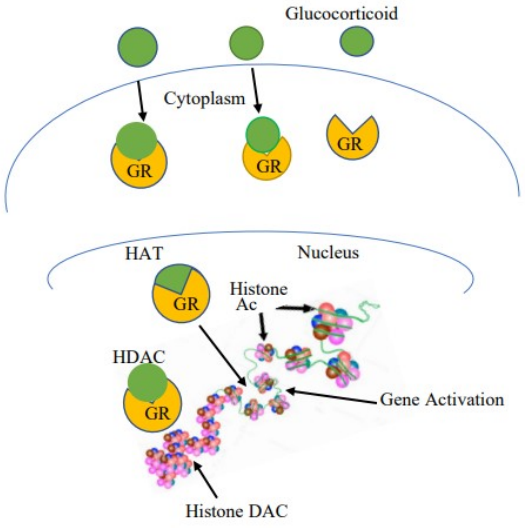
A cellular process called histone modification can alter gene transcription without modifying the genetic sequence. The histone acetyltransferases (HATs) neutralize the charge of the histone tail by the transference of the acetyl enzyme. This acetylation of the histone tails can allow transcription factors to interact with the DNA (Tammen et al.,

2013). In contrast, histone deacetylases remove the acetyl enzyme causing a positive charge to the histone tail, which compacts the chromatin structure, thus not allowing transcription to occur (Tammen et al., 2013). John et al. (2011) conducted an analysis of the chromatin accessibility state and pattern of GR binding. These investigators found in the presence of corticosteroids, GRs had an affinity to bind at open chromatin sites.

In a review article, Buckingham (2006) described the process where cortisol activated the actions of GR. When GR becomes activated, they function as transcription factors. Wang et al. (2021) investigated the role of GR in cell regulation. These researchers discovered long-term treatment of cells with dexamethasone resulted in increased GR. They also reported the dexamethasone-treated cells GR had increased histone acetylation. Therefore, the increase of cortisol-induced by chronic stress could produce a change in DNA expression by exposing the chromatin to GRs (see Figure 1).

Figure 1

Glucocorticoid, Glucocorticoid Receptors, and CRH Gene Activation



Note. GR - glucocorticoid receptor, HATs - histone acetyltransferases, HDAC - Histone Deacetylases, Ac - histone acetylation, DAC - deacetylation.

The fundamental assertion of the probabilistic epigenesis theory is variations in health outcomes may result from a wide range of genomic-environmental interactions, instead of being purely genetic (Gottlieb, 2007).

Chronic Stress Theory

The concept of psychosocial stress has been considered a stimulus–response type of reaction. This reaction occurs to individuals in the context of their social environment. An environmental stimulus is presented, and individuals react to them. The type of reaction to a stimulus varies greatly between individuals; a situation that elicits stress in one person may not do so for someone else (Lazarus, 1999). In any situation, there may be environmental demands, constraints, or opportunities, but it is the person's appraisal of the situation that determines whether the situation is deemed stressful. This appraisal occurs when an individual evaluates a situation as harmful, a threat, or a challenge. The characteristic of the person plays an integral role in appraising a situation. It is the characteristics of a person that determined the significance of the environmental stimulus and how to respond to it. The characteristics a person brings to a situation include their goals, aspirations, beliefs, and personal resources. People evaluate their goals and beliefs when dealing with environmental demands, constraints, or opportunities. If a person perceives environmental demands, constraints, or challenges as harmful or threatening to their goals and beliefs, the person must use their personal resources to cope with the situation. A stress reaction may occur if the environmental demands appear greater than the available personal resources the person has for coping (Lazarus, 1999).

Lazarus (1999) described personal resources as the enduring personal attributes that influence the options a person has available to deal with the demands, constraints, or

opportunities of the environment. These personal resources include intelligence, ethnicity, social skills, wealth, education, energy, physical appearance, social support, and health. When confronted with an environmental demand, the lack of adequate personal resources to cope increases a person's vulnerability. Over time, the consequence of lack of personal resources to meet environmental demands can result in poor health. Lazarus (1999) suggested chronic stress was the "daily annoyances of life that can impair the morale, social functioning, and health" (p. 146). The personal attributes that could affect maintaining the perpetual daily balance between a person's goals and aspirations versus the demands of society include factors such as socioeconomic status, ethnicity, gender, and role transitions.

Chronic Stress Emotions Theory

The chronic stress emotions theory (CSET) has a relevant theoretical lens for providing a more focused and less abstract conceptualizing of the connection between person–environment human experience and health inequity. The CSET is a middle-range theory that purports poor health outcomes may be the consequence of a chronically stressful environment (Peters, 2006). This theory posits living in a stressful environment may produce poor emotional regulation and physical health outcomes. The concept of weathering is like the CSET theory; both of these concepts describe the impact of chronic stress on health. However, the weathering concept focuses specifically on the impact of chronic stress on women's lives, but its constructs do not explain stress in the context of epigenomic adaptation (Kramer et al., 2011; Peters, 2006). Both weathering and CSET theories can be analyzed from the ethical perspective of social justice.

On the other hand, CSET theory uses four constructs obtained from Lazarus's (1999) stress theory to create this middle range theory. These constructs include antecedents, appraisal, coping, and adaptive outcomes. The antecedent construct describes personal resources such as socioeconomic status, education, income, and employment that may affect a person's appraisal of their environment and their coping options. The appraisal construct is described as events occurring in the social–cultural environment that creates an arousal of threat. Coping represents a person's ability to identify, process, and regulate emotions. Adaptive outcomes depict emotional and somatic health. Emotional health further signifies personality traits resulting from chronic stress and displayed by attributes such as anger, anxiety, and depression. A somatic outcome indicates the physiological responses to stressful person–environment interactions (Peters, 2006). Peters (2006) evaluated the four constructs of this theory using a sample of 162 individuals and structural equation modeling. The results found a positive relationship between perceiving racism and chronic stress emotions, but not with blood pressure. The CSET theory was an appropriate middle-range theory for situating the phenomenon of chronic stress adaptation based on its description of the relationship between exigent environmental interactions and chronic stress reactions.

Chronic Stress Epigenomic Adaptation Conceptualization

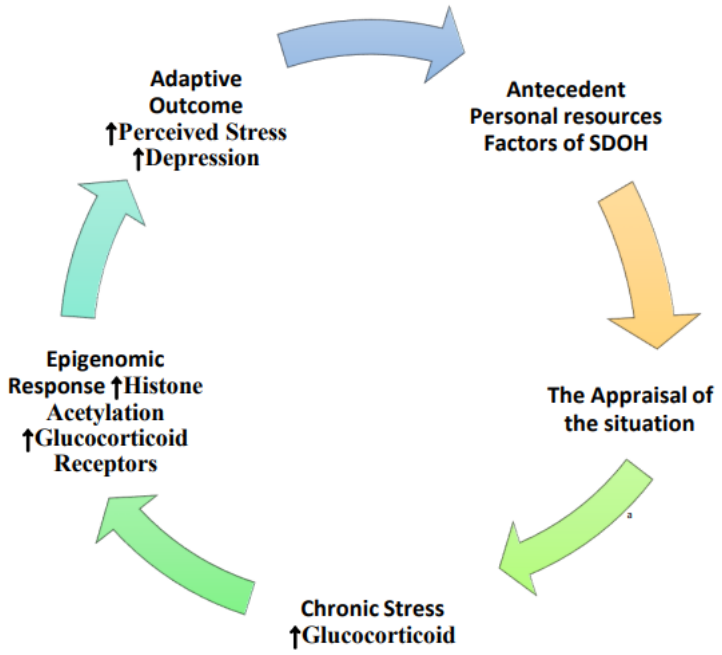
This researcher conceptualized the phenomenon of chronic stress epigenomic adaptation as a person's biopsychological adaptive response to the socioeconomic and environmental circumstances in which they live. Societal structures shape the conditions in which people are born, live, work, and age. When people live with lack of personal resources, they develop chronic stress from perceptions of being unfairly treated, which

contributes to poor psychological and physiological health outcomes. The WHO defined health inequity as the systematic differences in the health status of different population groups, which were unfair and could be reduced by a mix of government policies (Whitehead, 1992). The social determinants of health refer to factors such as race, gender, socioeconomic status, education, income, and employment that may influence a person's health status (Whitehead, 1992). Like the social determinants of health, personal resources refer to factors such as race, education, and socioeconomics that may affect a person's appraisal of their environment and their coping options.

The Centers for Disease Control identified the disproportionately high maternal mortality and PTB rate of non-Hispanic Black women as a health inequity. Additionally, some researchers have linked cortisol dysregulation of chronic stress to poor pregnancy outcomes (Kramer et al., 2011, 2013; Shapiro-Mendoza et al., 2016; Yu et al., 2013). As shown in Figure 2, this researcher conceptualized a chronic stress epigenomic adaptation model as an integration of concepts from the nursing as caring, chronic stress emotions, and probabilistic epigenesis theories.

Figure 2

Chronic Stress Epigenomic Adaptation Model



Boykin and Schoenhofer (2010) explained nursing brings an intentional, nurturing caring relationship to every nursing situation, thus enhancing a person's growth and development. Peters (2006) posited antecedent (personal recourses), appraisal of the social–cultural environment, having adaptive outcomes, and coping with negative psychological and physiological responses occurred when interacting in a stressful environment. The concept of antecedent refers to a person's personal resources. Gottlieb (2007) indicated human beings need an acceptable support system for their growth, development, and manifestation of health. The concept of appraisal implies people strive in caring environments. Consequently, a person's appraisal of discriminatory treatment may have a negative impact on their psychological and physiological health and well-being. The concept of adaptive outcome suggests antecedent factors such as

socioeconomic status are interconnected to the health and wholeness of persons. Peters' (2006) final concept of coping indicates people require a nurturing and just social system to ensure optimal growth and development. Therefore, this researcher identified the study's operational indicators as race, perceived stress, depression, GRs, and histone acetylation, as shown in Table 1. These variables were measured using the Perceived Stress Scale, the profile in Mood Depression Scale, and ChIP to qPCR analysis.

Table 1

Connecting Nursing as Caring, Probabilistic Epigenesis, and Theories Chronic Stress Emotions

Nursing as caring concepts	Probabilistic epigenesis concepts	Chronic stress emotions concepts	Relationship of nursing as caring, chronic stress emotions, and epigenomic adaptation
1. All persons are innately caring.	Human beings thrive in a caring environment.	A caring environment can provide the resources necessary for optimal growth and development.	A caring environment is necessary for optimal health.
2. Persons live caring person to person, moment to moment.	Caring social interactions influence healthy genomic expression.	A person's appraisal of a situation influences their response.	Persons living in a caring environment have the likelihood of healthy genomic expression.
3. Persons are whole and complete living and growing in a caring environment.	Caring promotes the optimal reciprocal interactions of our psychosocial, and physiological environments.	Adaptive outcomes: are indicative of psychological and physical health.	A caring environment supports healthy outcomes for all population groups.
4. Life is enhanced through nurturing, supportive, caring relationships.	Developmental outcomes are understood in relation to their environmental conditions.	Coping: a person's ability to process, and regulate emotions is enhanced by supportive relationships.	Understanding life has an epigenomic nature with physiological, psychological, and social factors. The nurse provides expressions of nurturance to enhance life.

Consequently, in the context of stress and pregnancy, the chronic stress epigenomic adaptation model theorizes there is a relationship between a woman's social environment and her psychological and physiological responses during pregnancy. When a woman is exposed to emotional stressors, her physiological response increases her cortisol and CRH levels. The increase of these stress hormones leads to a rise in genomic posttranscription factors such as GRs and HATs. When a person lives in a state of chronic stress, their cortisol does not shut off as in the case of acute stress. The increased availability of cortisol results in increased production of placental CRH in the 2nd trimester of pregnancy. The sociopolitical way of knowing enables the nurse to recognize factors of the social determinants of health, such as racism or low socioeconomic status. The nurse's understanding of the social determinants of health informs a call for sociopolitical action to advocate for equitable healthcare policies to enhance the health and well-being of all persons.

Definitions of Terms

1. **Depression** is defined as a person's self-reported mood or feelings of dejection as measured by the Profile of Mood State (POMS), depression subscale (Norcross et al., 1984). The scoring is on a 5-point scale ranging from *Not at all* (0) to *Extremely* (5). It describes feelings of helplessness, worthlessness, unhappiness, hopelessness, and sadness.
2. **Glucocorticoid receptor** is defined as the cellular posttranscription factor identified by ChiP analyses and qPCR quantification (John et al., 2011).
3. **Histone acetylation** of the nucleosome is considered the presence of acetyltransferases at the terminal histone tails of H3 and H4N and is determined by

chromatin immunoprecipitation (ChIP) analyses and qPCR quantification (Tammen et al., 2013).

4. **Perceived Stress** is a person's self-reported appraisal of stressful life events during the prior month as measured by the Perceived Stress Scale (Cohen et al., 1983). The scoring is on a 5-point scale ranging from *Never* (0) to *Often* (5). It is described as a self-appraisal of adverse life events.
5. **Race** is defined by the U.S. Census Bureau as a person's self-identified social group (e.g., non-Hispanic Black or non-Hispanic White) and **ethnicity** as whether a person is of Hispanic origin or not (i.e., non-Hispanic; U.S. Census Bureau, n.d.).
6. **The 2nd trimester of pregnancy** is self-reported as 16–26 weeks of gestation for each participant.

Summary

In summary, researchers have suggested the hormones activated in chronic stress are associated with adverse health outcomes (An et al., 2016; Cain et al., 2019; Kuzawa & Sweet, 2009; Sahle et al., 2020). Black women are twice as likely to experience PTBs and maternal mortality (Hoyert, 2022). People living and working in adverse social conditions experience more adverse psychological and physiological health outcomes (Healthy People, 2030). Stressful situations may activate hormone mediators to aid in adaptation in a bidirectional, interactive, probabilistic pattern. The discipline of nursing has foundational concepts of caring at its core (Boykin & Schoenhofer, 1990; Leininger, 1981; Smith, 2013; Watson, 2012). Therefore, the chronic stress epigenomic adaptation model emerged as the appropriate theoretical model to guide this research. This

conceptual model's operational indicators were perceived stress, depression, levels of the GR, CRH, and histone acetylation.

CHAPTER 2: LITERATURE REVIEW

The purpose of this study was to explore differences in perceived stress, depression, and modifiable epigenomic changes in the modulation of the corticotropin-releasing hormone (CRH) gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. This chapter was organized by the research and scholarship on health equity, stress in pregnancy, caring nursing theory, probabilistic epigenesis theory, and the chronic stress emotion theory. The chapter begins with research on health inequities and concludes with identifying the knowledge gap in the literature on stress and preterm birth (PTB).

Health equity aims to eliminate inequities in health relative to social position (Braveman, 2014). Health inequities are considered unfair and unjust when a more privileged social group has better health outcomes than a less privileged social group (Braveman, 2006). Health inequities are shaped by distribution of money, power, and resources in a society (WHO, 2018a). People who live and work under discriminatory social conditions have restricted choices, which may result in health differences that could be considered unjust (Whitehead, 1992). Women living and working under disadvantageous and stressful social conditions may activate hormone mediators that induce early labor. Researchers have indicated psychosocial stress may induce mediators that cause maternal susceptibility to PTB, anxiety, depression, and preeclampsia (Corwin et al., 2013; Gillespie et al., 2017; Giurgescu et al., 2013; Harville et al., 2009; Mohamed et al., 2018; Yu et al., 2013). The pathway of increased glucocorticoid (cortisol)

availability, elevated serum CRH, and posttranscription factors have been described in some investigations. The remainder of this chapter explores relevant literature on health inequities, and stress during pregnancy.

Health Inequalities/Disparities

In 1984, the U.S. Department of Health and Human Services (USDHHS) commissioned a taskforce to investigate health differences between White people, Black people, and people from other minority groups. Investigators reported 42.5% higher mortality rate in the Black population compared to the White population (Nickens, 1986). The mortality rate was higher for Black Americans than for Native Americans and Asian/Pacific Islanders. The taskforce implicated six health conditions before death. Those health indicators were cancer, cardiovascular disease, cirrhosis of the liver, diabetes, unintended accidental death, and infant mortality (Nickens, 1986). In 2002, the Institute of Medicine (IOM) reported Black Americans were less likely to receive the medications, treatments, and surgeries they needed compared to White Americans (Smedley et al., 2003). These researchers concluded the development of this health inequity was linked to social and economic systems ingrained in society (IOM, 2003). WHO described these social and economic conditions as social determinants of health. The term social determinants of health refers to the circumstances under which people are born, live, work, and age in the sociopolitical structure in place. The social determinants of health represent the social and environmental conditions that dominate a person's daily life and social situations, such as affordable healthcare, transportation, education, and employment. Other environmental conditions necessary for a good quality of life include safe neighborhoods, fair housing, and adequate social networks.

According to Yearby (2018), racism's sociopolitical structure has continued to support the activities that lead to these health inequities. Yearby maintained the sociopolitical structure remained intact because the government did not enforce civil rights laws that gave White Americans advantage over Black Americans in obtaining wealth and employment. The federal government gave White Americans more access to obtaining housing loans than Black Americans. Likewise, a Black American with the same qualifications as a White American would be less likely to be hired. Yearby reported due to the aforementioned factors, the wealth gap between Black and White Americans had continued to widen over the past 30 years.

Maternal Characteristics

The factors underlying the difference in pregnancy outcomes between Black and White women are complex and poorly understood. These factors have not been explained by the difference in behavior and socioeconomic status of the groups alone. Historically, PTB has been investigated in the context of understanding the infant mortality rate. Infant mortality was first investigated in 1913. Yankauer (1994) reported the 1913 investigation used surveys to analyze factors such as prematurity, parental income, maternal age, and parity. Although these factors are still being studied, they have not provided all the answers to the differences in pregnancy outcomes between Black and White women. For instance, some researchers have concluded the social factors underlying the PTB disparity were more complicated than socioeconomic status (Braveman et al., 2015; Carmichael et al., 2017).

Braveman et al. (2015) conducted a study to analyze the socioeconomic factors associated with racial disparities and PTB. These researchers used a population-based

survey with a sample of 3,286 U.S.-born Black and 7,114 U.S.-born White women. The researchers found 49.3% of Black women's incomes were below the poverty level compared to 15.3% of White women. Additionally, the PTB rate in the study was 12.8% among Black women and 7.4% among White women. The results also showed PTB had a significantly elevated adjusted odds ratio (OR) of 1.61 to 1.90 for Black women compared to White women (Braveman et al., 2015).

More recently, Carmichael et al. (2017) conducted a study to analyze the socioeconomic factors related to PTB inequities among Black and White women in California. The sample population consisted of 130,882 non-Hispanic Black and 625,778 non-Hispanic White singleton infants. The variables evaluated included maternal education, type of health insurance, mother's address, household income, and gestational age on birth certificate. The researchers used logistic regression to estimate OR with 95% confidence interval and found the PTB rate was 10.2% for Black and 6.3% for White infants. The OR for PTB was 1.25 for Black women compared to 1.40 for White women. These researchers reported early preterm delivery was 3 times higher among Black infants than White infants. These investigators concluded that the variables under investigation could not explain the disparity in birth outcomes (Carmichael et al., 2017).

Chambers et al. (2019) investigated the difference in PTB among women with known risk factors using the California Birth Cohort Database. Risk factors included previous PTB, hypertension, preeclampsia, diabetes, infection, mental illness, smoking, and drug or alcohol dependence. The study population consisted of 2,320,020 singleton deliveries among non-Hispanic Black, Hispanic White, and non-Hispanic White women between 20–44 weeks' gestation. They used logistic regression to compare the odds of

PTB among the women who had no risk factors and among women with each risk factor. The researchers found PTB rates were 9.9% for Black women, 6.9% for Hispanic women, and 6.0% for White women. The OR for PTB was 1.4 for Black women compared to 1.6 for White women. Additionally, PTB rates across risk groups were the highest among Black and Hispanic women with preeclampsia 33.0% and 29.5%, respectively, and previous PTB 30.5% and 29.6%, respectively (Chambers et al., 2019).

DeSisto et al. (2018) examined the influence of sociodemographic, behavioral, and medical risk factors on PTB. The study population consisted of 1,904,513 records of singleton births to non-Hispanic Black women born in the United States or abroad and non-Hispanic White women born in the United States. The gestational age of the births ranged from 20–44 weeks. These researchers used a chi-square to determine differences between groups and Oaxaca-Blinder decomposition methods to estimate the group differences in PTB. The researchers found PTB rates were 11.1% for U.S.-born Black women, 7.9% for foreign-born Black women, and 6.8% for U.S.-born White women. However, the variables did not explain the PTB disparity between U.S.-born Black and White women (DeSisto et al., 2018).

Elo et al. (2014) investigated the difference in the PTB rate between U.S.-born Black women and foreign-born Black women. These researchers used vital statistics from birth records of 27 states to assess birth weight, gestational length, maternal race, Hispanic origin, age, education, marital status, reproductive history, medical risk factors, prenatal care use, and smoking status of 344,121 women. The sample population consisted of 86.2% U.S.-born non-Hispanic Black women and 13.8% foreign-born non-Hispanic Black women. The data were analyzed using logistic regression ORs for the

mother's place of birth with their 95% confidence interval for PTB. The researchers found U.S.-born Black women had a PTB rate of 12.4% in contrast to 9.4% for foreign-born Black women. These researchers reported controlling for explanatory variables with multivariate analysis could not explain the difference in PTB between U.S.-Black women and foreign-born Black women. The foreign-born non-Hispanic Black women had significantly lower odds of PTB (OR = 0.727; 95% CI [0.726, 0.727]) than U.S.-born non-Hispanic Black women. Foreign-born non-Hispanic Black women showed a higher rate of diabetes compared to U.S.-born non-Hispanic Black women, 6.2% and 4.1%, respectively (Elo et al., 2014). These researchers concluded the difference in pregnancy outcome between these groups of women could not be explained by the risk factors available on the birth certificates.

Stress Response

Another path to understanding differences in birth outcomes between White and Black American women is the relationship between the stress response and chronic activation of hypothalamic-pituitary-adrenal (HPA) during pregnancy (Kramer et al., 2011). Selye (1936) introduced the General-Adaptation-Syndrome in which he described the response of the HPA axis as the pathway of the body's response to psychological stress. McEwen (2018) expanded on Selye's theory by advancing the concept of allostasis. Allostasis explains the physiological processes through which the body responds to daily psychological stressors and maintains homeostasis. McEwen (2017a) explained in stressful psychosocial situations, the body activates hormone mediators, such as CRH, adrenocorticotropic hormone (ACTH), and cortisol to maintain homeostasis and help in adapting to the situation. These hormone mediators are turned on

in response to a stressful experience and turned off after the challenge has ended, and they aided in adaptation (McEwen, 2017b). However, if these hormone mediators are excessively activated and the body is unable to maintain equilibrium over an extended period, dysregulation of the hormones occur in the body (McEwen, 1998). The hormones of the brain (e.g., CRH, epinephrine, and norepinephrine) are central to maintaining physiological balance, but when they are overstimulated, these hormones become dysregulated. Postgenomic transcription factors such as histone acetyltransferases (HATs) and histone deacetylases regulation are also influenced by the stress response (McEwen, 2018).

Alhusen et al. (2016) conducted an integrative review of the impact of racial discrimination on birth outcomes using four qualitative and 11 quantitative studies. The studies in this review explored racial discrimination in relation to access to prenatal care, employment, and neighborhood characteristics. The qualitative studies in this review described stress related to racial discrimination as a risk factor for PTB. The reviewers found studies in which investigators inquired about racial discrimination and PTB detected significant relationships. Some investigators reported a significant relationship between racial discrimination and inflammatory markers (Alhusen et al., 2016).

Giurgescu et al. (2013) conducted a mixed-method study to understand the stressor, stress response, and personal resources affecting African American women during their pregnancy. The sample was comprised of 11 pregnant women, four fathers of the babies, three friends, and one mother. The data collected included a depression scale, a psychological well-being scale, blood samples for cortisol and cytokine levels, and a focus group interview. These researchers found high and low stress response patterns

among the women. The causes of stress were described as racial discrimination, neighborhood safety, job security, finance stability, or social support system. Moreover, the researcher reported 50% of the women had high depressive scores.

Sealy-Jefferson et al. (2016) conducted a study to examine the association between perceived stress, psychological distress, and neighborhood context (e.g., safety, walking environment, healthy food availability) on PTB. The sample population consisted of 399 African American women with less than 12 years of education. Wilcoxon rank sum, chi-square, and logistic regression were used to analyze the data. The women who had a PTB reported more symptoms of depression and perceived stress than the women who delivered term births. The highest correlation was between neighborhood safety and depression (r = -0.72). The researcher also found an association between depression, perceived neighborhood safety, and PTB (Sealy-Jefferson et al., 2016).

Slaughter-Acey et al. (2016) conducted a study on the relationship between racism, perceived stress, depression, and PTB. The sample population consisted of 1,410 Black women. The data were analyzed using a log-binomial to determine the PTB prevalence ratio (PR) at 95% confidence interval. The researchers found a 16.6% prevalence of PTB in the sample and a significant association between racism score and PTB. Severe depression scores were significantly associated with PTB (adjusted PR = 1.75; 95% CI [1.29, 2.36]) and mild to moderate depressive symptoms were associated with perceived racism among women with PTB. The predicted probability of PTB increased with daily experience of racism scores between 40–70 the decreased Slaughter-Acey et al., 2016). These researchers concluded that racism in the form of micro-

aggression may be a risk factor for Black women with mild symptoms of depression, but it had less impact women experiencing severe depression

Braveman et al. (2017) investigated the relationship between chronic worry about racial discrimination and PTB in a sample of 8,122 Black and 2,201 White women. The data for the study were obtained from the California Maternal and Infant Health Assessment and were analyzed using prevalence ratios and logistic regression. The researchers found 36.9% of Black women and 5.5% of White women reported chronic worry. Chronic worry was associated with 9.2% of Black women and 5.8% of White women who had a PTB. Older Black women who were married with higher income or education levels were more likely to report chronic worry. Chronic worry was related to PTB among Black women (PR = 1.73; 95% CI [1.12, 2.67]). The researcher also found an association between neighborhood poverty and PTB among Black women (Braveman et al., 2017).

Tsai et al. (2017) investigated the relationship between lifetime stress, stress during pregnancy stress, and PTB among Black women. The sample population consisted of 628 U.S.-born mothers and 493 foreign-born Black women. The data were analyzed using linear and logistic regression models. The researchers found a significant inverse relationship between lifetime stress and PTB among all study participants. However, there was a significant relationship stress during pregnancy and PTB among the foreign-born Black women. Half of the significant relationships became nonsignificant after controlling for covariates such as maternal age, educational level, body mass index (BMI), marital status, use of illicit drugs, smoking, and alcohol use. The researchers also

reported the participants with higher stress during pregnancy and higher African ancestry had significantly higher rate of PTB (Tsai et al., 2017).

Grobman et al. (2018) investigated the relationship between psychosocial stress and racial disparities in PTB. The sample population included 5,721 women, 5,721 (60.4%) were non-Hispanic White, 1,307 (13.8%) were non-Hispanic black, 1,586 (16.7%) were Hispanic, 379 (4.0%) were Asian, and 477 (5.0%) were another race. They analyzed the data using multivariable logistic regression models and OR and 95% confidence interval. The researchers found non-Hispanic Black women were more likely to experience PTB compared to non-Hispanic White women (OR = 1.60; 95% CI [1.32, 1.93]; Grobman et al., 2018). These researchers reported after adjusting for confounding factors, non-Hispanic Black women have continued to show the highest risk for PTBs.

Stress Hormones in Pregnancy

Psychosocial stress causes the activation of the HPA axis that maintains homeostasis and promotes adaptation in the body (Silverman & Sternberg, 2012). When an acutely stressful event occurs, the hypothalamus will activate the secretion of CRH, which stimulates the pituitary gland to produce ACTH and the adrenal glands to secrete cortisol. Next, cortisol returns to the hypothalamus and stops CRH production through a negative feedback loop system (Silverman & Sternberg, 2012). Chronic stress may cause impairment in the regulatory feedback system of the HPA axis resulting in increased cortisol availability.

Kramer et al. (2013) investigated the relationship between cortisol, CRH, and progesterone plasma levels in the 2nd trimester of pregnancy and birth outcome with measures of stress. The investigation was designed as a prospective cohort, nested case–

control study, and the data were collected when the participants were between 24–26 weeks of gestation. The sample size consisted of 206 women who delivered at preterm and 442 women who delivered at term. The sample population consisted of 537 White, 41 Black, 26 Latina, 17 Middle Eastern, and 24 Asian women between the age of 20–35. The data were analyzed using multivariable logistic regression analysis. The researchers reported high CRH level was associated with an increased risk of PTB (OR = 1.3; 95% CI [1.0, 1.9]). They also found significant positive associations between CRH and cortisol (OR = 1.5; 95% CI [1.03, 2.2], p <.01). There was a positive correlation between CRH and cortisol (p <.01).

Stress, Cortisol, and Preterm Birth

Some researchers have argued the various stressors pregnant women experience, and the internal mediator produced in assisting the body to adapt may contribute to PTB. Several investigators have studied the internal mediators and their relationship to acute and chronic stress in pregnant women. Some researchers have studied the effect of perceived stress and cortisol on PTB and found a positive relationship (Gillespie et al., 2017).

Gillespie et al. (2017) investigated the relationship between stress, plasma cortisol, and birth timing. The sample contained 89 African American women aged 18–34 years old and between 28–32 weeks of gestation. The data were analyzed using multivariate linear regression models. The researchers reported positive associations between stress scores and birth timing (r_s = 0.27, p < 0.05), and cumulative childhood stress and cumulative stress in adulthood (r_s = 0.36, p < 0.01; Gillespie et al., 2017).

Christian et al. (2013) investigated the differences in stress-induced inflammatory responses in Black and White pregnant and nonpregnant women. The sample consisted of 80 women, 20 Black and 20 White pregnant women in their 2nd trimester, matched with 40 nonpregnant women. A Trier Social Stress Test was given, proceeded by blood sample collections at 45 and 120 minutes after testing. Saliva samples were also collected 25 minutes before the test; at the time of testing; and 15-, 30-, 45-, 60-, and 90-minutes posttest. A positive and negative affect scale was administered before the Trier Social Stress Test, and depression, anxiety trait, perceived stress, hostility, perceived social support and childhood trauma scales were administered after testing (Christian et al., 2013). Researchers found Black women had higher pro-inflammatory cytokines, such as interleukin-6 (IL-6) cytokine levels, than White women. Black women reported greater racial discrimination in total frequency ($p < 0.07$). Researchers found a correlation between the perceived stress and depression scores which approached statistical significance ($r = 0.32$, $p < 0.06$).

Some researchers have not found any association between internal mediators functioning to assist the body to adapt and perceive stress. Duffy et al. (2018) examined relationships between hair cortisol levels and perceived stress in PTB and term birth participants. The sample population consisted of 52 women over 18 years of age of diverse ethnicities who delivered preterm or term births. Data were analyzed using correlations, repeated measures mixed models, and *t* tests. The researchers found the mean hair cortisol level in the term birth group was 15.8 pg/mg and in the PTB group was 9.0 pg/mg. In addition, the perceived stress scores of PTBs were higher than those term birth ($t = 2.96$, $df = 50$, $p < 0.05$; Duffy et al., 2018).

Other investigators studying the effect of perceived stress, cortisol, and proinflammatory cytokines on PTB found increased levels of proinflammatory cytokines (Corwin et al., 2013; Gillespie et al., 2016; Giurgescu et al., 2016). Giurgescu et al. (2016) examined the association between experiencing racial discrimination and systemic inflammation in the 2nd trimester of pregnancy. The sample population consisted of 96 African American women over 18 years old. The data were analyzed using correlations and hierarchical multiple linear regression. These investigators reported an association between experiences of racial discrimination and IL-4 cytokine ($b = 2.161$; 95% CI [1.02, 3.30], $p < 0.01$), and IL-6 ($b = 1.859$; 95% CI [0.61-3.11], $p < 0.04$) and higher levels of cytokine IL-6 ($r = .236$, $p < 0.02$; Giurgescu et al., 2016).

Gillespie et al. (2016) investigated the inflammatory response occurring during pregnancy and postpartum to determine whether racial differences were involved. The study sample comprised 76 pregnant women. Blood samples were obtained at 9–17, 19–24, and 26–35 weeks' gestation, and at 7–11 weeks postpartum. They analyzed the data using repeated measures. Researchers found cytokine IL-6 and TNF-α values rose from early to mid-pregnancy ($p < 0.05$) and mid- to late pregnancy ($p < .05$). Black women had greater TNF-α cytokine during mid-pregnancy ($p < 0.02$) and lower IL-1β cytokine at postpartum ($p = .05$; Gillespie et al., 2016).

Giurgescu et al. (2015) investigated the association between stress-induced biomarkers, preeclampsia, and PTB among pregnant African American women. The sample population included 48 women between 18–39 years old. Seventy nine percent of the women were single and 55% were unemployed, and 47% of households were below the poverty line. Social support was measured with the Medical Outcomes Study social

support survey, optimism was measured with the Life Orientation Test, and avoidance was measured with the Prenatal Coping Inventory. The data were analyzed using chi-square, correlations, and two-tailed *t* tests. Researchers reported women with PTB were more likely to have preeclampsia. Women who delivered PTBs had higher levels of optimism and lower levels of avoidance. The women with preeclampsia had lower levels of cortisol and IFN-γ and IL-10 levels. Social support was also associated with lower stress and proinflammatory markers (Giurgescu et al., 2015).

Catov et al. (2015) examined the relationship between anxiety, optimism, and inflammatory biomarkers with PTB. The study sample included 434 pregnant women—119 (27.4%) who were African American and 315 (72.5%) who were Caucasian. The women were interviewed around the 20th week of their pregnancy using anxiety and optimism scales; blood samples were collected concurrently. The data were analyzed using chi square, multivariable logistic regression, Wilcoxon tests, and Spearman correlations. These researchers found a significantly higher percentage (27.3%) of African American women who reported higher anxiety traits compared to 19.2% of the White women. The higher anxiety level among African American women was associated with shorter gestations (OR = 0.71; 95% CI [0.50, 1.02], $p < 0.06$). There was also a correlation between C-reactive protein and anxiety ($r = 0.16$, $p < 0.09$) among African American women (Catov et al., 2015).

Corwin et al. (2013) hypothesized low-income and minority women would be affected by increased levels of proinflammatory cytokines and cortisol dysregulation during pregnancy. The sample size included 96 participants in the 2nd and early 3rd trimester of pregnancy. Each participant gave five saliva samples over the course of a

day, starting with early morning to night, following a strict protocol. Data were also collected on perceived stress and depression scales on the second home visit. The data were analyzed using *t* test and chi square, multiple linear regression, and hierarchical models. The researchers reported the mean perceived stress scores were higher in the low income and African American groups ($p < .04$). Black women had significantly higher level of morning cortisol levels than White women (.41 vs. .31 ug/dl, $p < .01$) and had significantly higher levels of 11:00 a.m. cortisol (.40 vs. .30 ug/dl, $p < .01$; Corwin et al., 2013).

Depression

The activation of the HPA axis has been linked to the stress response and depression (Christian et al., 2013; Orta et al., 2018). Hoffman et al. (2016) investigated the relationship between stress, mood, and PTB. The study population consisted of 90 pregnant women between 18–45 years old and less than 16 weeks of gestation. Hair cortisol levels, Perceived Stress Scale, Epidemiologic Studies-Depression Scale, and the State–Trait–Anxiety Inventory were obtained at 16, 22, 28, and 40 weeks of gestation. The data were analyzed using chi square and Pearson correlation.

The researchers found 12% of the participants who delivered preterm had higher 2nd-trimester hair cortisol concentration (2.74, $p < 0.01$). Participants who delivered PTB at less than 37 weeks of gestation had an above the median 2nd-trimester hair cortisol concentration at 2.3 pg/mg ($r = -.25$, $p < 0.02$). The 2nd trimester hair cortisol concentration was correlated with 16 weeks of gestation measures of Perceived Stress Scale (0.24, $p < 0.02$), Epidemiologic Studies-Depression Scale (0.32, $p < 0.02$), and State–Trait–Anxiety Inventory (0.21, $p < .05$; Hoffman et al., 2016).

Shelton et al. (2015) investigated the relationship between perceived stress, depression, plasma cortisol, and cytokine levels in a group of 2nd trimester pregnant women. The sample consisted of 105 healthy participants aged 18–45 years old, between 16- and 26-week gestation. These researchers used Pearson correlation and hierarchical linear regression to analyze their data. The researchers found elevated plasma cortisol levels ranging between 5.19–43.54. Eight percent of the participants met the criteria of clinical depression. Perceived stress and depressed mood scores were strongly correlated (.56, $\alpha = .01$; Shelton et al., 2015).

Glynn and Sandman (2014) conducted a study on the relationship between placental corticotrophin-releasing hormone and developing postpartum depression. The study population included 170 pregnant women who were less than 16 weeks of gestation when recruited. The study variables consisted of evaluating cortisol and placenta corticotropin releasing hormone levels and administrating the Epidemiologic Studies Depression Inventory scale and the Edinburgh Postnatal Depression Scale. Pearson correlation was used to analyze the data. The researchers found placenta CRH levels at 25, 31, and 36+ weeks' gestation predicted postpartum depression symptoms at 3 months postpartum (0.277 [138]; Glynn & Sandman, 2014).

CRH

Another internal stress mediator frequently investigated in association with PTB is CRH. Some researchers have expressed (Bruce et al., 2001; Smith, 2007) although cortisol decreases CRH in the hypothalamus, it increases CRH in the placenta. Both Bruce et al. (2001) and Smith (2007) indicated hypothalamic CRH is difficult to detect in peripheral circulation even under stressful situations. However, as placental CRH

production increases during pregnancy, the CRH level increases in maternal circulation. There have been mixed reports regarding the associations between stress, CRH, and pregnancy.

Borders et al. (2015) conducted a prospective cohort study to identify the differences in perceived and biological measurements of chronic stress between African American and White pregnant women of similar socioeconomic status. The sample consisted of 100 pregnant women divided equally into Medicaid and private insurance groups. The measures of self-reported stress included the Home Hardships Scale, Household Food Security Scale, Neighborhood Satisfaction Scale, State Hope Scale, Medical Outcomes Study-Social Support Survey, Buffers of Stress Index, Center for Epidemiologic Studies-depression Scale, and the Perceived Stress Scale.

Epstein-Barr virus, C-reactive protein, CRH, and ACTH were used to measure biological stress using enzyme immunoassay. Researchers analyzed the data using students' *t* test and chi-square. The researchers found non-Hispanic White women reported higher buffers against stress ($p < .04$) and increased neighborhood satisfaction *(*$p < .02$). Whereas, Black women reported higher rates of discrimination ($p < .01$), depression ($p < .05$), and food insecurity ($p < .04$). There were no differences in CRH levels between the racial groups (Borders et al., 2015).

Mohamed et al. (2018) evaluated the relationships between vitamin D, placenta corticotropin releasing hormone, and PTB. Samples were obtained from the Nashville Birth Cohort Biobank and consisted of plasma from 79 women between 18–40 years old. Blood samples were acquired when the women were admitted to the hospital for delivery. Personal data collected included age, race, prepregnancy BMI, and medical history. The

statistical methods used were correlation, analysis of covariance, and one-way analysis of covariance. The researchers found there was no demographic differences in birth outcomes. They reported plasma CRH was significantly higher for PTBs 34 weeks or less (397 ± 30 pg/ml, $p < .20$), as compared to later preterm and term births (Mohamed et al., 2018).

Ruiz et al. (2016) investigated the likelihood of CRH predicting PTB among African American and Hispanic women. These researchers recruited 707 women from New York and Texas. The participants were African American and Hispanic women, between the ages of 14–43 years old and 22–24 weeks pregnant. They analyzed the data using unpaired *t* tests and Fisher's exact tests. The researchers reported the median CRH levels were significantly higher for women who had PTB. The median was CRH level was 23 for women delivering at term ($p < .04$; Ruiz et al., 2016).

Transcription Factors

Likewise, there have been investigations of epigenomic, post transcription changes associated with cortisol and CRH during pregnancy. Ross et al. (2019) examined the association between prenatal stress and post transcription expression in the 3rd trimester of pregnancy. The study population sample consisted of 116 women (Latina = 50%; White = 25%; Black = 25%) and the mean age of the women were 26 years old. These researchers found an association between higher levels of stressful life events during pregnancy and higher expression of pro-inflammatory cytokines. These researchers concluded post transcription factors—NF-κB and AP-1—upregulated the expression of cytokines (Ross et al., 2019).

Di Stefano et al. (2015) hypothesized epigenetic modifications triggered by cortisol were up regulating the CRH in the human placenta as pregnancy progressed toward parturition via chromatin remodeling of the CRH gene. In a laboratory experiment, these researchers used human placentas from cesarean section between 37- and 41-weeks' gestation, and mid-trimester placentas between 16- and 20-weeks' gestation, from elective pregnancy terminations to evaluate the chromatin structure transcriptional activities. They performed analyses using successions of cultures with antibodies with subsequent evaluation with western blot, ChIP assays, and reverse transcription quantitative PCRs. They repeated each experiment three times; and they analyzed the data with one-tailed *t* tests to compare control conditions (i.e., histone deacetylase inhibitor) in each group of individual tests. The western blot showed CRH was amplified in response to cortisol exposure. The Western blot analysis also showed enhanced acetylation at H3 lysine 9 (H3K9) in full-term placenta in comparison to mid-trimester cells. The researchers reported the CRH promoter region of H3K9 had acetylation amplification in full-term cells. This was an in vitro experiment of human placenta, trophoblast, which provided vital information about the internal environment of the pregnant uterus. Investigating whether a similar reaction will occur in the blood would increase understanding of PTB and assist in identifying appropriate biomarkers. The finding that CRH increases in response to cortisol exposure in the term, but not 2nd-trimester placentas, was related to histone acetylation. These findings suggest changes in post transcription factors between the 2nd and 3rd trimester of pregnancy (Di Stefano et al., 2015).

Stress and Maternal Mortality

Some studies have reported relationships between stress, birth outcome, and preeclampsia/eclampsia (Chambers et al., 2019; Giurgescu et al., 2015; Yu et al., 2013). Giurgescu et al. (2015) and Chambers et al. (2019) reported Black women were more likely to develop preeclampsia and deliver PTBs. Yu et al. (2013) evaluated the association between perceived stress, chronic hypertension, and preeclampsia among Black and non-Black women at Boston Medical Center. The sample consisted of 4,314 pregnant women who delivered less than 37 weeks of gestation versus those who delivered greater than 37 weeks of gestation. They analyzed the data by using *t* test, chi square, analysis of covariates, and logistic regression. These researchers reported the women with preeclampsia had higher perceived stress, higher BMI, and more preterm deliveries, and were more likely to be Black ($p < .1$). They found the risk for developing preeclampsia increased with stress (OR = 2.1; 95% CI [1.6e2.9]; $p < .0001$; Yu et al., 2013).

Harville et al. (2009) conducted a study evaluating the relationship of cortisol, CRH, psychosocial stress, and PTB. The sample consisted of 1,587 pregnant women over 16 years old, and 20% of the women were Black. The data were analyzed by correlation, *t* test, one-way analysis of covariance, linear regression, and hierarchical linear models. The results showed higher stress levels were associated with reduced cortisol or CRH levels. CRH is the strongest predictor of preeclampsia. Cortisol was highest in nulliparous young women.

MacDorman et al. (2021) conducted a study to examine the ethnic and racial inequities in the U.S. maternal mortality rate and identify the leading causes. They used

death certificates retrieved from the National Vital Statistic System. They analyzed the data by comparing maternal mortality rate by ethnicity and race. They used risk ratios to determine the differences in maternal mortality rates, and the leading causes for mortality in non-Hispanic Black and White women. These researchers reported the non-Hispanic Black women mortality rate was 3.6 times higher than the rate for non-Hispanic White women. These researchers reported embolism, eclampsia, and preeclampsia as leading causes of mortality for the general population. However, eclampsia and preeclampsia were the leading cause of mortality for non-Hispanic Black women.

Singh (2021) evaluated the pattern of maternal mortality based on race, sociodemographic characteristics, marital status, maternal education, and immigration status. They analyzed National Vital Statistic System data from 1969–2018. They analyzed the data by pooling 5 years of demographic information. They used a log-linear regression model to determine maternal mortality by race and socioeconomic status and relative risk ratios to calculate disparities in maternal mortality. Although the overall population maternal mortality rated declined, the risk remained 2–5 times higher for Black women than White women. They reported college educated non-Hispanic Black women had a significantly (i.e., 4 times) higher maternal mortality rate than non-Hispanic White women without a high school diploma. They reported the overall leading cause of maternal mortality was hemorrhage, hypertension, embolism, infection, and other medical conditions. Maternal mortality from eclampsia and preeclampsia was 3 times higher for non-Hispanic Black women than non-Hispanic White women.

Mesner et al. (2019) used a machine learning algorithm to analyze data from a secondary dataset from which they reported several relationships. They reported

relationships between Hispanic women, pregestational diabetes, and PTB ($p < .05$), and they reported relationships between hair cortisol, CRH, preeclampsia, and PTB for Black women ($p < .01$).

Discussion of Gap in Knowledge Base and Links to Caring Science

The gap in knowledge identified in this literature review indicates the need for additional exploration of the relationship between increased cortisol availability, elevated CRH, and transcription factors in circulating maternal plasma. The increased availability of cortisol may be related to increased glucocorticoid receptors (GRs) and histone acetylation, which stimulates the placenta to produce more CRH in non-Hispanic Black women (see Figure 1). As mentioned earlier, Di Stefano et al. (2015) found increased histone acetylation in the term placenta than in the 2nd trimester placenta. Therefore, increased post transcription factor, HATs presence in the 2nd trimester instead of the 3rd trimester may be inducing early labor. Identifying whether histone acetylation of the CRH gene is present in the 2nd trimester circulating maternal blood could add to the previous findings.

This study explored this knowledge gap by comparing the differences between non-Hispanic Black and non-Hispanic White women in perceived stress, depression, GRs, and histone acetylation of CRH gene in their 2nd trimester of pregnancy. The 2nd trimester is the period of many spontaneous PTBs. The proposed indicators of health inequity measured in this study included race, perceived stress, depression, GR, and acetylation of the CRH gene.

The knowledge gained from this study could strengthen the call for nursing care for women at risk for PTB. The chronic stress emotion theory is relevant to evaluating

women's perception of stress and understanding factors that were antecedents to poor coping and the cellular changes that may occur. Pregnancy is a time of transition in a woman's life; the addition of stressful life events could require special coping skills and support that nurses could provide. Understanding the reciprocal nature of person–environment–health interactions could also provide nurses with the knowledge necessary to advocate for social policies to optimize healthy growth, development, and healing.

Summary

Differences in health outcomes favoring a more advantaged social group over a less advantaged social group have been linked to the social and economic systems embedded in society (IOM, 2003). The nursing discipline's commitment to caring obligates nurses to explore the sociopolitical factors that interfere with the health and well-being of population groups. The social determinants of health, such as race, socioeconomic status, access to quality education, and access to quality housing, interfere with the health and well-being of marginalized population groups. Therefore, it is essential nurses explore ways to transform the sociopolitical structure to improve health equity by advocating for changes in social policy. The social policies that will improve education and employment, for example, providing a supportive, nurturing environment for all population groups, thus allowing people to thrive and attain their highest level of health.

The disproportional differences in PTBs between Black and White women in the United States have not been explained by maternal characteristics such as socioeconomic status, parental income, health insurance, or education (Braveman et al., 2015; Chambers et al., 2019). Additionally, differences in PTB have not been explained by health or

behavioral risk factors such as previous PTB, diabetes, infection, mental illness, smoking, drugs, or alcohol dependence (Chambers et al., 2019; DeSisto et al., 2018).

Exploring the role of the stress response and chronic activation of the HPA axis during pregnancy provides another pathway to understanding differences in PTBs between population groups. Black women have reported experiencing stressful situations with racism, lack of social support, distress about neighborhood conditions, and financial distress (Alhusen et al., 2016; Giurgescu et al., 2013; Grobman et al., 2018; Sealy-Jefferson et al., 2016; Slaughter-Acey et al., 2016). Some researchers have reported Black women were more likely to report experiencing maternal stress and PTB than White women (Braveman et al., 2017; Manuck et al., 2015). Other researchers have reported finding a positive relationship between perceived stress, cortisol, and PTB (Duffy et al., 2018; Gillespie et al., 2017; Hoffman et al., 2016). Additionally, other investigators have studied the effect of perceived stress, cortisol, and proinflammatory cytokines on PTB, and found increased levels, but some did not (Giurgescu et al., 2015, 2016; Kramer et al., 2013). Whereas other studies have found stress significantly increased proinflammatory cytokines during pregnancy (Catov et al., 2015; Corwin et al., 2013; Gillespie et al., 2016).

Some researchers have reported the association between depression and elevated cortisol among pregnant women (Giurgescu et al., 2015; Shelton et al., 2015). African American pregnant women have reported experiencing more stress, anxiety, and depression than White women (Christian et al., 2013). Glynn and Sandman (2014) described a relationship between prenatal CRH levels and postpartum depression.

Another internal stress mediator frequently investigated in association with PTB was CRH. Border et al. (2015) reported no differences in CRH levels between African American and White women. Nevertheless, other investigators have found a positive association between CRH and PTB (Kramer et al., 2013; Mohamed et al., 2018; Ruiz et al., 2016). Additionally, Ruiz et al. (2016) concluded CRH was a significant predictor of PTB among African American women.

There have been investigations of epigenomic, post transcription changes associated with cortisol and CRH during pregnancy. Some researchers have found proinflammatory transcription factors, NF-κB, and AP-1 had increased activity in women who experienced stressful life events during pregnancy (Ross et al., 2019). Whereas Di Stefano et al. (2015) found there was histone acetylation in the promoter region of the CRH gene only in term placentas.

An evaluation of the variables associated with the pathway of increased cortisol availability, elevated maternal CRH, and post transcription factors could assist in elucidating greater understanding of this PTB. Probabilistic epigenesis has posited the involvement of molecular activities, whereas the chronic stress emotions theory purports poor health outcomes are related to a chronically stressful social environment. Nursing as caring theory has recognized the nuances of a nurturing relationship in developing a more equitable healthcare system.

The chronic stress epigenomic adaptation model is defined as an individual's personal resources, coupled with the appraisal of their social environment, chronic stress reactions, which lead to adaptive biopsychosocial outcomes (Gottlieb, 2007; Peters, 2006). This model theorizes there is a relationship between a woman's social

environment and her psychological and physiological responses during pregnancy. When a person lives in a state of chronic stress, their cortisol does not shut off as in the case of acute stress (McEwen, 2017a). When a woman is exposed to chronic emotional stressors, she responds physiologically by increasing her cortisol and CRH levels. The increase of these stress hormones leads to an increase in genomic post transcription factors such as HATs and GRs. The increased availability of cortisol results in increased production of CRH in the 2nd trimester of pregnancy. Such a situation may become calls for nursing. Nurses use multiple patterns of knowing to answer the call in a nursing situation. In the context of the situation, the nurse comes to know the person as living, thereby caring and recognizing the sociopolitical factors influencing the person's health. Nurses can contribute to the transformation of the sociopolitical structure by advocating for healthcare policies to promote health equity and enhance the health and well-being of communities.

CHAPTER 3: RESEARCH METHODOLOGY

The purpose of this study was to evaluate differences in perceived stress, depression, and epigenomic modification of the corticotropin-releasing hormone (CRH) gene between non-Hispanic Black women and non-Hispanic White women in their 2nd trimester of pregnancy. This study analyzed data collected from a repository of cells from pregnant and postpartum women (M. Groer, personal communication, 2016). This chapter describes the design and procedures used in conducting this study. It gives details of the research design, research question, population, sampling procedures, setting, data collection protocol, measures, and data analysis method.

Research Question

The research question used in this study asked, is there a difference between Black and non-Hispanic White women in perceived stress, depression, glucocorticoid receptors (GRs), and histone acetylation of the CRH gene in their 2nd trimester of pregnancy?

Hypotheses

Hypothesis 1

Hypothesis 1 stated non-Hispanic Black women will have a significantly higher level of perceived stress than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by the Perceived Stress Scale.

Hypothesis 2

Hypothesis 2 stated non-Hispanic Black women will have a significantly higher level of depression than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by the Profile in Mood Depression scale.

Hypothesis 3

Hypothesis 3 stated non-Hispanic Black women will have a significantly higher expression of GRs then non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by chromatin immunoprecipitation (ChIP) to quantitative Polymerase chain reaction (qPCR) analysis.

Hypothesis 4

Hypothesis 4 stated non-Hispanic Black women will have a significantly higher expression of histone acetylation of the CRH gene than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by ChIP–qPCR analysis.

Hypothesis 5

Hypothesis 5 stated non-Hispanic Black women will have a significantly higher expression histone acetylation of the CRH gene than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age and the quantity of GRs as measured by ChIP–qPCR analysis.

Research Design

This study was a secondary analysis using a cross-sectional research design to describe differences in perceived stress, depression, GRs, and histone acetylation of the CRH gene between non-Hispanic Black women and non-Hispanic White women in their

2nd trimester of pregnancy. This design compared two groups, with the predictor variables being non-Hispanic Black women and non-Hispanic White women and the outcome variables being perceived stress, depression, GRs, and histone acetylation levels. It was important for the study samples to be as similar as possible in all variables except those under study. This study was designed to determine if the groups were the same or different on specific characteristics.

Description of Parent Study

The data used to conduct this study were from a metadata repository and cells connected to an NIH R01 parent grant number NR005000 (i.e., influence of lactation on postpartum stress and immunity). When the grant was renewed, a proposal was made to create a repository of cells study. The study aimed to establish a repository of peripheral blood mononuclear cells (PBMC) collected from healthy pregnant and postpartum women. The University of South Florida (USF) Institutional Review Board (IRB) approved the storing of surplus plasma cells collected as part of for participants agreeing to future analysis (M. Groer, personal communication, 2016). The purpose of the parent study was to screen for thyroid disorder, so the thyroid peroxidase antibody was measured in all pregnant women. The parent study consisted of 247 pregnant women, ages 18–45, from two prenatal clinics connected to an extensive university practice in the southeastern United States (M. Groer, personal communication, 2016). Researchers had to apply for USF IRB approval to access the plasma cells and metadata file maintained by the USF College of Nursing.

The parent study principal investigator (PI) and USF signed a Pre-Approved Material Transfer Agreement (see Appendix A) with Florida Atlantic University (FAU)

and this investigator for access to the deidentified questionnaires and PBMC data. FAU IRB approved this study. The approval notification was sent to the parent study PI and USF for the release of the data. A copy of the FAU IRB approval letter has been maintained on a file of the parent study (M. Groer, personal communication , 2016).

Data Collection

Study participants were recruited from a university obstetrics practice, a Genesis clinic, and a county health department. The participants were identified by their physicians, nurses, or midwives and informed about the study. If interested, the participants were pre-consented by the nurse researcher by providing them with consent forms and answering questions (M. Groer, personal communication, 2016).

At their next prenatal visit, the participants signed consent forms and completed a demographic survey and questionnaires and provided blood samples obtained by venipuncture between November 2007–December 2010. The data collected consisted of the participants' age, race/ethnicity, marital status, education, income, perceived stress scale, mood state profile scale, and PMBCs of women in the 2nd trimester of pregnancy.

Sample

Inclusion Criteria. The participants of the parent study were included in the sample if they were between 16–26 weeks of gestation and between the ages of 18–45.

***Exclusion Criteria*.** The women were excluded from the parent study if they (a) had any chronic diseases; (b) had a BMI less than 20; or (c) were currently on mood altering, immunosuppressive, or hormone medications. Other criteria for exclusion were alcohol use, drug abuse, and mental illness. Women who did not sign consent for future studies were also excluded (M. Groer, personal communication, 2016).

Plasma Storage Procedure

The plasma cells were extracted from 15 mL of blood; the sera were separated, preserved in DMSO, and stored at -80º C in liquid nitrogen until tested (M. Groer, personal communication, 2016). The samples were monitored with a continuous monitoring thermometer and the temperature documented. The College of Nursing biobehavioral laboratory technician staff maintained the liquid nitrogen tanks for levels and temperature. The other data were stored on a G drive as a password-accessible file (M. Groer, personal communication, 2016).

Measures

The Perceived Stress Scale. The Perceived Stress Scale (PSS; see Appendix B) was developed to measure self-reported stress over the previous 8 weeks. It is a 14-item instrument constructed to discover the extent an individual may find their life unpredictable, uncontrollable, and overloaded, including the current stress levels. The PSS scale measures stress on a Likert scale from 0 (*never*) to 4 (*very often*). The measure was designed to be receptive to stressful future events and reactions to specific events (Cohen et al., 1983). The PSS was initially tested in two colleges and one community program setting. The scale has subsequently been used extensively across many racial and income groups. The instrument was created for participants with at least a seventh-grade level of education. It was reported to have internal reliability coefficients of .84, .85, and .86, and test–retest reliability between .55–.85 for the three groups. The PSS also showed evidence of concurrent and predictive validity with correlations varying from .14–.76 with life events, depression, and anxiety (Cohen et al., 1983).

Scoring. The scores for this instrument range from 0–56, with 0 being no stress and 56 indicating the highest stress level.

The Profile of Mood States Scale. The Profile of Mood States (POMS; see Appendix C) Scale is a 65-item instrument that assesses multiple aspects of emotional states. The instrument measures seven feeling states of anxiety, anger, fatigue, depression, confusion, friendliness, and happiness (Norcross et al., 1984). The POMS Scale contains 65 adjectives that depict moods that can be rated on a 5-point Likert scale with a score ranging from 0 (*not at all*) to 4 (*extremely*). The POMS is reported to have internal validity correlations of .83 and .85 with a stable factorial structure, which explains a high amount of the total variance. The scale was reported to have a high coefficient alpha between .92–.91 (Norcross et al., 1984).

Scoring. The scores for this instrument range from 0–260, with 0 being the low and 260 the high score. Depression was a subscale of the POMS consisting of 15 items that described dejection. The depression scale scores ranged from 0 = *Not at all*, 1 = *A little*, 2 = *Moderate*, 3 = *Quite a bit*, and 4 = *Extremely*. The maximum score on the depression scale is 60.

Measurement of GRs and Histone Acetylation by Chromatin Immunoprecipitation

Chromatins consist of DNA complexes wrapped around a core of two sets of four histone proteins (i.e., histone 2A, H2A; histone 2B, H2B; histone 3, H3; and histone 4, H4). Nucleosomes are repeating units of chromatins. The nucleosomes are structured like beads on a string forming chromatin fibers, and when condensed, become chromosomes (Luger et al., 2012). Acetylation of the histone tails enables the chromatin structure to open and allow access to transcription factors causing gene activation (Vettese-Dadey et

al., 1996). Morales and Richard-Foy (2000) reported acetylation of Histone 3 and 4 (i.e., H3 and H4), N-terminal histone tails increased the accessibility of transcription factors, such as the GR to the DNA and provided the pathway for posttranscription modification of the DNA structure.

Immunoprecipitation (IP) is a laboratory technique used to measure the interactions between proteins and DNA inside the cell (Collas, 2010). The purpose of chromatin immunoprecipitation (ChIP) is to determine the presence of chromatin associated proteins at a particular genomic site. The process involves fragmenting the chromatin and pulling it out of the solution with a specific antibody to identify the protein that binds to the DNA. This IP process isolates and concentrates a specific protein/DNA complex for analysis.

The ChIP assay can be analyzed by PCR, qPCR, microarray, or sequencing to identify the DNA sequence associated with the protein. DNA sequencing is a molecular method used to analyze the interactions between DNA, proteins, and transcription factors in the genome (Kidder et al., 2011). ChiP sequencing can identify regions of the genome associated with specific transcription factors. A qPCR measures the expression of specific genomic material in a sample (Kaung et al., 2018). The qPCR measures cycles of DNA amplification of the ChIP DNA assay using a fluorescent dye and a thermocycler with a fluorescence-detection system. Therefore, ChiP to qPCR were used to identify the following:

- The presence of GRs receptors at the promotor region of the CRH gene.
- The presence of histone acetylation at H3K9 of the CRH gene promoter region.

Procedures for Measuring GRs and Histone Acetylation. This researcher contracted with Active Motif, a commercial laboratory, to analyze the PBMCs. Active Motif has provided products and services for epigenetics and gene research for over 20 years. After IRB approval, this researcher arranged to meet with the parent study PI at the USF College of Nursing Biobehavioral Laboratory in Tampa to retrieve the PBMC samples, pack them on dry ice, and ship them overnight to the Active Motif lab. Federal Express notified the investigator of the PBMC arrival to Active Motif. This researcher emailed the lab manager and verified the PBMC samples had arrived at their lab.

One hundred and two specimens were selected by choosing sample numbers from a list and submitting them in five groups to the Active Motif lab. Before proceeding with the ChIP to qPCR analysis, the lab quantified the chromatin yield of two pilot samples. The cells were fixed with a 1% formaldehyde solution made from a commercially available 37% stock (i.e., Sigma #F-8775), immediately after the spin down to ensure crosslinking of the proteins to the DNA. The chromatin yields for the two pilot samples were 20 and 52 µg. Next, the lab performed ChIP reactions using 15 µg of the PBMC chromatin and 6 µg of antibody (i.e., Active Motif, cat # 39917) from the two pilot samples. They performed qPCR analyses using a positive control primer (GAPDH–TAGGCGCTCACTGTTCTCTC; CGTTGACTCCGACCTTCAC) and primers for the promoter region of the CRH and NR3C1 (G.R.) genes. A negative control primer pair that amplifies a region in a gene desert on chromosome 12 (i.e., Untr12 Human negative control primer set 1 Active Motif catalog number 71001) was also performed.

The analysis found the chromatin was good quality, and the ChIP to qPCR reactions worked well. However, they did not notice strong signals or enrichment of the

CRH promoter. As that analysis was only on the two pilot samples, the researcher and advisor met with the lab team and decided to proceed with analyzing 10 samples.

Ten samples were randomly selected by using an online random number generator. Only this researcher had access to any other information about the selected samples. The chromatin yields for this sample of 10 varied from 5 µg to 130 µg. The Active Motif lab analyzed 10 samples because they understood the antibody reacted with a minimum of 5 ug of chromatin. H3K9Ac (i.e., histone acetylation of octamer 3K9) ChIP–qPCR assay was performed on the 10 samples using 10 µg of human PBMC chromatin and 5 µg of antibody (i.e., Active Motif, cat # 39917). The qPCR analysis was performed using both positive and negative control primer pairs and primers for the promoter region of the CRH and NR3C1 genes, as previously mentioned. Although the chromatin quality was good and the ChIP reactions worked, amplification at the NR3C1 gene was weak, and the H3K9 acetylation of the CRH gene promoter was not present.

Members of the Active Motif lab and the researchers convened again to discuss how to proceed. The lab team offered their sequencing service to determine the regions in the CRH gene and GR gene suitable for primer design. Subsequently, the lab combined the 10 samples and performed a ChIP assay using the pooled chromatin. They extrapolated 30 ug of chromatin yield and precleared it with A agarose beads (i.e., Invitrogen, catalog number 15918014). The genomic DNA regions of interest were isolated using 5 ug of antibody against H3K9Ac (i.e., Active Motif, cat #: 39917, lot #: 28720006). qPCR reactions were carried out in triplicate on specific genomic regions using SYBR Green Supermix (Bio-Rad). To identify ideal locations for qPCR primer design, an Illumina sequencing library from the ChIP DNA of one sample was prepared

using an automated system (i.e., Apollo 342, Wafergen Biosystems/Takara). The library was quantified and sequenced on Illumina's NextSeq 500 (i.e., 75 nt reads, single end). Sequence data passed Illumina specifications. The 29 million mapped reads analysis identified 22,982 peaks with a fraction of reads in peaks score of 0.16. Visualization of the data in genome browsers showed strong peaks at the expected locations (i.e., > 50% in promoters) and with the typical H3K9Ac profiles.

The Active Motif senior bioinformatician analyzed the sequenced data of the H3KAc (i.e., histone acetylation of octamer 3K) and discovered the primer they used for NR3C1 (GR) was too much upstream the five prime end (5') end of the DNA coding strand. However, the CRH promoter appeared not to be active. The lab team designed a new set of primers based on peaks identified from the H3K9Ac sequencing data and tested them using the pooled ChIP DNA. Primer pair NR3C1 +211 (GTGCTTCCGTTGGACACATG; CCAAATCACTGGACCTTAGAAG) showed the highest signals for the GR. They also designed new primer pairs for the CRH gene and found primer pair CRH-1441 (GAGGAGGTGGAAGGTGAGATC; GAGGCACCGGAGAGAGAAAG) amplification had signals above background. Active Motif analyzed another batch of 10 samples using the new primer pairs based on these results.

The lab prepared 20 samples for ChIP assay, but I.P. was only performed for 17 samples using 10 ug chromatin, and one was done with 5ug. Two samples had chromatin yield below 5ug. Next, the lab completed ChIP–qPCR analyses on the second group of 8 samples (2 samples were below 5 ug) using the 10 ug chromatin and 5 µl of antibody per

I.P. and the new primers. The data revealed differences in acetylation at the GAPDH and NR3C1 genes, but the signaling was similar for all samples at the CRH gene.

With the results of the eight samples, the researchers decided to continue the analysis of the other 92 samples. After completing approximately 30 ChIP–qPCR reactions, the lab discovered the Agarose A beads used for the assay were discontinued and recommended using Agarose G beads instead. Before converting to the G beads, the lab compared three types of beads (i.e., protein A, protein G, and Sepharose). The lab reported the Agarose G beads worked as well as the A beads. They also compared two ChIP reactions to agarose A and G beads using a sample from the current study. The results of this experiment showed the signals were the same in both I.P.s of all three genes of interest (i.e., GAPDH, NR3C1, and CRH). Based on these results, the lab used the 20 remaining Agarose A beads and switched to the B beads to complete the other 72 samples. The lab delivered the data in five Microsoft Excel spreadsheets and one spreadsheet showed which reactions received protein A versus protein G beads, samples that had too little chromatin, or instances where we had to use less chromatin in the reactions.

The following is the Active Motif protocol used to analyze the PBMCs:

1. Active Motif crosslinked samples with 1% formaldehyde (i.e., Sigma, F-8775) for 15 minutes and quenched with 0.125 M glycine (i.e., Sigma, G-7403).
2. Chromatin was isolated by adding a lysis buffer, followed by disruption with a Dounce homogenizer. The DNA was sheared to an average length of 300–500 bp with Active Motif's EpiShear probe sonicator (53051) and cooled sonication platform (53080).

3. Genomic DNA (i.e., Input) was prepared by treating aliquots of chromatin with RNase (i.e., Sigma, R6513), proteinase K (i.e., Sigma, P-6556), and heat for de-crosslinking, followed by ethanol precipitation.
4. Pellets were resuspended, and the resulting DNA was quantified on an Invitrogen Qubit 4 Fluorometer (i.e., Invitrogen, Q33238). Extrapolation to the original chromatin volume allowed quantitation of the total chromatin yield.
5. Aliquots of chromatin (25 ug) were precleared with protein A agarose beads (i.e., Invitrogen).
6. Genomic DNA regions of interest were isolated using 4 µl of an antibody against H3K9Ac (i.e., Active Motif, 39917).
7. Complexes were washed, eluted from the beads with SDS buffer, and subjected to RNase and proteinase K treatment.
8. Crosslinks were reversed by incubation overnight at 65° C, and ChIP DNA was purified by phenol–chloroform extraction and ethanol precipitation.
9. qPCR reactions were carried out in triplicate on specific genomic regions of the *CRH* gene using SYBR Green Supermix (i.e., Bio-Rad).
10. The resulting signals were normalized for primer efficiency by carrying out qPCR for each primer pair using input DNA.
11. The data were represented as binding events detected/1000 cells.
12. A successful ChIP reaction had a minimum of 5-fold higher signal with a positive control site as compared to a negative control site.

13. Active Motif delivered the results report and a Microsoft Excel spreadsheet showing raw data for ChIP reactions and input. Data are also presented in another sheet as normalized data which are presented as a bar graph.
14. Active Motif Lab will store the remaining materials, such as extra samples shipped or chromatin left over, for 2 years.

Ethical Considerations

This investigation used questionnaire data and PBMC cells from a repository of cells from pregnant women who participated in a previous study (M. Groer, personal communication, 2016). This investigator obtained FAU IRB approval to use the plasma and other secondary data from the parent study for the current study. Upon obtaining the FAU IRB's approval, a letter was sent to the principal investigator of the repository for the release of the PMBC samples and other data. The specimens were sent directly to the Active Motif laboratory for analysis. The rest of the data were transferred electronically to this investigator and was stored on the university's Biomedical Health Research Informatics Core (BHRIC), a secured system managed by the Office of Information Technology at the College of Nursing. Only the student investigator and her advisor can access any of the data.

Risks

This study was conducted on peripheral blood cells from a deidentified data repository. The most significant risk to the participants would be a breach of confidentiality. All data files will be maintained in the BHRIC with a password accessible only by the investigator to safeguard the participants' confidentiality for 7 years.

Benefits

There was no direct involvement with human participants; only secondary, deidentified data were used in this study. The knowledge obtained from this study may provide information to assist health professionals in better understanding the prevalence of maternal mortality and preterm birth (PTB) outcomes.

Sampling Method

The sample consisted of deidentified data from a secondary data set and a repository of cells. The sample size was calculated using G-power Version 3 computer software (Faul et al., 2009). The G*power was conducted using the linear fixed model algorithm based on a medium effect size of 0.50, a power of 80%, four predictor variables, and a significance level of 0.05. A sample of 102 participants was determined as an appropriate size to address the research questions.

The sample for this study was obtained from secondary data of PBMC cells and other data. The secondary data set consisted of age, race, education, income, perceived stress scale, mood state profile depression-dejection scale, and PMBCs of women in their 2nd trimester of pregnancy. This investigator selected all 29 non-Hispanic Black participants, and randomly selected 73 of the non-Hispanic White participants from the remaining 136 participants. The non-Hispanic White participants were selected by using a random sampling approach. This investigator divided the non-Hispanic White sample participants (i.e., 136) by the number needed for the current study (i.e., 73), which equaled 2. The selection process began by randomly selecting the first participant from a table of numbers, and after that, every other participant was selected.

Inclusion Criteria

The participants for this study were based on race/ethnicity—non-Hispanic Black and non-Hispanic White—and the volume of PBMCs' cells available for 5 years. The parent study divided the PBMCs by putting 1–2 million cells per aliquot. The parent study PI selected aliquots with the most cell volume (M. Groer, personal communication, February 12, 2020).

Exclusion Criteria

In addition to parent study exclusion criteria, women from ethnic or racial groups other than non-Hispanic Black and non-Hispanic White were excluded from this study.

Informed Consent Process

This study used secondary data obtained from a repository at USF. The parent study reported participants completed consent for their data to be used in the future.

Data Collection Procedures

In the parent study, participants completed a demographic survey, pregnancy history, the PSS, and the POMS scale. The blood samples were collected by venipuncture after the participant completed the questionnaires (M. Groer, personal communication, 2016).

Data Analysis

The sample for this study was obtained from an existing data set of women from two prenatal clinics connected to an extensive university practice in the southeastern United States who volunteered to participate. Therefore, this sample population was acquired from a secondary data source and repository of cells. The secondary data set consisted of the age, race, education, income, PSS, POMS profile, depression-dejection

scale, and PMBCs of women in the 2nd trimester of pregnancy. The data were analyzed using descriptive statistics, Pearson correlation, and analysis of covariance.

Inferential Statistics

The independent variable for these hypotheses was race/ethnicity, and the dependent variables were perceived stress, depression, GRs, and histone acetylation of the CRH gene. Data analysis began with preparatory activities such as treating missing data, identifying outliers, and doing other such data cleaning tasks. A detailed descriptive analysis of all quantitative data was performed, involving the summarization of data and inferential and graphical exploratory data analytic techniques.

The first phase of the analysis consisted of using descriptive statistics in computing the summary measures (i.e., mean, median, standard deviation, and range) for the PSS and POMS profile variables were measured on interval or ratio scales, and frequency distributions (i.e., absolute frequency and percent) for age. BMI variables were measured on nominal or ordinal scales. A linear model will explain the relationship between perceived stress, depression, GRs, and histone acetylation. Therefore, the one-way analysis of covariances (ANCOVA) was used to analyze the relationships between perceived stress, depression, GRs, and histone acetylation of the CRH gene of non-Hispanic Black women and non-Hispanic White women in their 2nd trimester of pregnancy. The ANCOVA was used to examine the interaction effects of GRs and histone acetylation between the non-Hispanic Black women and non-Hispanic White women while controlling for age. The ANCOVA will provide a more accurate estimate of the differences among groups by controlling for the extraneous variable. All statistical analyses will be carried out using SPSS Version 28.

The potential threat to internal validity was history because any unexpected event occurring when the data were collected may affect the study outcome. An unexpected event could be the possibility of hurricanes or other environmental conditions competing with the independent variable for explaining the outcome of the study. Other possible threats to internal validity were the extraneous variable of all participants in this research project being volunteers and the sensitivity and specificity of the laboratory test.

Significance level. The significance level was set at a *p* value equal to or less than 0.05 and a confidence interval of 95%.

Type I error. Bonferroni correction was used to reduce the chances of obtaining type I error. With the *p* value set at .05, there was an increased risk of committing type I error of rejecting the null hypothesis when it is true because it was less stringent than the .01 level of significance. Therefore, a Bonferroni correction was performed. The 0.05 critical *p* value (α) was divided by the number of comparisons in this study, which was four. So, the new critical *p* value was α divided by 4, which equaled 0.01.

Summary

This chapter describes the design used in conducting this study. It provides details of the research design, research question, hypotheses, population, sampling procedures, and data analysis method. The study used a cross-sectional design to describe differences in perceived stress, depression, GRs, and histone acetylation of the CRH gene between non-Hispanic Black women and non-Hispanic White women in their 2nd trimester of pregnancy. This design compared two groups, with the predictor variables being non-Hispanic Black women and non-Hispanic White women and the outcome variables being perceived stress, depression, GRs, and histone acetylation levels. This study used

secondary data consisting of the PSS, POMS scale, and PBMCs (M. Groer, personal communication, 2016). The ChIP–qPCR technique was used to analyze the PBMCs. Descriptive statistics were used to summarize the data, Pearson correlation measured relationships, and ANCOVA to test the five hypotheses.

CHAPTER 4: RESULTS

This cross-sectional descriptive study aimed to evaluate differences between non-Hispanic Black and non-Hispanic White women in perceived stress, depression, and modifiable epigenomic changes modifying the corticotropin-releasing hormone (CRH) gene in their 2nd trimester of pregnancy. In this chapter, the results of the data analysis are presented.

This study used secondary deidentified data from a repository on pregnant women (M. Groer, personal communication, 2016). This study evaluated the difference between non-Hispanic Black and non-Hispanic White women in perceived stress, depression, glucocorticoid receptors (GRs), and histone acetylation (HAT) of the CRH gene in their 2nd trimester of pregnancy. The descriptive statistics on the demographic characteristic of the sample are presented, followed by the analysis of each of the five research hypotheses.

Research Question

What is the difference between non-Hispanic Black and non-Hispanic White women in perceived stress, depression, GRs, and HAT of the CRH gene in their second 2nd trimester of pregnancy? The following five hypotheses were generated and tested to answer this research question.

Hypothesis 1

Non-Hispanic Black women will have a significantly higher level of perceived stress than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by the Perceived Stress Scale.

Hypothesis 2

Non-Hispanic Black women will have a significantly higher level of depression than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age as measured by the Profile in Mood Depression Scale.

Hypothesis 3

Non-Hispanic Black women will have a significantly higher expression of GRs than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age, as measured by chromatin immunoprecipitation (ChIP) to quantitative polymerase chain reaction (qPCR).

Hypothesis 4

Non-Hispanic Black women will have a significantly higher expression of histone acetylation of the CRH gene, than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age, as measured by ChIP to qPCR analysis.

Hypothesis 5

Non-Hispanic Black women will have a significantly higher expression histone acetylation of the CRH gene than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age and the quantity of GRs, as measured by ChIP to qPCR analysis.

Demographic Characteristics

Table 2 shows the analysis of the demographic characteristics of the sample. The sample population consisted of 105 women, 72% White (n = 73) and 31% Black (n = 32). The women were between the ages of 18–44, with a mean age of 29 (SD = 6). There was a significant difference between the groups in age and body mass index (BMI; $p > .01$). The White participants' minimum age was 18, and their maximum age was 44. Black participants' minimum age was 18 and the maximum age was 36. One hundred and three (n = 71 White and 32 Black) participants reported their BMIs. The mean BMI for the sample was 27 (SD = 7). The mean BMI for the White participant was 26, with a minimum of 18 and a maximum of 46. The mean BMI for the Black participants was 31, with a minimum of 21 and a maximum of 46.

Table 2

Descriptive Data by Race Depression Stress GR and HAT CRH

Variable	White					Black					Total		Between group difference	
	N	*M*	*SD*	Min	Max	*N*	*M*	*SD*	Min	Max	*N*	*M*	*SD*	*p*
Age	73	30	5.9	18	44	32	26	5.4	18	36	105	29	6.0	.01
BMI	71	26	6.3	18	46	32	31	7.3	21	46	103	27	6.9	.01
Stress	73	20	6.9	8	43	32	23	8.4	7	45	105	21	7.4	.08
Depression	73	4.5	8.0	0	46	32	5.7	9.1	0	49	105	4.8	8.3	.50
GR	69	8.0	5.3	0.3	24	28	8.3	5.2	0.6	23	97	8.0	8.0	.81
HAT CRH	69	1.3	0.6	0.1	2.8	28	1.5	0.8	0.1	2.9	97	1.4	0.7	.15

Note. GR = Glucocorticoid receptor; HAT CRH = Histone acetylation of CRH gene.

The mean stress score for the White participants was 20 (*SD* = 6.9). The White participants' stress scores ranged from 8–43. In comparison, the Black participants' mean stress score was 23 (*SD* = 8.38). The Black participants' stress scores ranged from 7–45. There was no significant difference between the groups in stress scores ($p > .08$). The mean depression score for the White participants was 4.48 (*SD* = 7.95), and the range was 0–46. In comparison, the Black participants' mean depression score was 5.66 (*SD* = 9.15), ranging from 0–49. There was no significant difference between the groups in depression scores ($p > .50$).

Nine peripheral blood monocyte samples could not be analyzed due to low chromatin yields. The sample size for the analyzed histone acetylation (HAT) of the CRH gene and GR was decreased to 96 (*n* = 68 White and 28 Black participants). The mean GR score for the White participants was 7.91 (*SD* = 5.28), ranging from 0.34–23.45. In comparison, the mean GR score for the Black participants was 8.28 (*SD* = 5.24), and the range was between 0.55–23. There was no significant difference between the groups in GR score ($p > .81$). The mean HAT of the CRH gene score for the White participants was 1.29 (*SD* = 0.63), and the range was from 0.10–2.81. The mean HAT of the CRH gene of the Black participants was 1.52 (*SD* = 0.77), ranging from 0.13–2.87. There was no significant difference between the groups in HAT of the CRH gene ($p > .15$). As shown in Table 3, over 40% of the participants did not report some aspects of their demographic information. Overall, 41% of the participants did not report their education, 47% did not report their income, 41% did not report their marital status, and 59% did not report their history of smoking. Therefore, the education, income, marital status, and smoking

variables were omitted from the analysis to decrease the likelihood of distorting the findings.

Table 3

Missing Descriptive Data

Variable	White		Black		Total	Total	Total
	n	%	*n*	%	*n*	%	% missing
Education	48	66	14	44	62	59	41
Income	43	53	13	40	56	53	47
Marital status	48	66	14	44	62	59	41
Smoking	31	43	12	38	43	41	59

Figure 3 provides a boxplot visualization of the difference in the distribution of stress between groups. After excluding two outliers from the White group, and one outlier from the Black group, the score range was wider for the Black participants than for the White participants ($n = 30$ and $n = 24$, respectively). The median was larger at 24 for the Black group compared to 18 for the White group. The middle 50% of the score for the Black group was 17–27, so the interquartile range (IQR) was 10. In contrast, the middle 50% of the score for the White group was 16–24 with an IQR of 8. Therefore, the Black group showed more variability and higher stress scores than the White group.

Figure 3

Simple Boxplot of Stress by Race

Figure 4 is a boxplot visualization of the difference in the distribution of depression between groups. After excluding outliers, the range of scores was wider for Black participants (n = 15) than for White participants (n = 12). The Black group had a higher median at 8, and the White group's median was 5. The middle 50% of the score for the Black group was 0–8, so the IQR was 8. In contrast, the middle 50% of the score for the White group was 0–5 with an IQR of 5. Therefore, the Black group showed more variability than the White group. When outliers were excluded, the White group had lower depression scores than the Black group.

Figure 4

Simple Boxplot of Depression by Race

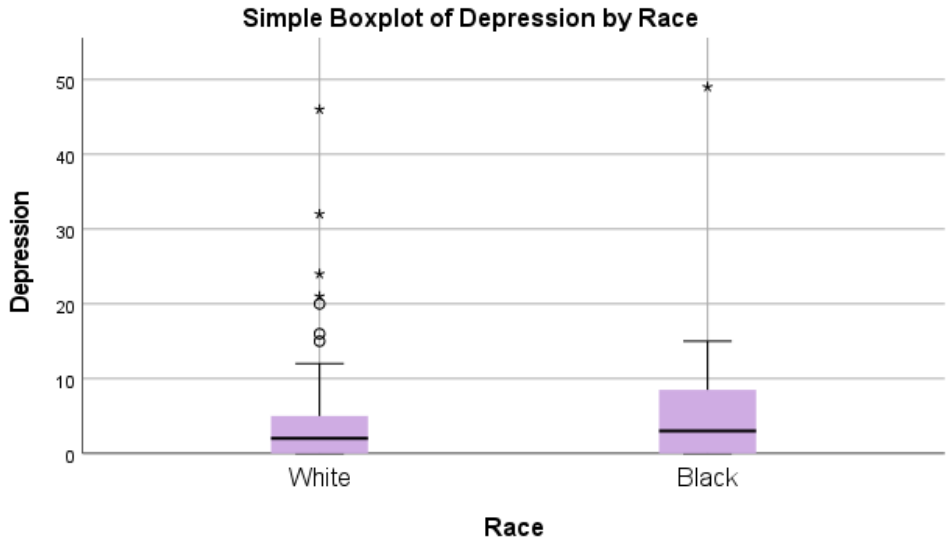


Figure 5 is a boxplot visualization of the difference in the distribution of GRs between groups. The range of scores was slightly wider for the White group (n = 17.5) than for the Black group (n = 12.5) after excluding outliers. The middle 50% of the score for the Black group was 5–11, so the IQR was 6. The middle 50% of the score for the White group was 4–10 with an IQR of 6. The IQR showed equal variability for both groups. The Black group had a higher median score of 8 and the White group median score was 6. After excluding outliers, the Black group had higher GR scores than the White group.

Figure 5

Simple Boxplot of Glucocorticoid Receptors by Race

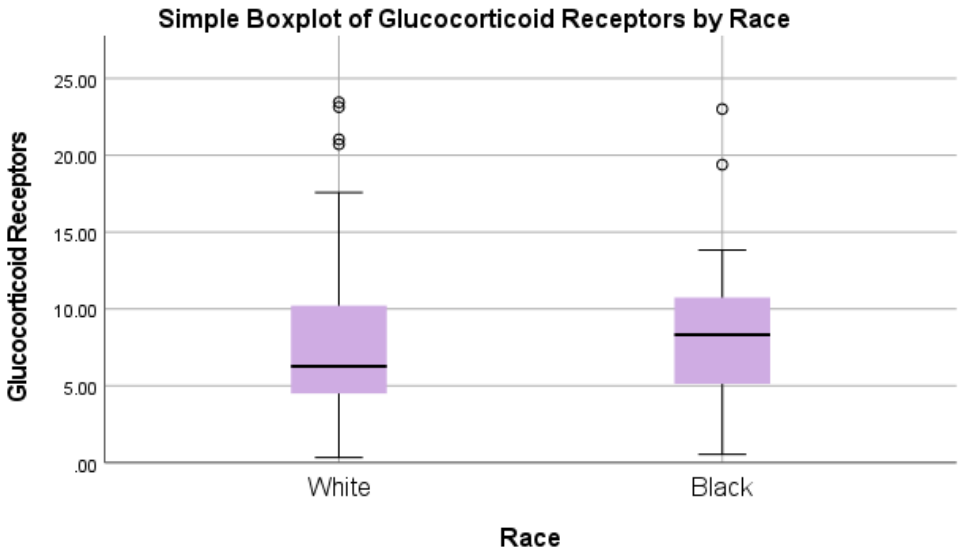
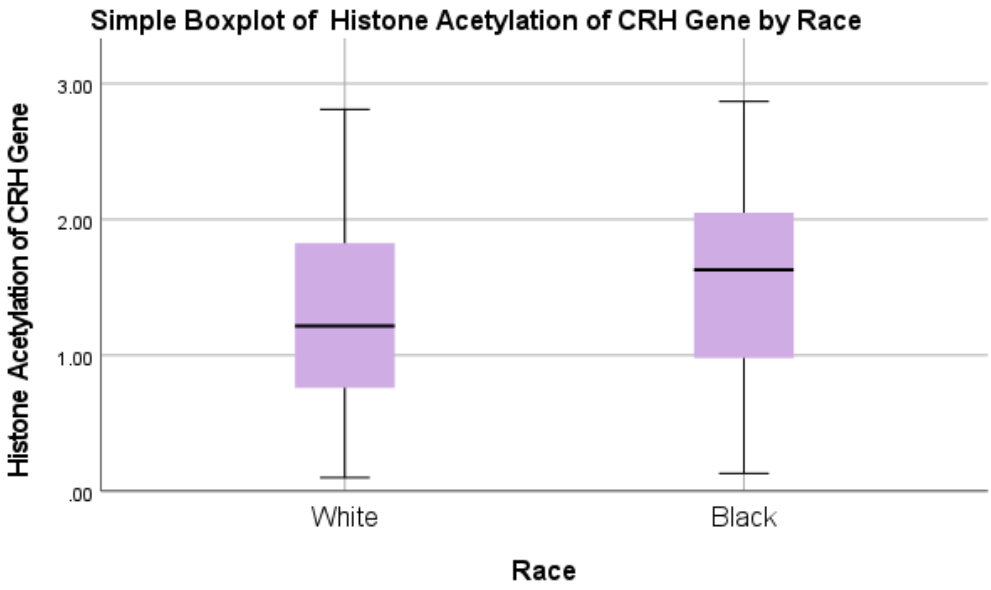


Figure 6 is a boxplot visualization of the difference in the CRH gene's acetylation distribution between groups. The range of scores were equal for both groups at 2.6. The middle 50% of the score for the Black group was 1–2.15, so the IQR was 1, and the middle 50% of the score for the White group was .75–1.75 with an IQR of 1. Therefore, IQR showed equal variability in both groups. The Black group had a higher median at 1.70 compared to the White group's score of 1.25. Overall, the Black group had a higher level of HAT of the CRH gene scores than the White group.

Figure 6

Simple Boxplot of Histone Acetylation of CRH Gene by Race



Correlation Analysis

Before testing the hypotheses, a correlation analysis was performed to examine the strength of the relationships between the dependent and covariate variables of depression, stress, GR gene, acetylation of the CRH gene, age, and BMI. Table 4 represents the correlation findings among the dependent and covariate variables. The acetylation of the CRH gene had a strong relationship with GRs (Pearson's $r = .65$, $p < .01$). Likewise, stress had a strong relationship with depression (Pearson's $r = .64$, $p < .01$) and a weak relationship with acetylation of the CRH gene (Pearson's $r = .20$, $p < .05$). Additionally, age had a weak negative relationship with stress and GRs (Pearson's $r = -.20$, $p < .05$ and Pearson's $r = -.24$, $p < .05$; Field, 2013).

Table 4

Bivariate Correlations for the Dependent and Covariates

Measures	Depression	Stress	GR	HAT CRH	Age	BMI
Depression	-					
Stress	.636**	-				
GR	-.125	.029	-			
HAT CRH	.130	.202*	.651**	-		
Age	-.057	-.197*	-.235*	-.090	-	
BMI	.011	.079	.005	.122	.005	-

Note. * $p < .05$, ** $p < .01$ (one t-tailed significance);

GR = Glucocorticoid receptor; HAT CRH = Histone acetylation of CRH gene.

Figure 7 is a scatter plot of the association between HAT CRH and GR. The scatter plot trend showed a positive, strong, and linear association between the HAT CRH and GR.

Figure 7

Scatter Plot of HAT CRH Gene by GR by Race

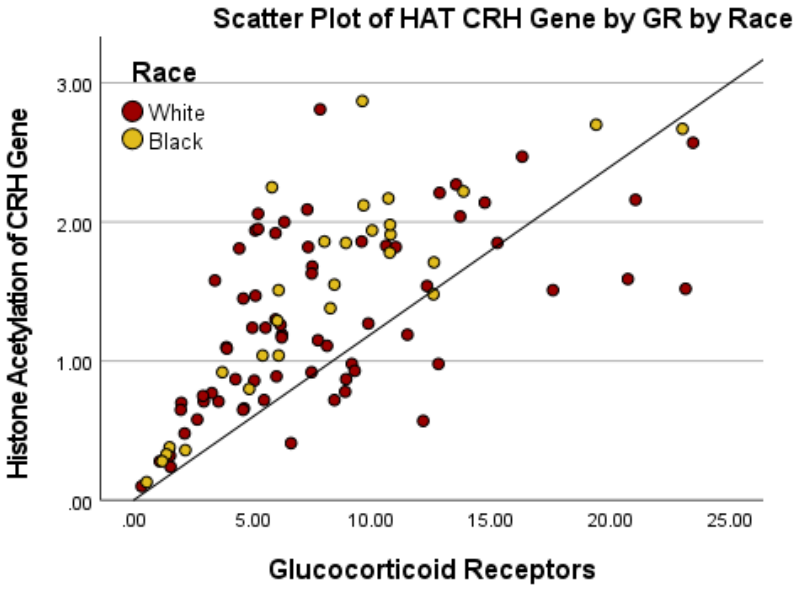


Figure 8 is a scatter plot of the association between depression and stress. The scatter plot showed a strong, positive, and linear trend between depression and stress.

Figure 8

Scatter Plot of Depression by Stress by Race

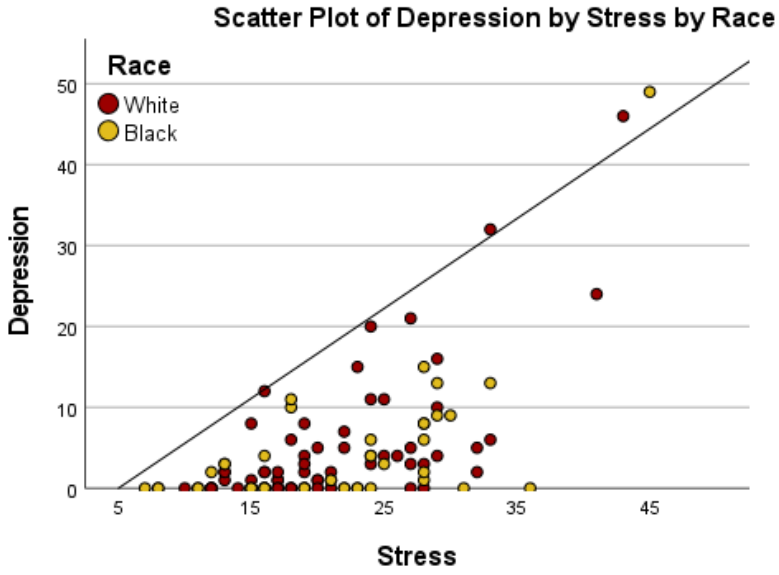


Figure 9 is a scatter plot of the association between stress and age. The scatter plot showed a weak, positive, and linear trend between stress and age.

Figure 9

Scatter Plot of Stress by Age by Race

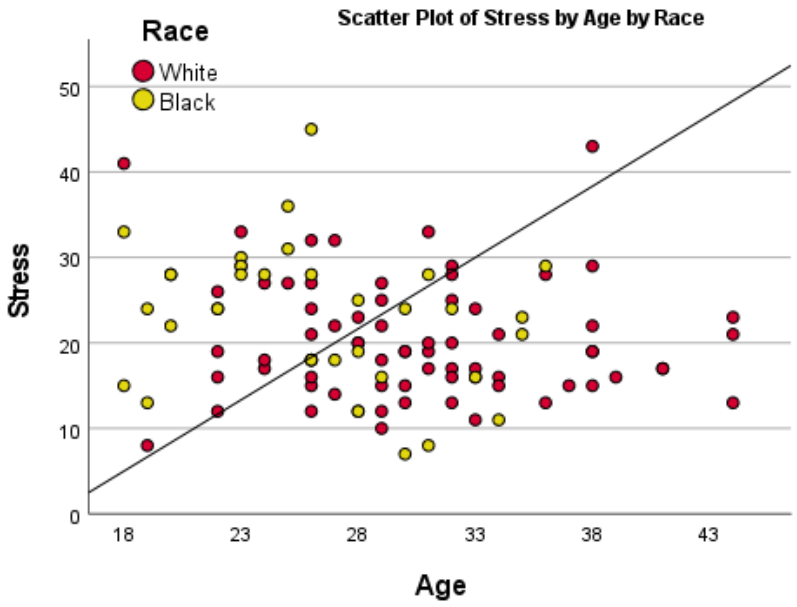


Table 5 shows the crosstabulation of age groups by racial groups. The results showed there were a higher percentage of Black women in a younger age group: ages 18–28 years and the White women ages ranged from 29–44 years.

Table 5
Age Group by Race

	White		Black	
Age	*n*	%	*n*	%
18–23	9	45.0	11	55.0
24–28	20	66.7	10	33.3
29–33	26	78.8	7	21.2
34–38	12	75.0	4	25.0
39–44	6	100	0	0.0

This section addresses the research question outlined by Hypotheses 1, 2, 3, 4, and 5. The general linear model was used to analyze the difference between the predictor variable of race and the outcome variables of depression, stress, GR, and HAT CRH. Analysis of covariance (ANCOVA) was used to test the hypotheses of differences between groups in perceived stress, depression, GR, and HAT CRH while controlling for age. An ANCOVA is a statistical method controlling another variable and may influence the dependent variables. Performing an ANCOVA test can reduce the bias of confounding variables by including them in the model as a covariate (Field, 2013). Because there was a significant difference in age between the two groups, an ANCOVA was performed to control for age as a confounding variable. I further developed the model to test for a potential interaction that could help explain the role of race and how this role may change across age groups. BMI was initially included in the models but was not retained as it accounted for less than 1% of the variability across all the outcomes and for depression and GR, BMI accounted for 0% of the variability.

As seen in Table 6, the differences between the races in HAT CRH while controlling for age and the differential effects of race across a person's age there was a statistically significant difference, $F(1, 88) = 8.26$, $p = .005$, $\eta^2 = .086$. However, because there was an interaction between race and age ($F[1, 92] = 5.34$, $p = .023$, $\eta^2 = .055$) interpretation of the main effect of age cannot be determined and interpretation of the plotted interaction is done instead. Seen in Figure 10, Black women who had higher HAT CRH were younger, between the ages of 18–28 years, but fell below the HAT CRH for White women between the ages of 29–33.

Table 6

ANCOVA Results for Race, Age, and the Interaction Between Race and Age Across the Outcomes of Depression, Stress, GR, and CRH

H	Source	*SS*	*df*	*MS*	*F*	*p*	ηp^2	Post Hoc Power	R^2
H1	**Stress**								
	Corrected Model	359.0	3	119.7	2.22	.091	0.062	0.55	0.062
	Intercept	2822.8	1	2822.8	52.33	<.001	0.341	1.00	
	Race	**76.6**	**1**	**76.6**	**1.42**	**.236**	**0.014**	**0.22**	
	Age	182.4	1	182.4	3.38	.069	0.032	0.45	
	Race * Age	49.4	1	49.4	0.92	.341	0.009	0.16	
	Error	5447.8	101	53.9					
	Total	52998.0	105						
	Corrected Total	5806.8	104						
H2	**Depression**								
	Corrected Model	107.5	3	35.8	0.51	.675	0.015	0.15	0.015
	Intercept	243.6	1	243.6	3.48	.065	0.033	0.46	
	Race	**77.7**	**1**	**77.7**	**1.11**	**.295**	**0.011**	**0.18**	
	Age	46.0	1	46.0	0.66	.420	0.006	0.13	
	Race * Age	65.8	1	65.8	0.94	.335	0.009	0.16	
	Error	7078.7	101	70.1					
	Total	9644.0	105						
	Corrected Total	7186.2	104						
H3	**GR**								
	Corrected Model	184.4	3	61.5	2.33	.079	0.071	0.57	0.071
	Intercept	744.8	1	744.8	28.25	<.001	0.235	1.00	
	Race	**32.3**	**1**	**32.3**	**1.22**	**.272**	**0.013**	**0.20**	
	Age	180.9	1	180.9	6.86	.010	0.069	0.74	
	Race * Age	37.6	1	37.6	1.42	.236	0.015	0.22	
	Error	2425.9	92	26.4					
	Total	8785.4	96						
	Corrected Total	2610.3	95						
H4	**CRH**								
	Corrected Model	3.5	3	1.2	2.63	.055	0.079	0.63	0.079
	Intercept	11.8	1	11.8	26.96	<.001	0.227	1.00	
	Race	**2.8**	**1**	**2.8**	**6.40**	**.013**	**0.065**	**0.71**	
	Age	1.2	1	1.2	2.64	.108	0.028	0.36	
	Race * Age	**2.3**	**1**	**2.3**	**5.34**	**.023**	**0.055**	**0.63**	
	Error	40.3	92	0.4					
	Total	221.2	96						
	Corrected Total	43.7	95						

Figure 10

Differential Effect of Race on CRH Across Age

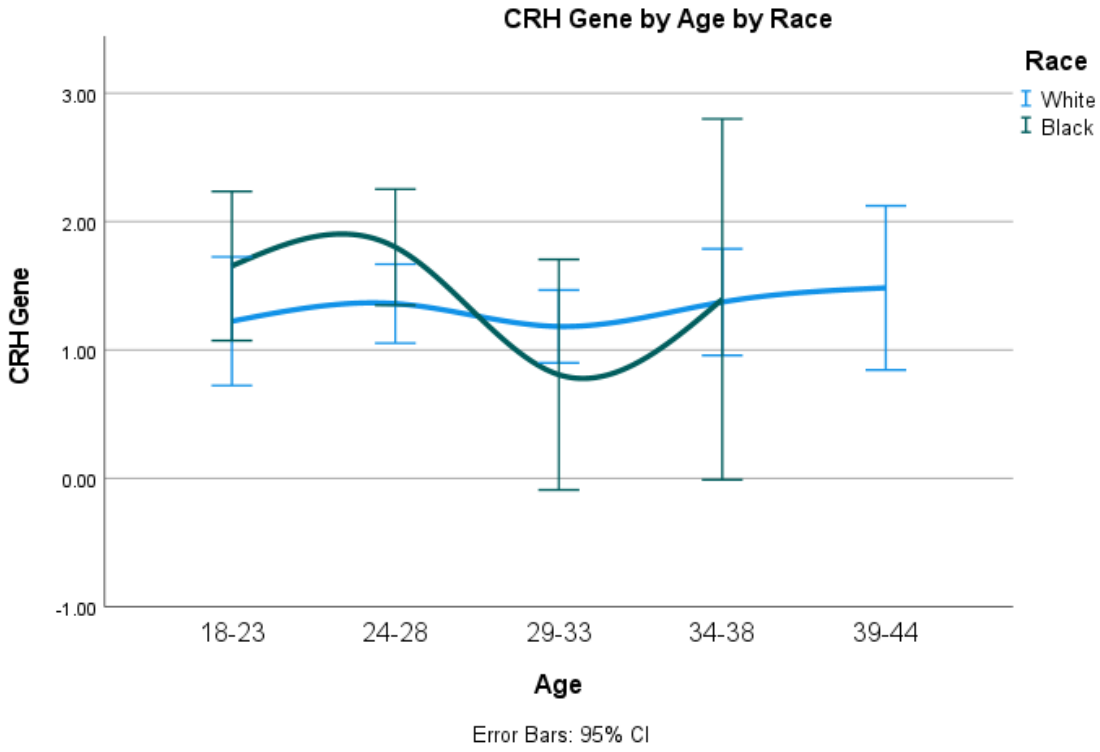


Table 7 shows the ANCOVA results of Hypothesis 5, which focused on differences in HAT CRH between racial groups while controlling for GR, age, and the interaction between race and age. Statistically significant differences in HAT CRH were found across race while controlling for all variables, $F(1, 91) = 5.6$, $p = .020$, $\eta^2 = .058$. However, there was a statistically significant interaction between race and age across HAT CRH results that had to be interpreted by plotted interactions. These interpretations mirror those found in Hypothesis 4 where Black women initially had higher CRH levels but fell below White women aged 29–33. Additionally, there was a statistically

significant relationship between GR and CRH levels that accounted for approximately 43% of the total variability in CRH Levels, $F(1, 91) = 69.8$, $p = <.001$, $\eta^2 = .43$.

Table 7

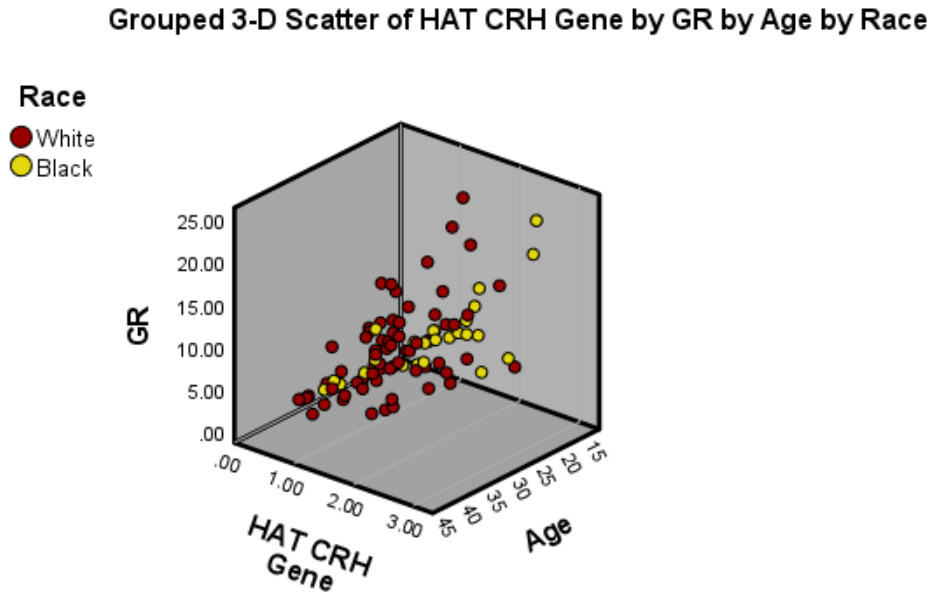
ANCOVA Results for Race, Age, GR, and the Interaction between Race and Age Across the CRH Levels

Source	*SS*	*df*	*MS*	*F*	*p*	η_p^2	Post Hoc Power	R^2
Corrected Model	20.8	4	5.2	20.6	<.001	.475	1	0.475
Intercept	1.0	1	1.0	3.9	.052	.041	0.495	
Race	**1.4**	**1**	**1.4**	**5.6**	**.020**	**.058**	**0.647**	
Age	0.0	1	0.0	0.0	.907	.000	0.052	
GR	17.3	1	17.3	68.6	<.001	.430	1	
Race * Age	**1.0**	**1**	**1.0**	**4.0**	**.049**	**.042**	**0.507**	
Error	23.0	91	0.3					
Total	221.2	96						

Figure 11 provides a 3-D scatter plot visualization of the association between HAT CRH, GR, and age, by race. The plot trend showed a strong, positive, and linear association between HAT of the CRH gene, GR, and age, by race.

Figure 11

Grouped 3-D Scatter of HAT CRH Gene by GR by Age by Race



Note. GR = Glucocorticoid receptor; HAT CRH = Histone acetylation of CRH gene.

Summary

This chapter presents the data analysis results for the research question and the five hypotheses of this study. This study aimed to analyze differences in perceived stress, depression, and modifiable epigenomic changes in changes of the CRH gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. The total sample was 105 women in their 2nd trimester of pregnancy, 73 were non-Hispanic White women and 32 were non-Hispanic Black women. An ANCOVA was used to measure the difference in perceived stress, depression, GRs, and HAT of the CRH gene between these two groups of pregnant women, while controlling for age. There were no significant differences between groups for the first three hypotheses. The

ANCOVA results for Hypothesis 4 showed significant differences in HAT of the CRH gene between racial groups while controlling for age. The fifth hypothesis measured the difference in HAT of the CRH gene between groups while controlling for the number of GRs and age. The ANCOVA results for Hypothesis 5 showed significant differences in HAT of the CRH gene between groups while controlling for GR and age ($p = .05$).

CHAPTER 5: DISCUSSION

This chapter summarizes the study and interprets the major findings. It begins with the study overview, then discusses the study's implications, limitations, and recommendations. This study aimed to evaluate differences in perceived stress, depression, and epigenomic modification of the corticotropin-releasing hormone (CRH) gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. The study used a secondary dataset and a cross-sectional design to describe the differences between the two groups of women. Thus, the overarching research question was: What is the difference in perceived stress, depression, glucocorticoid receptors (GRs), and histone acetylation (HAT) of the CRH gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy? The data were analyzed using descriptive statistics, correlations, and analysis of covariance (ANCOVA).

Overview of Findings

The sample population for this study consisted of 105 women between the ages of 18–44 years in their 2nd trimester of pregnancy. Seventy-two percent ($n = 73$) of the women were White, and 31% ($n = 32$) of the women were Black. Additionally, the groups had a significant difference in age and body mass index (BMI).

Pearson's correlation showed a strong relationship between HAT of the CRH gene and GRs (Pearson's $r = .65$, $p < .01$). Similarly, there was a strong relationship between stress and depression (Pearson's $r = .64$, $p < .01$) and weak relationships

between stress and histone acetylation of the CRH gene (Pearson's $r = .20$, $p < .05$). There were relative, weak negative relationships between age, stress, and GRs (Pearson's $r = -.20$, $p < .05$, and Pearson's $r = -.24$, $p < .05$, respectively).

Other researchers have reported a strong relationship between stress and depression. Slaughter-Acey et al. (2016) reported depressive symptoms were associated with perceived racism and preterm birth (PTB). Christian et al. (2013) reported a moderate correlation between perceived stress and depression. Likewise, Hoffman et al. (2016) reported correlations between perceived stress and depression.

Hypothesis 1

Non-Hispanic Black women will have a significantly higher level of perceived stress than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age, as measured by the Perceived Stress Scale.

The ANCOVA results found no significant difference between the two groups in perceived stress. However, Corwin et al. (2013) reported higher levels of perceived stress scores and higher cortisol levels among the Black participants in their study. Whereas other researchers evaluated the role of stress during pregnancy and found positive associations between stress, maternal mortality, and PTB disparities (Gillespie et al., 2017; Sealy-Jefferson et al., 2016; Yu et al., 2013). Some researchers have reported significant associations between stress related biomarkers such as cortisol, proinflammatory cytokines, c-reactive protein, CRH, and disparities in maternal birth outcomes (Borders et al., 2015; Brou et al., 2011; Catov et al., 2015; Christian et al., 2013; Corwin et al., 2013; Gillespie et al., 2016; Giurgescu et al., 2015, 2016; Mohamed

et al., 2018; Ruiz et al., 2016). Hoffman et al. (2016) reported significant correlation between PTB, perceived stress, and elevated hair cortisol levels.

Hypothesis 2

Non-Hispanic Black women will have a significantly higher level of depression than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age, as measured by the Profile in Mood Depression Scale.

The ANCOVA results found no significant difference between the two groups in depression. Borders et al. (2015) reported higher levels of depression among Black participants in their study. Other researchers reported an association between PTB, neighborhood safety, and depression (Sealy-Jefferson et al., 2016). Slaughter-Acey et al. (2016) found a significant association between severe depression and PTB in a population of Black women. Hoffman et al. (2016) reported significant correlation between PTB and depression. Likewise, Giurgescu et al. (2015) reported Black women who acknowledged experiencing racial discrimination had higher depression scores.

Hypothesis 3

Non-Hispanic Black women will have a significantly higher expression of GRs then non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age, as measured by chromatin immunoprecipitation (ChIP) to quantitative polymerase chain reaction (qPCR).

The ANCOVA results found no significant difference between the two groups in the expression of GRs. When GRs becomes activated, the GRs function as transcription factors. John et al. (2011) found in the presence of corticosteroids; GRs had an affinity to bind at open chromatin sites. Buckingham (2006) reported elevated glucocorticoid

(cortisol) levels activate the actions of GRs. Wang et al. (2021) found long-term treatment of cells with cortisol produced increase levels of GR and cortisol-treated cells GR had increased histone acetylation. Kramer et al. (2013) also reported a significant difference in cortisol and CRH between delivering term versus PTBs.

Hypothesis 4

Non-Hispanic Black women will have a significantly higher expression HAT of the CRH gene than non-Hispanic White women in their 2nd trimester of pregnancy, when controlling for age, as measured by ChIP to qPCR analysis.

The ANCOVA results showed significant differences between the two groups in the expression of the HAT of the CRH gene while controlling for age. During pregnancy, CRH from the placenta regulates gestation length (Sandman et al., 2006). CRH is not detectable in maternal circulation before pregnancy but rises exponentially with rapid acceleration after 25 weeks. Multiple researchers have linked high CRH levels to PTB and eclampsia/preeclampsia (Kramer et al., 2013; Mesner et al., 2019; Mohamed et al., 2017; Ruiz et al., 2016). Borders et al. (2015) reported no difference in CRH levels between participants in their study. Other researchers have reported significant associations between CRH and disparities in maternal birth outcomes (Mohamed et al., 2018; Ruiz et al., 2016). Harville et al. (2009) reported higher stress levels were associated with reduced cortisol or CRH levels, but CRH was the strongest predictors of preeclampsia.

Hypothesis 5

Non-Hispanic Black women will have a significantly higher expression histone acetylation of the CRH gene than non-Hispanic White women in their 2nd trimester of

pregnancy, while controlling for age and the quantity of GRs as measured by ChIP to qPCR analysis.

The ANCOVA analyzed the difference in HAT of the CRH gene while controlling for GR and age between the two groups found significant differences between groups. Researchers have suggested the CRH hormone is the biological clock, which induces labor. Some researchers have indicated post transcription factors such as acetyltransferases may upregulate CRH through histone acetylation and increased cortisol (Di Stefano et al., 2015; Wang et al., 2021). Di Stefano et al. (2015) reported CRH increased and histone acetylation of the CRH gene in response to cortisol exposure in the term placentas, but not 2nd trimester placentas.

This study sought to identify the gap in the literature review regarding an additional explanation of a relation between increased cortisol availability, elevated CRH, and transcription factors in circulating maternal plasma. The findings of differences in HAT of the CRH gene while controlling for GR and age provide evidence genomic activities could increase CRH's upregulation during pregnancy. This finding supports the theoretical preposition that developmental outcomes should be understood in relation to their environmental conditions (Gottlieb, 2007). This finding relates to adaptive outcomes involving human growth and development, influenced by social, economic, and political factors and genomic activities. These adaptive outcomes occur at the molecular level of the cells and manifest gradually.

This study's finding of differences in HAT of the CRH gene while controlling for age and GR in Black compared to White pregnant women is aligned with the notion of social position as an antecedent to health inequity. This study focused on two variables

related to the social determinant of health: social position (race) and biopsychosocial factors. This study regarded race as part of the societal structural determinant of health, and perceived stress, depression, and changes in transcription factors were intermediary biopsychosocial determinants. The World Health Organization (WHO, 2010) conceptualized the social determinants of health in the context of the structural and intermediary determinants. The WHO (2010) suggested social hierarchy as the primary determinant of health inequity. The Centers for Disease Control (n.d.) and Healthy People 2030 (n.d.) have identified five social determinants of health: economic stability, access to quality education, access to quality healthcare, neighborhood environment, and social relationships. Socioeconomic factors such as income, education, occupation, and discrimination are social determinants. Social relationship factors, in combination with intermediary factors such as living conditions, food availability, health behavior, and psychosocial vulnerability, determine health outcomes. Therefore, a social position such as race shapes the conditions where people live, work, and play, influencing the intermediary determinants of health and an individual's health status. Social status is considered the antecedent to intermediary biopsychosocial factors because people of lower social status are more likely to experience uncertainty, insecurity, and stressful life events.

In the past, race was perceived as biological differences between racial groups, and the differences in health outcomes were considered genetic differences. In contemporary society, the concept of race has been acknowledged as a social construct and part of societal structure. As the understanding of genetics and societal structure evolved, health disparities have been identified to be related to sociodemographic factors.

Social status is a complex phenomenon encompassing economic resources, power, and prestige (Williams et al., 2016). Social status influences health through various circumstances such as neighborhood, education, and social connections. Racial differences in socioeconomic status are recognized as an indicator of health inequity because these differences persist across racial groups (Williams et al., 2016). For example, although education should improve maternal mortality, college educated Black women had a 1.6 times higher pregnancy related mortality ratio than White women without a high school diploma (Singh, 2021). Black and Hispanic individuals receive less income at the same level of education as their White counterparts. Likewise, racial discrimination in housing segregation, education, and employment remains pervasive. The healthcare system also functions as an intermediary determinant of health because the system plays a role in mediating the consequences of illness.

Implications

The study's findings of uncovering a significant difference between the two groups in HAT of the CRH gene while controlling for the GR and age showed evidence of post transcriptional epigenomic adaptive activity. This difference between groups in HAT of the CRH gene may explain the difference in maternal health outcomes between the groups. Several researchers have reported significant relationships between CRH levels, PTB, and preeclampsia (Harville et al., 2009; Kramer et al., 2013; Mesner et al., 2019; Mohamed et al., 2017; Ruiz et al., 2016). This finding is consistent with the chronic stress epigenomic adaptation model developed to guide this research. The chronic stress epigenomic adaptation model proposed women's response to the social environment produces epigenomic, biological, and psychological changes and how it

could affect their health outcomes. In this model, social position, a category which encompasses race, education, income, and employment, is considered an antecedent to effectively coping. When people lack the resources to function adequately, they have fewer coping options. Ineffective coping leads to psychological, physiological, and epigenomic changes. For example, in pregnancy, chronic stress may increase cortisol, which increases GRs, which may increase the expression of CRH during pregnancy, which could result in preeclampsia and PTB. Therefore, the difference between groups in HAT of the CRH gene could be recognized as epigenomic, adaptive changes occurring in the body, leading to variation in pregnancy outcomes.

Implications for Nursing

The foundation of professional nursing begun grounded in advocacy. Florence Nightingale vigorously campaigned for public health policies to address health inequities during her lifetime despite her privileged position in society. Nightingale recognized social structure contributed to health inequities and advocated for social improvement in housing and wages for the poor (Hegge, 2013). The nursing profession has a long tradition of advocating for the healthcare need of individuals and populations, and nurses can play a critical role in promoting health equity.

Advocating for health equity means striving to attain the highest level of health for all population groups in society and requires sociopolitical activism. The ethical code of nursing urges nurses to advocate for social justice to improve health equity in different population groups (ANA, 2015). The nursing code of ethics suggests nurses should advocate for social justice in areas such as better living wages, housing, food deserts, and education for population groups in need.

Additionally, nurses should advocate for eliminating racial discrimination against marginalized populations, decreasing the disparity in pregnancy outcomes for Black women. The U.S. Department of Health and Human Services (USDHHS, 2022) reported Black women receiving care in hospitals had poorer health outcomes than White and Hispanic women. This disparity was related to the quality of clinical care these women received, such as non-Hispanic Black women receiving the highest rate of low risk cesarean deliveries. The USDHHS (2022) explained healthcare system factors contributed to over half maternal deaths. Issues related to providers, such as inappropriate or incomplete care management, were cited as the most frequent cause of preventable maternal deaths (Howell & Zeitlin, 2017). Nurses are the largest group of healthcare professionals. Therefore, the nursing profession must evaluate and correct underlying system factors. Furthermore, nurse educators are obligated to teach the next generation of nurses about the social determinants of health and the need to advocate for system changes in the profession and society in general.

Implication for Health Policy

This study found an association between stress and depression and a significant difference between groups in age. The U.S. Preventive Services Task Force (USPSTF, 2019) has recommended interventions to consider in this area. These interventions include screening for depression, intimate partner violence, and other mental health issues and assessing for socioeconomic risk factors. There was a small negative correlation between stress and age; the Black women reported being significantly younger than the White women. This difference may indicate the need for more supportive services for younger Black women. This finding is supported the national

statistics, showing Black women give birth at younger ages than White women (USDHHS, 2022). The U.S. Department of Health and Human Services (2022) suggested providing care coordination services in communities impacted by high maternal morbidity and mortality. Services such as community health workers could assist in linking women to health care providers for services such as prenatal and postpartum care. Community health workers could also provide initial screenings for depression and anxiety then link the women to services for mental health, breastfeeding, and childcare. The doula service has been shown to offer emotional and educational support to women during their prenatal and postpartum periods. Nurses should advocate insurance companies reimburse for the services of community health workers and doulas (USDHHS, 2022).

The finding of a significant difference in HAT of the CRH gene while controlling for GR and age between groups indicates biological factors such as post transcription factors involved in the differences in health outcomes. Other researchers have reported CRH leads to adverse pregnancy outcomes such as preeclampsia and PTB (Harville et al., 2009; Kramer et al., 2013; Mesner et al., 2019; Mohamed et al., 2017; Ruiz et al., 2016). Black women are more likely to develop preeclampsia and are at increased risk of experiencing kidney damage, cardiovascular sequela, PTB, and cesarean section. The finding of this study adds to the body of research evidence that implicates epigenomic changes and CRH during pregnancy, influencing pregnancy outcomes. The CRH could become a biomarker to assist in the early detection and treatment of adverse pregnancy outcomes. Identifying a biomarker for screening could aid in early diagnosis and treatment for women at risk of adverse pregnancy outcomes (USDHHS, 2022).

Limitations

This study's limitations include using a secondary dataset with a disproportionately higher number of White than Black women and missing sociodemographic data. Missing data prevented the inclusion of education, income, marital status, and smoking as variables for data analysis. The analysis of these variables was critical as they could be confounding factors to perceived stress. Other missing data included the number of pregnancies and the type of previous deliveries of the participants. The secondary dataset also prevented the examination of outliers for inputting errors.

Another limitation was the lab using the chromatin immunoprecipitation (ChIP) two different agarose beads to isolate the DNA complex. The lab began the ChIP process using agarose A beads, but they had to switch to agarose G beads because their supplier discontinued the A beads. According to Abcam Biotechnology company, both agarose A and G beads have strong binding affinity to human antibodies (Abcam, n.d.). The Active Motif lab performed a side-by-side comparison of the two beads, and they obtained identical signals with both bead types with the H3K9Ac antibody, but there could have been minimal differences between the two types of beads.

This study inferred increased cortisol availability by measuring GRs because cortisol could not be measured directly from frozen peripheral blood mononuclear cells. This indirect method was used based on the premise cortisol action regulates GRs (Tammen et al., 2013). Few studies have analyzed the contribution of post transcription factors to adverse maternal health outcomes. This study may be one of the first to evaluate HAT CRH in maternal blood. Ross (2019) investigated genome wide

transcription factors of dry blood cells and stress during the 3rd trimester of pregnancy. They reported post transcription factors NF-kB and AP-1 upregulated proinflammatory gene expression. DiStefano (2015) evaluated the association between cortisol and CRH in the placenta. Pan et al. (2017) reported DNA histone acetylation and methylation control CRH gene expression in placentae tissues. Some investigators have evaluated DNA methylation, another epigenomic marker in cervical tissues. These investigators reported a positive association between 2nd trimester cervical tissue DNA methylation and PTB (Burris et al., 2014). Another post transcription factor investigated in relation to PTB is telomere length. Researchers have examined telomere length when studying differences between mother and newborn telomere lengths, or the micronutrients such as Vitamins A, C, D, and N-acetyl cysteine. Other investigators have hypothesized lack of these micronutrients shorten the telomere length in Black women due to the increased stress they experience and may induce early labor (Entringer et al., 2015; Nsereko et al., 2020; Phillippe, 2022).

Recommendations

This study's finding of a significant difference in HAT CRH gene between a group of Black and White pregnant women while controlling for age and GR warrants further investigation. CRH is considered the biologic time clock of pregnancy. CRH has also been implicated in PTB and preeclampsia. The role of psychosocial stress in pregnancy outcomes remains debatable. The connection between psychological and physiological measures of stress will increase the understanding of its impact on health. Continued research into the relationship between stress, increased cortisol availability, elevated CRH, and transcription factors in circulating maternal plasma are essential in

understanding differences between Black and White women in PTB and maternal mortality rates.

This study used secondary data to evaluate the differences in perceived stress, depression, and the expression of the CRH gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. The use of secondary data prevented the analysis of variables such as income, education, marital status, and smoking. Therefore, the researcher recommends repeating this study using primary data collect. The sample population of this study was not equally distributed between groups. Two thirds of the sample population was White (n = 73), and one third was Black (n = 32), and there was more variability among the Black participants for every statistical analysis performed. A larger sample size of approximately 408 would be more appropriate based on the small effect sizes results of the observed post hoc power across this study. A larger sample would also allow more homogeneity of variance between groups and could be more generalizability to the general population (Field, 2013).

The third recommendation would be to consider participatory research to understand the women's viewpoints better and engage them in identifying solutions. The idea of participatory community research would be to develop a collaborative relationship with community members around the issue of maternal health (Burns et al., 2011). Through the research process, the community members will be involved in all aspects of the research, from the design phase to data collection, data analysis, dissemination, and action. For example, a mixed method research design could be implemented. In the first phase of the research, a qualitative methodology could be used to gain different perspectives and understanding of the issue. The results of the qualitative

phase of the study could be used to develop and test a quantitative intervention. When a community becomes actively involved with an issue and its solution, it will more likely bring about permanent change.

Conclusion

The findings of differences in HAT CRH while controlling for GRs and age provide additional information to the gap identified in the literature review related to elevated CRH and transcription factors in circulating maternal plasma during pregnancy. The health inequities associated with maternal mortality and PTB remain a significant issue in the United States. Finding an explanation for the disproportionate difference in maternal health between Black and White women could assist in achieving health equity by attaining the highest level of health for all population groups. This study aimed to evaluate differences in perceived stress, depression, and modifiable epigenomic changes in the expression of the CRH gene between non-Hispanic Black and non-Hispanic White women in their 2nd trimester of pregnancy. The results found significant differences in HAT CRH between groups while controlling for GR and age. These significant differences in HAT CRH may indicate epigenomic adaptive changes related to the construct antecedent of stress in the social environment. The construct of the antecedent of stress in the social environment refers to the lack of resources available to some population groups. This lack of resources includes secure employment, safe neighborhoods, access to nutritious foods, and education encompassing the social determinants of health. The results also found no significant difference in perceived stress, depression, and GRs between these two groups of pregnant women.

The nursing profession has a long tradition of advocating for changes in health inequities and should advocate for improving disparities in maternal health outcomes. Nursing is responsible for evaluating its role in the healthcare system's contribution to maternal health inequity. Further research using primary data collection and a larger sample size is recommended. A larger sample of about 408 would be appropriate based on the small effect size across this study. A community participatory research methodology could be warranted to bring more awareness to the issue and involve all stakeholders in solving the inequity in maternal health care. More research is necessary on the implication of a significant difference in HAT CRH between Black and White pregnant women. CRH could be an essential biomarker in determining a healthy pregnancy outcome.

APPENDICES

APPENDIX A

Pre-Approved Material Transfer Agreement University of South Florida

University of South Florida

Pre-Approved Material Transfer Agreement

Based upon the UBMTA

This Agreement effective this 14 day of July, 2020, is between The University of South Florida Board of Trustees, a public body corporate (hereinafter referred to as "PROVIDER"), with offices at 3802 Spectrum Boulevard, Suite 100, Tampa, Florida 33612 and Florida Atlantic University Board of Trustees, with offices at 777 Glades Road, Boca Raton, FL 33431 ("RECIPIENT"), and Marlene Brennen, DNP, FNP-BC, PMHNP-BC. APRN, Assistant Professor of Nursing ("RECIPIENT SCIENTIST"). Subject to the terms of this Agreement, Dr. Maureen Groer ("PROVIDING SCIENTIST") at the University of South Florida agrees to provide ORIGINAL MATERIAL (as described herein) for use solely in the specific research study hereinafter described:

The purpose of this study is to elucidate differences between non-Hispanic Black and non-Hispanic White women in perceived stress, depression, and modifiable epigenomic changes in the modulation of the CRH gene in their second trimester of pregnancy. This study intends to analyze data collected from a repository of cells from pregnant and postpartum women (Groer, 2016).

I. Definitions:

1. ORIGINAL MATERIAL: The description of the material being transferred is as follows: De-identified aliquots of cells) peripheral blood monocytes (PMBCs) and data set age, race, ethnicity, education, income, marital, hours working, body mass index, perceived stress scores, Profile of Mood States scores from pregnant women (repository Pro#00024848.)

   ORIGINAL MATERIAL also includes any know-how related to the material being transferred.

2. MATERIAL: ORIGINAL MATERIAL, PROGENY, and UNMODIFIED DERIVATIVES. The MATERIAL shall not include: (a) MODIFICATIONS, or (b) OTHER SUBSTANCES.

3. PROGENY: Unmodified descendant from the MATERIAL, such as virus from virus, cell from cell, or organism from organism.

4. UNMODIFIED DERIVATIVES: Substances created by the RECIPIENT, which constitute an unmodified functional subunit or product, expressed by the ORIGINAL MATERIAL. Some examples include: subclones of unmodified cell lines, purified or fractionated subsets of the ORIGINAL MATERIAL, proteins expressed by DNNRNA supplied by the PROVIDER, or monoclonal antibodies secreted by a hybridoma cell line.

5. MODIFICATIONS: Substances that are not ORIGINAL MATERIAL, PROGENY OR UNMODIFIED DERIVATIVES created by the RECIPIENT which contain/incorporate the MATERIAL.

6. OTHER SUBSTANCES: Substances created by the RECIPIENT through the use of the MATERIAL which are not MODJFICATIONS, ORIGINAL MATERIAL, PROGENY, or UNMODIFIED DERIVATIVES

7. COMMERCIAL PURPOSES: The sale, lease, license, or other transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. COMMERCIAL PURPOSES shall also include uses of the MATERIAL or MODIFICATIONS by any organization, including RECIPIENT, to perform contract research, to screen compound libraries, toproduce or manufacture products for general sale, or to conduct research activities that result in any sale, lease, license, or transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. However, industrially sponsored academic research shall not be considered a use of the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES per se, unless any of the above conditions of this definition are met.

8. NONPROFIT ORGANIZATION(S): A university or other institution of higher education or an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1954 (26 U.S.C. 501(c)) and exempt from taxation under section 501(a) of the Internal Revenue Code (26 U.S.C. 501(a)) or any nonprofit scientific or educational organization qualified under a state nonprofit organization statute. As used herein, the term also includes government agencies.

II. Terms and Conditions of this Agreement

1. The PROVIDER retains ownership of the MATERIAL, including any MATERIAL contained or incorporated in MODIFICATIONS or OTHER SUBSTANCES. The PROVIDER also retains any and all rights, including but not limited to patent rights, trademarks, and other proprietary rights, in and to the MATERIAL.

2. The RECIPIENT retains ownership of: (a) MODIFICATIONS (except that, the PROVIDER retains ownership rights to the MATERIAL included therein), and (b) OTHER SUBSTANCES. If either 2 (a) or 2 (b) results from the collaborative efforts of the PROVIDER and the RECIPIENT, joint ownership shall be negotiated in good faith.

3. The RECIPIENT and the RECIPIENT SCIENTIST agree that the MATERIAL:

   (a) will be used solely in the specific research study herein described;

   (b) is to be used solely for teaching and academic research purposes;

   (c) will not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects without the written consent of the PROVIDER;

   (d) is to be used only at the RECIPIENT organization and only in the RECIPIENT SCIENTISTs laboratory under the direction of the RECIPIENT SCIENTIST or others working under his/her direct supervision; and

   (e) will not be transferred to anyone else within the RECIPIENT organization or to anyone else outside of the RECIPIENT organization without the prior written consent of the PROVIDER.

4. The RECIPIENT and the RECIPIENT SCIENTIST agree to refer to the PROVIDER any request for the MATERIAL from anyone other than those persons working under the RECIPIENT SCIENTIST's direct supervision or any other uses of MATERIAL than herein described. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agrees to make the MATERIAL available, under a separate agreement to other scientists at NONPROFIT ORGANIZATION($) who wish to replicate the RECIPIENT SCIENTIST'S research; provided that such other scientists (i) agree to be bound by the same or substantially the same terms of this agreement, (ii) reimburse the PROVIDER for any costs relating to the preparation and distribution of the MATERIAL. For clarity, Provider, in its discretion, may under a separate agreement, make MATERIAL available for other uses not covered by this Agreement.

5. (a) The RECIPIENT and/or the RECIPIENT SCIENTIST shall have the right, without restriction, to distribute OTHER SUBSTANCES, unless such OTHER

SUBSTANCES are subject to joint ownership and any Agreement related to the joint ownership prevents such distribution.

(b) Under a separate agreement at least as protective of the PROVIDER's rights as this Agreement, the RECIPIENT may distribute MODIFICATIONS to NONPROFIT ORGANIZATION(S) for research and teaching purposes, provided that RECIPIENT give written notification to PROVIDER prior to distribution. Any such distribution without prior written notification to PROVIDER shall be in breach of this Agreement and RECIPIENT rights to use the MATERIALS shall cease immediately.

(c) Without written consent from the PROVIDER, the RECIPIENT and the RECIPIENT SCIENTIST may NOT use or provide MODIFICATIONS for COMMERCIAL PURPOSES. It is recognized by the RECIPIENT that such COMMERCIAL PURPOSES may require a commercial license from the PROVIDER and the PROVIDER has no obligation to grant a commercial license to its ownership interest in the MATERIAL incorporated in the MODIFICATIONS. Nothing in this paragraph, however, shall prevent the RECIPIENT from granting commercial licenses under the RECIPIENT's other intellectual property rights (e.g. patent rights) claiming such MODIFICATIONS, or methods of their manufacture or their use.

6. The RECIPIENT acknowledges that the MATERIAL is or may be the subject of one or more patent applications or patents. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the RECIPIENT under any patents, patent applications, trademarks, trade secrets or other proprietary rights of the PROVIDER, including any such rights to MATERIAL, MODIFICATIONS or OTHER SUBSTANCES made by the PROVIDER, which may be covered by any such patents, patent applications, trademarks, trade secrets or other proprietary rights. In particular, no express or implied licenses or other rights are provided to use the MATERIAL, MODIFICATIONS, or any related patents of the PROVIDER for COMMERCIAL PURPOSES.

7. If the RECIPIENT desires to use or license the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES, the RECIPIENT agrees, in advance of such use, to negotiate in good faith with the PROVIDER to establish the terms of a commercial license. It is understood by the RECIPIENT that the PROVIDER shall have no obligation to grant such a license to the RECIPIENT, and may grant exclusive or non-exclusive commercial licenses to others, or sell or assign all or part of the rights in the MATERIAL to any third party(ies), subject to any pre-existing rights held by others and obligations to the Federal Government.

8. The RECIPIENT is free to file patent application(s) claiming inventions made solely by the RECIPIENT, RECIPIENT SCIENTIST or others working under his/her direct supervision, through the use of the MATERIAL but agrees to notify the PROVIDER upon filing a patent application claiming MODIFICATIONS or OTHER SUBSTANCES or method(s) of manufacture or use(s) of the MODIFICATIONS or OTHER SUBSTANCES. RECIPIENT shall consult with PROVIDER as soon as practical in the event that a joint invention respecting MODIFICATIONS or OTHER SUBSTANCES is made by RECIPIENT and PROVIDER, and the parties shall discuss in good faith the details respecting filing, prosecution and commercial licensing of such joint invention. Inventorship of inventions shall be determined according to US Patent Laws.

9. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. The PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR REPRESENTATIONS OR WARRANTIES THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

10. Except to the extent prohibited by law, the RECIPIENT assumes all liability for damages, which may arise from its use, storage or disposal of the MATERIAL, MODIFICATIONS or OTHER

SUBSTANCES. The PROVIDER will not be liable to the RECIPIENT for any loss, claim or demand made by the RECIPIENT, or made against the RECIPIENT by any other party, due to or arising from the use of the MATERIAL, MODIFICATIONS or OTHER SUBSTANCES by the RECIPIENT or third parties to whom the RECIPIENT has distributed MODIFICATIONS or OTHER SUBSTANCES, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the PROVIDER.

11. This Agreement is not assignable without the prior written consent of PROVIDER.

12. This Agreement shall not be interpreted to prevent or delay publication of research findings resulting from the use of the MATERIAL, MODIFICATIONS, or OTHER SUBSTANCES. The RECIPIENT SCIENTIST agrees to provide appropriate acknowledgement of the source of the MATERIAL in all publications.

13. The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations, including Public Health Service, Food and Drug Administration, Environmental Protection Agency, United States Department of Agriculture, and National Institutes of Health regulations and guidelines such as, for example, those relating to research involving the use of animals or recombinant DNA.

14. Subject to paragraph 15, this Agreement shall expire one (1) year after its date of execution or on the earliest of the following dates: (a) when the MATERIAL becomes generally available from third parties, for example, though reagent catalogs or public depositories or (b) on completion of the Recipients specific research study described herein or (c) on thirty (30) days written notice by either party to the other, provided that:

    (i) if termination should occur under 14(a), the RECIPIENT shall continue to be bound to the PROVIDER by the least restrictive terms applicable to the MATERIAL obtained from the then-available resources; and

    (ii) if termination should occur under 14(b) above, the RECIPIENT will discontinue its use of the MATERIAL and will, upon direction of the PROVIDER, return or destroy any remaining MATERIAL. The RECIPIENT, at its discretion, will also either destroy the MODIFICATIONS or remain bound by the terms of this agreement as the apply to MODIFICATIONS; and

    (iii) in the event the PROVIDER terminates this Agreement under 14(c) other than for breach of this Agreement or for cause such as an imminent health risk or patent infringement, the PROVIDER will defer the effective date of termination for a period of up to one year, upon request from the RECIPIENT, to permit completion of research in progress that is part of the specific research study described herein. Upon the effective date of termination, or if requested, the deferred effective date of termination, RECIPIENT will discontinue its use of the MATERIAL and will, upon direction of the PROVJDER, return or destroy any remaining MATERIAL. The RECIPIENT, at its discretion, will also either destroy the MODIFICATIONS or remain bound by the terms of this agreement as they apply to MODIFICATIONS.

15. PROVIDER shall have the right to terminate this Agreement at any time if RECIPIENT, RECIPIENT SCIENTIST or others working under his/her direct suspension breaches any of the terms, covenants or conditions of this Agreement. Upon such termination, RECIPIENT shall immediately return any remaining MATERIAL to the PROVIDER.

16. The provisions of this Agreement are severable. In the event any provision of this Agreement is determined to be invalid or unenforceable, such invalidity or unenforceability shall not affect the validity or enforceability of the remaining provisions hereof and the provision shall be reformed to be enforceable and reflect as closely as possible the intent of the original provision.

17. Any waiver of compliance with the terms of this Agreement must be in writing, and any waiver in one instance shall not be deemed a waiver in any future instance.

18. This Agreement is the complete and exclusive statement of the understanding between the parties regarding the subject matter herein, and it supersedes all prior or contemporaneous communications or Agreements regarding the subject matter herein. This Agreement may be amended only by a writing signed by both the PROVIDER and the RECIPIENT.

19. Paragraphs 6, 9, and 10 of this Agreement shall survive termination.

20. The MATERIAL is provided at no cost other than a transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs.

[Remainder of Page Left Blank]

III. Agreed to and Accepted by:

PROVIDING SCIENTIST:

Name: Maureen Groer

Title: Professor

Signature: Maureen Groer

Organization: University of South Florida
Board of Trustees
College of Nursing

Address: 12901 Bruce D Downs Blvd
Tampa, FL 33612

Date: 07/14/2020

PROVIDER:

Authorized Official: _____

Title: _____

Signature: _____

Organization: University of South Florida
Board of Trustees

Address: 3802 Spectrum Boulevard
Suite 100
Tampa, FL 33612

Date: _____

RECIPIENT:

Authorized Official: _____

Title: _____

Signature: _____

Organization: Florida Atlantic University
Board of Trustees

Address: 777 Glades Road,
Boca Raton, FL 33431

Date: _____

RECIPIENT SCIENTIST:

Name: Marlene Brennen

Title: Assistant Professor, Nursing

Signature: _____

Organization: Florida Atlantic University
Board of Trustees

Shipping Address For Materials: Active Motif
1914 Palomar Oaks Way
Suite 150
Carlsbad, CA 92008

Date: _____

APPENDIX B

The Perceived Stress Scale

The Perceived Stress Scale (14 items) - Cohen et al., 1983 Recommended by The NIH Centers for Population Health and Health Disparities (CPHHD)-Measures and Methods Work Group (MMWG) CPHHD Taxonomy- Health and Mental Health [Well-being]-stress & hypervigilance-Perceived Stress Also recommended by MacArthur Foundation (see http://www.macses.ucsf.edu/research/psychosocial/stress.php#perceived)

1. In the last month, how often have you been upset because of something that happened unexpectedly?
2. In the last month, how often have you felt that you were unable to control important things in your life?
3. In the last month, how often have you felt nervous and "stressed"?
4. In the last month, how often have you dealt successfully with irritating life hassles?
5. In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?
6. In the last month, how often have you felt confident about your ability to handle your personal problems?
7. In the last month, how often have you felt that things were going your way?
8. In the last month, how often have you found that you could not cope with all the things that you had to do?
9. In the last month, how often have you been able to control irritations in your life?
10. In the last month, how often have you felt that you were on top of things?

11. In the last month, how often have you been angered because of things that happened that were outside of your control?
12. In the last month, how often have you found yourself thinking about things that you have to accomplish?
13. In the last month, how often have you been able to control the way you spend your time?
14. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

[0=never; 1=almost never; 2=sometimes; 3=fairly often; 4=very often] Note: Items 4, 5, 6, 7, 9, 10, and 13 are scored in reverse direction.

APPENDIX C

Profile of Mood States Questionnaire

Here is another version of the POMS questionnaire, very similar to the original. This is a 40 question modified form developed by Grove and Prapavessis (1992).

Below is a list of words that describe feelings people have. Please **CIRCLE THE NUMBER THAT BEST DESCRIBES HOW YOU FEEL RIGHT NOW**.

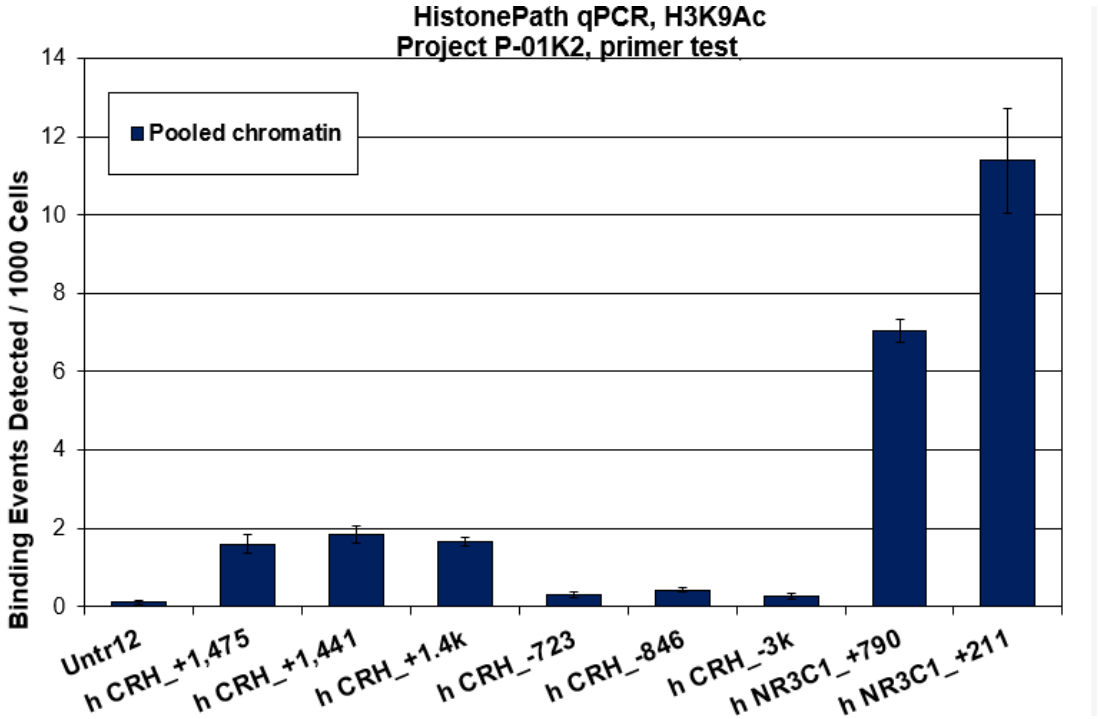
	Not at all	A little	Moderately	Quite a lot	Extremely
Tense	0	1	2	3	4
Angry	0	1	2	3	4
Worn out	0	1	2	3	4
Unhappy	0	1	2	3	4
Proud	0	1	2	3	4
Lively	0	1	2	3	4
Confused	0	1	2	3	4
Sad	0	1	2	3	4
Active	0	1	2	3	4
On-edge	0	1	2	3	4
Grouchy	0	1	2	3	4

Ashamed	0	1	2	3	4
Energetic	0	1	2	3	4
Hopeless	0	1	2	3	4
Uneasy	0	1	2	3	4
Restless	0	1	2	3	4
Unable to concentrate	0	1	2	3	4
Fatigued	0	1	2	3	4
Competent	0	1	2	3	4
Annoyed	0	1	2	3	4
Discouraged	0	1	2	3	4
Resentful	0	1	2	3	4
Nervous	0	1	2	3	4
Miserable	0	1	2	3	4
Confident	0	1	2	3	4
Bitter	0	1	2	3	4
Exhausted	0	1	2	3	4
Anxious	0	1	2	3	4

Helpless	0	1	2	3	4
Weary	0	1	2	3	4
Satisfied	0	1	2	3	4
Bewildered	0	1	2	3	4
Furious	0	1	2	3	4
Full of pep	0	1	2	3	4
Worthless	0	1	2	3	4
Forgetful	0	1	2	3	4
Vigorous	0	1	2	3	4
Uncertain about things	0	1	2	3	4
Bushed	0	1	2	3	4
Embarrassed	0	1	2	3	4

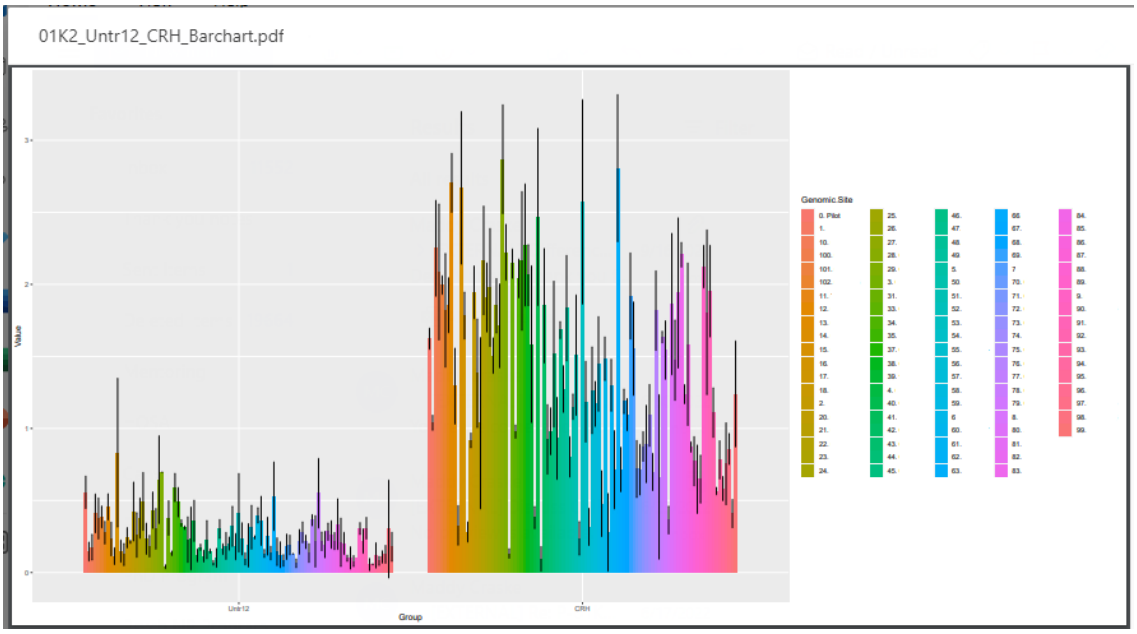
APPENDIX D

Results of Pooled Chromatin Primer Test



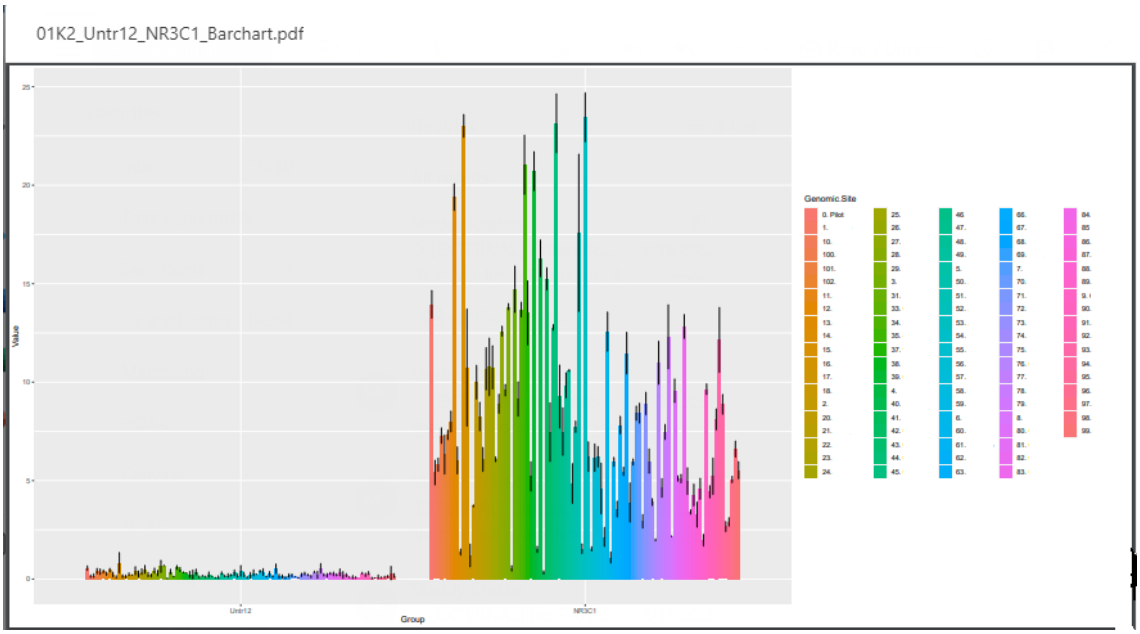
APPENDIX E

All samples with a Negative Control and CRH Primer



APPENDIX F

All samples with a Negative Control and GR (NR3C1) Primer



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