THE PHYSICAL BURDEN OF INEQUITY: STRESS, ALLOSTATIC LOAD, AND RACIAL DISPARITIES IN ADVERSE BIRTH OUTCOMES

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ABSTRACT

African American women experience disproportionately high rates of adverse pregnancy outcomes relative to women of other racial and ethnic groups in the United States. Allostatic load is a frequently hypothesized biological mechanism through which the differential exposure to adversity in the social and physical environment place African American women at higher risk for preterm delivery and low birth weight infants. It is an index of the cumulative physiological wear and tear wrought on the body by over-activation of the physiologic stress response that over time may lead to declines in physical health. The aims of the analyses presented here were to provide initial empirical tests of the hypothesized relationship between allostatic load and adverse birth outcomes among a bi-racial cohort of young women.

Data from women participants in the Bogalusa Heart Study were linked with birth records issued by the State of Louisiana for the years 1990-2009 to identify a cohort of mother-infant pairs. Allostatic load measures were derived from biomarkers measured at a Bogalusa Heart Study examination that occurred prior to conception of the woman's first born child. Data available from the birth records were used to identify infants born preterm, at a low birth weight, or small-for-gestational age.

Results indicate that a latent factor model of allostatic load provides a theoretically and statistically sound measurement of multisystemic physiologic dysregulation. However, there was no evidence of associations between allostatic load and any adverse birth outcome in this sample after adjustment for confounders and consideration of individual- and neighborhood-level socioeconomic indicators.

Refining measurements of chronic stress and identifying biologically-mediated pathways between life-course adversity and negative reproductive health outcomes should be a priority for future research. Equally important is translational research focused on identifying policy-relevant stressors experienced disproportionately by women in positions of racial and socioeconomic disadvantage in order to begin eliminating the root causes of reproductive health inequities.

DEDICATION

To my parents Deirdre and Richard Wallace and my sister Niamh, the pieces that I am.

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I am forever grateful to my mentor, committee chair, and long-time advisor Dr. Emily Harville for her guidance, immense intelligence, and inspirational commitment to perinatal health research. I received an enormous amount of assistance in the development and implementation of this research from Dr. Katherine Theall who imparts her wisdom with great patience, encouragement, and understanding. I am also thankful to Dr. Larry Webber and Dr. Wei Chen for serving on my dissertation committee and providing thoughtful feedback throughout the process. I am grateful to Dr. Pierre Buekens for his leadership, advice, and support through the Training in Global Reproductive Epidemiology program. I extend many thanks to Dr. Lyn Kieltyka and Dr. Tri Tran from the Louisiana State Office of Public Health for their time and patience in assisting me with data linkage procedures. I am indebted to Dr. Gerald Berenson and all of the Bogalusa Heart Study investigators for their generosity in sharing the invaluable wealth of data collected over so many years of work, as well as to the people of Bogalusa, Louisiana. Finally, I thank my dear friends Lillian Funke and Marci Brewer-Asling whose strength I have leaned on more than once, and who bring to the work of improving women and children's health unwavering humor, compassion, and love.

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CHAPTER 1. INTRODUCTION

1.1 Racial Disparities in Adverse Birth Outcomes

Racial/ethnic inequities in women's reproductive health are some of the largest and most disturbing in health research. Infants born to African American women in the United States are more than two times as likely to die before age 1 than those born to non-Hispanic White women.[1] This disparity is driven largely by the disproportionately higher percentage of preterm births (<37 weeks gestation) occurring to African American women; almost 20% of infants born to African American women are preterm, and their rate of death due to preterm-related causes is more than three times the rate among non-Hispanic white women.[1] Likewise, the rates of low birth weight (<2,500g) and very low birth weight (<1,500g) are two and three times higher, respectively, among African Americans compared to whites.[2]

These disparities have existed for as long as there have been data available.[1] They continue to persist despite decades of research, and the causes behind them remain largely unexplained.[3] Previous investigations have focused on potentially differential exposures at or around the time of pregnancy.[3] However, studies that control for differences in maternal education,[4] socioeconomic position,[5,6] health behaviors such as smoking, alcohol, and drug use,[7,8] and access to prenatal care[9] continue to demonstrate evidence of residual disparities in birth outcomes.

The apparent complexity of the mechanisms driving the disparities necessitates new ways of conceptualizing reproductive health determinants. The life-course perspective adapted by Lu and Halfon[10] provides a structural re-framing of reproductive

health in the broader context of women's health: the life-course perspective posits that birth outcomes are a result not only of exposures during the 9 months of pregnancy but of exposure to risk and protective factors that occur and accumulate across the woman's life span, beginning even in her own time in utero (Figure 1). This accumulation refers to the "wear and tear" wrought on the body by persistent and prolonged exposure to stressful physical, psychological and sociocultural environments that impacts the health and functioning of the body over time.[11] Racial/ethnic disparities in reproductive health, therefore, may be at least in part a manifestation of the differential life experiences and exposures of White and African American women in the United States and the resulting disproportionate burden borne by the latter.[12]

1.2 Stress, Allostasis, and Allostatic Load

The concepts of allostasis and allostatic load put forth by Sterling, Eyer, and McEwen provide a plausible biological mechanism behind the physically damaging effects of stress that may account for health differentials across the life-course (Figure 2).[13,14] Experiences of both acute stress (traumatic or major life events) and chronic stress (the accumulation of everyday challenges) involve a disruption homeostasis, or the maintenance of the body's internal physiological systems necessary to support life: blood pressure, oxygen, and pH levels, body temperature and glucose levels.[15] First described by Sterling and Eyer,[13] allostasis refers to the active process of physiologic regulation that allows the body to respond, adapt, and maintain after experiencing or perceiving stress. The biological systems involved in regulation of allostasis include the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, and the metabolic and immune systems[16]. When the brain recognizes a threat or stressor,

corticotropin-releasing hormone (CRH) is secreted from the hypothalamus and the allostatic response is initiated through subsequent activation of the HPA axis and sympathetic-adrenal-medullary (SAM) axis.[17] The HPA axis involves the production and secretion of glucocorticoids from the adrenal cortex while the SAM axis promotes the secretion of catecholamines from nerves of the autonomic nervous system.[18]

Glucocorticoids (including the stress hormone cortisol) catecholamines epinephrine and norepinephrine and inflammatory cytokines are primary chemical mediators of allostatic response.[19] Together they act in complex, interconnected, and nonlinear pathways to effect the functioning of cells, tissues, and organs throughout the body in order to adapt to the perceived challenge while maintaining regulatory control of vital homeostatic parameters.[19] This process can include an increase in heart rate and blood pressure, promotion of glucose production and fat metabolism, and redistribution of immune cells throughout the body.[19]

The cascade of events involved in the stress response process is regulated via negative feedback loops from the same mediators responsible for its initiation.[20] Circulating cortisol is detected by receptors in the hypothalamus/hippocampus which in turn cease further production of CRH.[21] Likewise, elevated levels of catecholamines exert down-regulation on the sympathetic nervous system. This inactivation returns cortisol, catecholamines, and their multiple downstream allostatic mediators to baseline-levels; the "normal" range in which the body's physiological parameters operate is restored.[18]

The biologic range (i.e. limits that define the "normal" operating levels of homeostatic systems and allostatic mediators) for activation of an adaptive stress response are dynamic and change over the life-course of an individual.[20] Both the

perception of stress and the ensuing physiological response are mechanisms influenced by genetics, environment, behaviors, and life events that together shape the way in which an individual's health is resilient or vulnerable to stress.[14,16] Constant accommodation to stress via chronic or persistent over-activity of the HPA and SAM axes leads to a loss of efficiency and effectiveness in the system's negative feedback mechanisms: cell receptor desensitization results in altered and sustained levels of the primary allostatic mediators.[20,22]

This physiologic dysregulation and the damaging effects it bears on multiple biological systems is known as allostatic load.[14] Figure 3 outlines a conceptual model of primary mediators and secondary effectors of allostatic load, and the tertiary (clinical) outcomes associated with allostatic load. The imbalance of primary allostatic mediators (their over and under-production) that results from dysregulation gradually alters the functioning of subsidiary systems as they attempt to overcompensate.[23] These so-called secondary outcomes involve the elevation of metabolic, cardiovascular, and immune system parameters to sub-clinical levels: an increase in blood pressure, dysfunctional glycemic control and cholesterol metabolism, and immunosuppression.[19] Unsustainable over time, this cumulative physiologic burden can begin to manifest pathologically, leading to tertiary outcomes through declines in physical and cognitive function[24-26] and ultimately increased risk of mortality.[27-29]

Physiologic wear and tear is a natural consequence of adaptation over time as humans respond and adapt to environmental challenges internal and external, real and perceived.[30] As such, allostatic load would be expected to increase as an individual ages. However, excessive systemic wear and tear engenders an increasingly ineffective

response which in turn impairs resiliency to stress and the ability to minimize physiological damage. In this manner, allostatic load essentially accelerates biologic "aging".[31] As a result, the individual experiences increased risks for a host of stress-related chronic diseases (tertiary outcomes such as cardiovascular disease, type 2 diabetes, cancer and autoimmune disorders, among others[23]), an earlier decline in overall health, and increased risk of mortality compared to counterparts of the same chronologic age.[24]

As a marker of stress age, it follows that allostatic load would be associated with adverse perinatal outcomes known to increase with maternal age and would be higher in groups at higher risk of idiopathic adverse outcomes such as those experienced disproportionately by African American women. In this context, allostatic load is closely aligned with Geronimus' *weathering hypothesis* or the way in which the chronic stress of disenfranchisement, racism, societal and economic disadvantage leads to a more rapid decline in health status – beginning in young adulthood – among African American women compared to whites in the US.[11] As evidence of weathering, Geronimus demonstrated striking racial differences in the pattern of birthweight to maternal age among black and white women.[12] She found that among African American women, the risk of LBW increased 3-fold with increasing maternal age, a trend not reflected in white women.[12] As further support, she cites that the magnitude of the racial disparity between infant mortality is larger at more advanced maternal ages, evidence of the cumulative consequences of "repeated experience with social, economic, or political exclusion [and] the physical cost of engaging actively to address structural barriers to achievement and well-being" (pg. 133).[32]

1.3 Race, Health, and Allostatic Load

African Americans in the United States bear disproportionate burdens of disease morbidity, disability and mortality that have continued and in some cases increased[33] despite vast political and cultural shifts since the civil rights movement.[34] In 2008, the age-adjusted mortality rate among the black population was 1.2 times that of white with an average risk of death 24.6% higher in blacks compared to whites.[35] Driving the mortality gap are higher rates of such conditions as diabetes (more than twice that of whites), cardiovascular diseases, hypertension, and obesity among others in non-Hispanic blacks compared to non-Hispanic whites.[36]

This broad and persistent African American health disadvantage compels the investigation of the impact of race-based discrimination on health outcomes. Indeed, literature has demonstrated the detrimental health effects of individual-level experiences of overt and perceived discrimination.[37-44] Significant associations indicate that experiences of race-based discrimination may impact health directly by increasing cardiovascular activity and blood pressure[37,39-41,43] and indirectly by influencing health behaviors such as smoking and alcohol use.[42,44]

Mays et al. further examine race-based health disparities as arising from "external effects of the contextual social space on the internal world of brain functioning and physiologic response" (pg. 201).[34] The allostatic load model bridges concepts from social science, psychology, and functional neuroscience, and may provide quantifiable evidence of this theory. Carlson and Chamberlain highlight the usefulness of the allostatic load model more specifically from the African American perspective given the magnitude of black-white health inequities, the socially-defined nature of the racial

category, and its "unique historical position in the context of American society shaped by the legacy of slavery" (pg. 312).[45] In fact, studies show consistently higher levels of allostatic load scores in blacks compared to whites and even other ethnic minorities using US nationally-representative data.[46-50] Moreover, gender-specific patterns of allostatic load indicate that women exhibit higher cumulative burden of physiologic regulation than do men,[51] and black women in particular have been shown to have the highest levels of allostatic load across race and gender.[48,52,53]

Moving beyond singular experiences of discrimination-induced stress to vast population-level disparities in health requires a broader awareness of the chronicity and magnitude of racial discrimination and its cumulative down-stream health effects.[34] Social science and public health research continues to elucidate multi-level factors that predispose African Americans to poorer health: intergenerational transmission of health risks, differential access to health care and behavior of health care providers, socioeconomic position, neighborhood environment, segregation, and institutionalized racism.[34] Developing a comprehensive understanding of how these experiences impact health – the mechanism by which they get "under the skin" – has required an interdisciplinary approach and an integration of theories from biology and the social sciences.[54]

Massey provides an orientation to this approach, arguing that persistent residential segregation undermines the social and economic well-bring of African Americans in the US, resulting in socioeconomic inequality and "involuntary confinement in areas of concentrated poverty and violence" (pg. 20).[55] Individuals residing in segregated neighborhoods may have restricted access to educational and employment opportunities,

as well as low levels of social mobility and social capital – limiting opportunities for income and wealth accumulation. As a result, concentrated poverty, increases in crime, dilapidated housing conditions, and lack of social support may engender higher allostatic load directly through prolonged exposure to such stressors and lack of social support for coping, or indirectly through higher rates of detrimental health behaviors (smoking or substance use).[56] Massey proposes a biosocial pathways model in which these contextual factors produce disproportionately high allostatic load among blacks, leading to elevated rates of disease (Figure 4).[55]

1.4 Allostatic Load and Perinatal Health

While a growing body of literature has examined the deleterious health effects of stress and anxiety on reproduction,[38,57-66] conflicting findings suggest inconsistency and inadequacy in definitions and measurements of stress among pregnant women.[67] Many have relied on subjective measures of stress and questionnaires that, while validated, may not capture the complex and multilayered nature of stress from a physiological or biobehavioral perspective.[67] For example, Lu and Chen[68] found no association between stressful life events and racial disparities in preterm birth, but they acknowledge the inadequacy of their stress assessment which may have failed to capture "those daily hassles, chronic stressors, or contextual factors that may be more pervasive in the lives of women of color" (pg. 698). To this extent, allostatic load may be a more appropriate measurement of the broader accumulation of stress over the life-course.[67,69]

With further regard to women of color, Rosenthal and Lobel[70] hypothesize three sources of stress that are unique to African American women and may affect reproductive health in particular: power disadvantages in obstetric practices and abuses of black

women by the medical system; contradictory societal pressures exerted on black women regarding whether they should or should not have children; and historical and contemporary stereotypes about black women related to sexuality and motherhood. According to the authors, prenatal stress that effects the health of both the woman and her fetus "arises in part from the legacy and accumulation of distinct lifetime experiences of discrimination and mistreatment, which continue, are heightened and augmented by discrimination during pregnancy" (pg. 978).[70]

Propelled by Geronimus' *weathering hypothesis*, a number of researchers have proposed evaluating allostatic load as a physical indicator of the cumulative exposure to such stressors that may account for increased rates of preterm birth and infant birthweight experienced by black women.[3,10,71-75] In terms of "stress-age", Rich-Edwards, et al., showed the lowest risk age group for preterm birth among non-Hispanic white women is 30-34, while for black women it is 25-29, as though the age-associated increase has been shifted younger.[76] Black women also show a steeper and earlier age-related rise of risk for term small-for-gestational-age and low birth weight infants.[77,78] Despite this evidence and the frequency with which allostatic load has been hypothesized as a contributor to racial disparities in adverse birth outcomes, only one study has directly quantified the effects of allostatic load on perinatal health indicators.[79] It did appear that increasing allostatic load was significantly associated with decreasing gestational age at birth, though given the small sample size, results should be interpreted with caution.

There are studies, however, that suggest the pathways by which allostatic load may impact length of gestation, fetal growth and development. Holzman et al., found that elevated levels of neuroendocrine catecholamine levels in maternal urine

(epinephrine, norepinephrine and dopamine) at mid-pregnancy contributed to an increased risk for spontaneous preterm delivery.[80] The association remained after excluding women with placental inflammation or vascular complications, suggesting the independent effect of catecholamines on preterm birth.[80] Excess CRH and cortisol transported via the placenta has been shown to slow fetal growth.[81] Romero et al. summarize the pathophysiological processes by which a maternal systemic inflammatory response driven by pro- inflammatory cytokines may cause premature parturition.[82] Other studies have confirmed the link between inflammation and preterm birth,[83-85] and Brou et al. reported on the racially differential pathways of immune biomarker dysregulation in the pathophysiology of preterm birth.[86] Dysfunction of maternal cardio-metabolic processes contribute to preterm labor and the pathogenesis of intrauterine growth restriction.[87,88]

While it is clear that individually the biological systems responsible for maintaining allostasis have direct impacts on fetal health, less is known about the effect of their collective dysregulation. This novel approach acknowledges their interconnected nature and emphasizes a multisystems view of reproductive health risks and differentials.

Figure 1. The life-course perspective of reproductive health. The cumulative exposure to risk (downward arrows) and protective (upward arrows) factors over the life-span effect reproductive health potentials thereby contributing to reproductive health disparities. Reprinted from Lu and Halfon, 2003.[10]

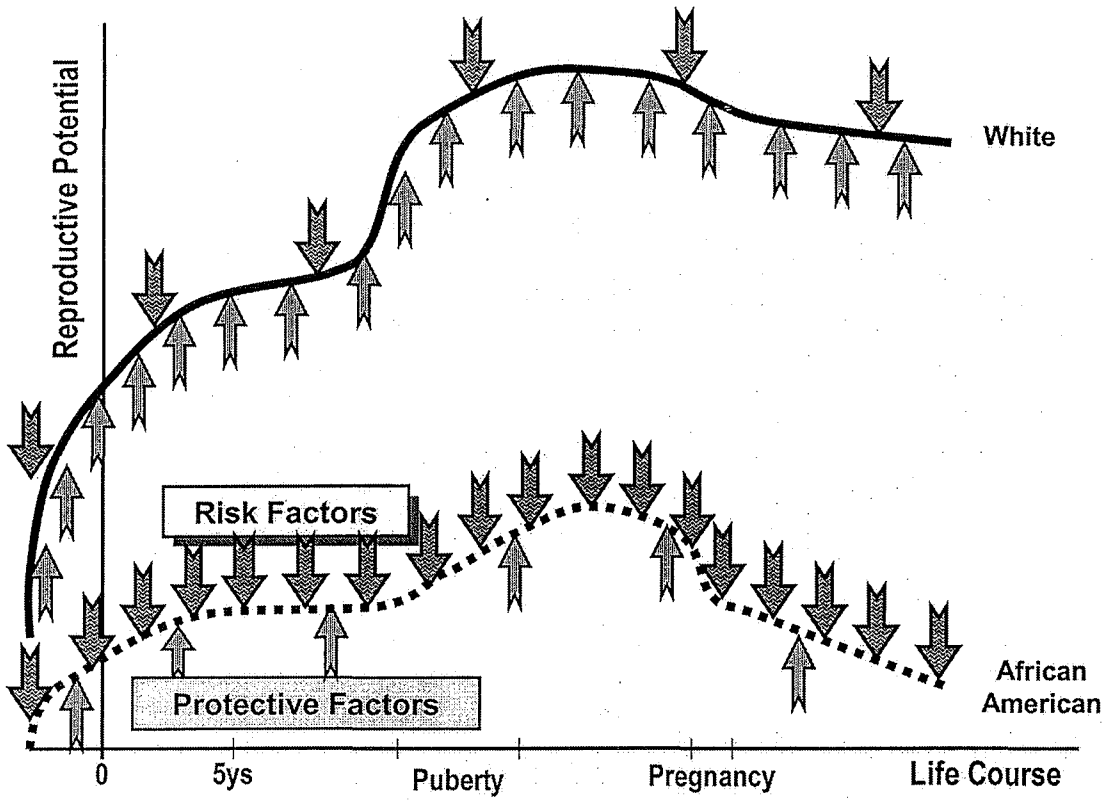


Figure 2. The stress response and development of allostatic load.[18] Perception of stress is influenced by one's experiences, genetics, and behavior. When the brain perceives an experience as stressful, physiologic and behavioral responses are initiated leading to allostasis and adaptation. Over time, allostatic load can accumulate, and the overexposure to neural, endocrine, and immune stress mediators can have adverse effects on various organ systems, leading to disease.

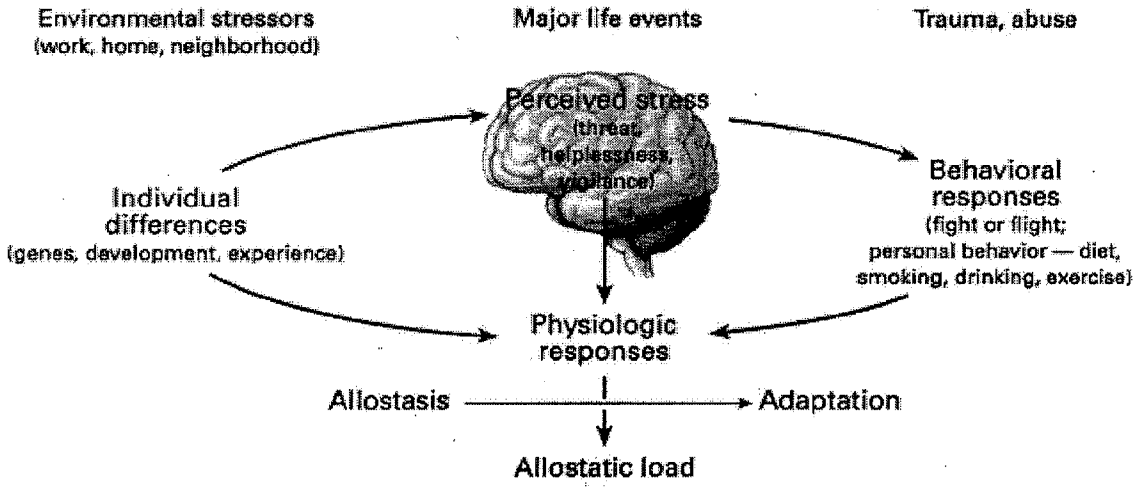
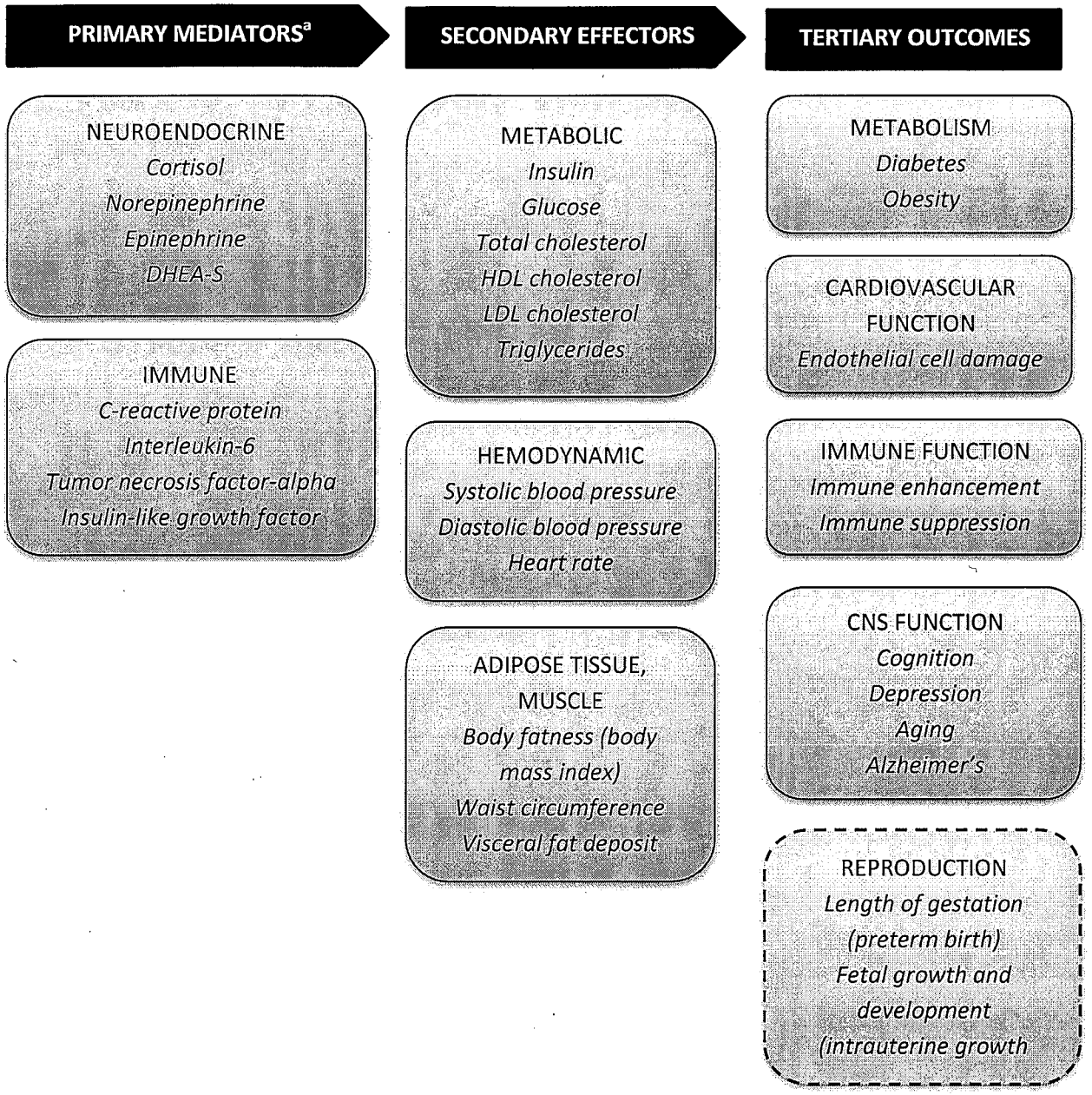
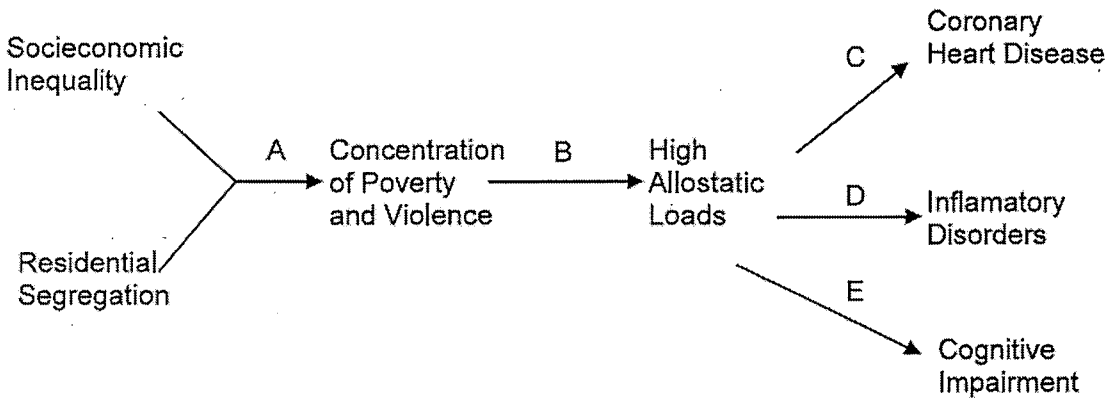


Figure 3. Conceptual model of systems (*and most frequently utilized constituent biomarkers*) involved in primary mediation, secondary effectors, and tertiary outcomes of chronic stress and allostatic load.



[a]Primary mediators act by regulating each other and multiple cellular, tissue, and organ systems thereby creating a non-linear network.

Figure 4. Massey's[55] biosocial model of racial stratification connects elements of social structure to distinctively high allostatic loads among African Americans to elevated risk of disease.



CHAPTER 2. PURPOSE

2.1 Significance

An allostatic load framework has been increasingly used to conceptualize the physical consequences of the multi-level biological, environmental, and social factors that drive racial disparities in health, including reproductive health.[10,34,45,54] It represents an integration of the life-course perspective and the harmful physical health effects of social hierarchy.[45]

Operationalization of the allostatic load model proposes that individuals at high risk for tertiary clinical outcomes can be identified by measuring the multi-systemic interactions and non-linear networks of allostatic mediators as well as sub-clinically relevant biomarkers of secondary effects.[23] Yet despite the theoretical plausibility of the multisystemic dysregulation as a mediator of health over the life-course and precursor to clinical pathologies, the impact of allostatic load has not yet been directly measured and analyzed with regard to its impact on reproductive outcomes. The significance of this research is implied by the magnitude of reproductive health disparities and the lack of explanation for their persistence. Furthering our understanding of the longitudinal and contextual determinants of reproductive health can help shape policy and interventions that promote health equity among all women and their infants.

2.2 Objective and Specific Aims

The overall objective of this analysis was to examine associations between maternal allostatic load in pre-pregnancy and birth outcomes of the infant and to describe its contribution, if any, to racial/ethnic disparities in reproductive health. Three

manuscripts addressed individual components of this objective with the following specific aims:

> Manuscript I. To utilize individual-level biomarker data to develop a latent factor model of allostatic load that captures the inter-relationships involved in the multiple biologic systems involved in physiologic regulation. Secondly, the purpose was to describe the differences in allostatic load levels among a bi-racial cohort of young women.
>
> Manuscript II. To examine the relationship between allostatic load prior to conception and the occurrence of preterm birth, small-for-gestational age, and low birthweight infants, and to identify any differences in effect size by maternal race and socioeconomic position (education).
>
> Manuscript III. To examine the associations between allostatic load, race, and adverse birth outcomes within the context of neighborhood-level poverty.

Each manuscript (Chapters 4, 5, and 6) contains details regarding the background, analytic methods, results, and discussion of results specific to each aim. Chapter 3 provides a brief initial overview of the study design, population, and methods utilized in each manuscript. The final chapters summarize the results collectively and present a further discussion of the strengths, limitations, conclusions, and recommendations drawn from this work.

CHAPTER 3. METHODS

3.1 Overview of Study Design Population

This study is a retrospective cohort design based on secondary analysis of women participants the Bogalusa Heart Study (BHS) and the linked birth records of their first-born infants. The Bogalusa Heart Study is a biracial (35% black, 65% white) community-based study that has been rigorously researching cardiovascular health in children and young adults since 1973. [89] The semirural town of Bogalusa, Louisiana, is located in Washington Parish, a micropolitian statistical area of approximately 45,000 residents. In 1973, the first of a series of nine cross-sectional surveys was conducted among school-aged children (5-17 years) in the community with a very high (>80%) participation rate.[90] Surveys of schoolchildren were repeated through 1994, examining newly enrolled school children as well as re-examining those previously enrolled. As children participants aged, they were eligible for reexamination in up to four of the ten surveys conducted among adults age 18-50 occurring between the years of 1997 and 2009.[91] This panel design enabled longitudinal follow-up of individuals and potentially up to 15 serial observations across their life-course.

As of 2011, the study includes data on almost 6,000 women, many of whom are now in their late reproductive years. For the purposes of this investigation, a data linkage procedure was used to match all women BHS participants with birth records of any and all children born to them in the state of Louisiana between the years of 1990 and 2009. Among the women successfully linked to the birth record of her first born child, analysis will include only those women with biomarker exposure data available from a BHS

examination that occurred prior to the date of their last menstrual period of her first pregnancy.

3.2 Summary of Methods

Structural equation modeling was used to investigate alternate models of allostatic load and to develop a final allostatic load measurement model for the purposes of Manuscript I. In this instance, the hypothesized model consisted of five latent factors corresponding to five domains associated with allostatic regulation: blood pressure, lipids, insulin resistance, inflammation, and adiposity. Each of the five latent factors was measured by two biologic parameters and each latent factor was allowed to covary with every other latent factor to account for the known relationships between them. Subject's scores on each latent domain were summed for a total allostatic load score and subjects in the top quartile were categorized as having high allostatic load. Log-linear modeling was used to estimate the relative risk of high allostatic load associated with age and race.

To address the specific aim of Manuscript II, a three-stage data linkage procedure was used to link women from the Bogalusa Heart Study to birth record of their firstborn child using LinkPro v3.0 for a dataset of mother-infant pairs. An allostatic load index was computed by summing the number of biomarkers falling within the highest risk quartile of the age-adjusted sample distribution. Log-linear modeling was used to examine relationships between allostatic load, race, education, and the three birth outcomes of interest (preterm birth, low birthweight, and small-for-gestational age), controlling for smoking during pregnancy, maternal age, date of BHS examination and length of time prior to conception.

Finally, Manuscript III involved geocoding BHS participant addresses at the time of the BHS examination from which the allostatic load measurement was derived into census block group in order to examine neighborhood-level contextual effects on the relationship between allostatic load and birth outcomes. Neighborhood-level poverty was estimated as the proportion of persons in a given census block group whose household income was below the federal poverty line, a measure ranging from 0 to 1.0. Individuals were propensity-score matched on the probability of living in an impoverished neighborhood in order to reduce structural confounding. Generalized estimating equations were used to estimate the odds of preterm birth and low birth weight associated with allostatic load, combined race and neighborhood-level poverty, and individual-level socioeconomic position (education) adjusted for maternal age, smoking during pregnancy, year of BHS examination, and preconception years. Models accounted for both matched individuals and clustering within block groups. Analyses for all three manuscripts were performed in SAS v9.2.

CHAPTER 4. Measuring Multisystemic Physiologic Stress in African American and White Women: The Bogalusa Heart Study (*Manuscript I*)

Maeve Wallace, MPH, Emily Harville, PhD, Katherine Theall, PhD, Larry Webber, PhD, Wei Chen, MD, PhD, Gerald Berenson, MD.

4.1 Introduction

Both the perception of stress and the ensuing physiological response are mechanisms influenced by genetics, environment, behaviors, and life events that together shape the way in which an individual's health is resilient or vulnerable to stress.[14,16] The concepts of allostasis and allostatic load provide a plausible biological mechanism behind the physically damaging effects of chronic or recurrent exposure stressful situations.[13,16] Allostasis refers to the active process of physiologic regulation that allows the body to respond, adapt, and maintain homeostasis when individuals encounter physical or psychological challenges in their environment.[13] Chronic, persistent and prolonged exposure to stress leads to increasing ineffectiveness and inefficiency in the body's regulatory processes.[20] The imbalance of primary allostatic mediators (stress hormones cortisol, epinephrine, norepinephrine, and dehydroepiandrosterone sulfate) gradually alters the functioning of the subsidiary systems they target.[23] These secondary effects involve the elevation of metabolic, cardiovascular, and immune system parameters to sub-clinical levels: an increase in blood pressure, dysfunctional glycemic control and cholesterol metabolism, and immunosuppression.[19] Unsustainable over time, this cumulative physiologic burden can begin to manifest pathologically, leading to tertiary clinically-relevant outcomes through declines in physical and cognitive function[24-26] and ultimately increased risk of mortality.[27-29]

Allostatic load is the index of such physiologic dysregulation and its damaging effects on multiple biological systems.[14] It is the cumulative "wear and tear" wrought on the body due to constant accommodation to stress.

Physiologic wear and tear is a natural consequence of adaptation over time as humans respond and adapt to environmental challenges internal and external, real and perceived.[30] As such, allostatic load would be expected to increase as an individual ages. However, excessive systemic wear and tear engenders an increasingly ineffective response which in turn more rapidly impairs resiliency to stress and the ability to minimize physiological damage. In this manner, allostatic load essentially accelerates biologic "aging".[31] As a result, the individual experiences increased risks for a host of stress-related chronic diseases (tertiary outcomes such as cardiovascular disease, type 2 diabetes, cancer and autoimmune disorders, among others),[23] an earlier decline in overall health, and increased risk of mortality compared to counterparts of the same chronologic age.[24] To this extent, allostatic load is closely aligned with Geronimus' *weathering hypothesis* or the way in which the chronic stress of disenfranchisement, racism, societal and economic disadvantage leads to a more rapid decline in health status – beginning in young adulthood – among African American women compared to Whites in the US.[11]

Despite the sound theoretical plausibility of allostatic load as a mechanism linking social inequities to disparities in health, the multiple, non-linear biological pathways involved in stress and adaptation make appropriately quantifying allostatic load difficult.[23] Researchers from the MacArthur Studies of Successful Aging were the first to examine the construct validity of an allostatic load index for the quantification of cumulative physiological burden across a range of regulatory systems.[24] The original

index was a summary measure of ten biological components representing parameters of the body's regulatory systems most relevant to disease risk: cardiovascular, metabolic, and neuroendocrine. An index was computed for each individual based on a count of the number of components scoring in the highest risk quartile of the sample distribution.[24] Acknowledging the possible over-simplicity of this methodologic approach, more recent studies have extended the research on allostatic load measurement using structural equation modeling[53] and confirmatory factor analysis[92] methods. These techniques enable modeling allostatic load as a collection of higher-order associations between parameters both within and across the physiological systems they represent. With theoretically and statistically coherent models that fit the data well, these methods suggest that allostatic load components share a common variance and that an index of dysregulation should reflect the inter-relationships among the biological systems included.

As the ability to quantify allostatic load and model its impact on health progress, it may begin to illuminate the ways in which repeated and chronic exposure to racial discrimination and societal disadvantage exerts damaging, long-term physical effects on people of color in the US.[34] The purpose of this investigation is to model allostatic load as a latent construct underlying dysregulation across the major biological systems involved in stress response. Secondly, the purpose is to describe the differences in allostatic load levels among a bi-racial cohort of young women. We hypothesize that a steeper age-related increase in allostatic load will occur among African American women compared to Whites.

4.2 Methods

Study Population

The Bogalusa Heart Study (BHS) is a biracial, community-based study that has been rigorously researching cardiovascular health in children and young adults since 1973.[89] The semirural town of Bogalusa, Louisiana, is located in Washington Parish, a micropolitian statistical area of approximately 45,000 residents. In 1973, the first of a series of nine cross-sectional surveys was conducted among school-aged children (5-17 years) in the community with a very high (>80%) participation rate.[90] Surveys of schoolchildren were repeated through 1994, examining newly enrolled school children as well as re-examining those previously enrolled. As children participants aged, they were eligible for reexamination in up to four of the ten surveys conducted among adults age 18-50 occurring between the years of 1997 and 2010.[91] This panel design enabled longitudinal follow-up of individuals and potentially up to 15 serial observations across their life-course.

For the purpose of the current study, analyses were based on all women who participated in at least one BHS examination and had non-missing data for all biologic indicators (N=157). For women who completed multiple exams, only the most recent was utilized. Depending on the number of exams completed and the year of enrollment, participants' age at their most recently completed exam could range from 25 to 42 years. Women included in this analysis were those of African American or White race, as are the vast majority of the BHS cohort (approximately 35% African American, 65% White). Further exclusions were those who reported use of diabetes, antihypertensive, or cholesterol-lowering medication at the time of exam.

Allostatic Load Measurement

Ten biological parameters were available for analysis: systolic and diastolic blood pressure (SBP and DBP), total cholesterol, triglycerides, insulin, glucose, white blood cells (WBC), C-reactive protein (CRP), body mass index (BMI) and waist circumference. Described in greater detail elsewhere,[89] standardized protocols for data collection were implemented by trained BHS examiners. The physical examination involved duplicate height and weight measurements, which were used in the calculation of body mass index (weight in kg/height m^2). Right arm blood pressure was measured in triplicate with mercury sphygmomanometers by each of 2 trained observers on subjects in a relaxed, seated position; means of 6 replicate blood pressure readings were used for both SBP and DBP. All subjects were instructed to fast for 12 hours prior to the examination and blood draw. An interview prior to the morning screening was used to assess compliance. Plasma glucose level was measured as part of a multiple chemistry profile (SMA20) with the multichannel Olympus Au-5000 analyzer (Olympus, Lake Success, NY). A radioimmunoassay kit was used to measure plasma insulin (Phadebas insulin kit, Pharmacia Diagnostics, Piscataway, NJ). Serum cholesterol and triglycerides levels were assayed enzymatically on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, Ind).[93] Plasma high sensitivity C - reactive protein (CRP) was measured by latex particle-enhanced immunoturbidimetric assay on the Hitachi 902 Automatic Analyzer. WBC count of whole blood was determined at the local Bogalusa Charity Hospital clinical laboratory using a Coulter counter method. All laboratories responsible for processing BHS samples are rigorously monitored for quality control, precision and accuracy by independent institutions.

Analyses

All ten biological parameters were initially assessed for normality and those that deviated were log (base $_e$) transformed. Structural equation modeling was used to investigate alternate models of allostatic load and to develop a final allostatic load measurement model. A measurement model is one that captures the nature of the relationships between a number of latent variables or factors, and the manifest (observed) indicator variables that measure those latent constructs.[94] Our hypothesized model consisted of five latent factors corresponding to five domains associated with allostatic regulation: blood pressure, lipids, insulin resistance, inflammation, and adiposity. Each of the five latent factors was measured by two biologic parameters (SBP and DBP; triglycerides and total cholesterol; insulin and glucose; WBC and CRP; BMI and waist circumference, respectively) and each latent factor was allowed to covary with every other latent factor to account for the known relationships between them.

A number of model fit indices were used to evaluate how well the hypothesized model represents the structure underlying the data: the chi-square test (χ^2), the ratio of the chi-square statistic to degrees of freedom, the comparative fit index (CFI), the non-normed fit index (NNFI) and the root mean square error of approximation (RMSEA). The chi-square test is intended to assess how well the hypothesized model fits the observed data by comparison of the estimated and observed variance-covariance matrices, and a relatively small or non-significant test statistic is desirable. However, due to the known sensitivity of the chi-square test to sample size and minor deviations in multivariate normality, the chi-square to degrees of freedom ratio provides a better measure of fit, and values of 2 or less are considered adequate.[95] Bentler and Bonett's

NNFI and the CFI both provide additional measures of model fit that are accurate regardless of sample size and values of 0.90 or greater are indicative of good fit on both indices.[96] RMSEA absolute fit values of 0.05 or less are desirable and indicate that the model fits the data well.[97] Finally, the relative fit of the hypothesized model was compared to a null model – one in which the latent factors were not allowed to covary and were modeled as uncorrelated, independent domains – by means of a chi-square model improvement test.

Based on the final measurement model, factor scores were used to quantify each subject's relative position on the latent continuum represented by each factor. Factor scores are estimated as a linear combination of the observed variables (standardized to the rest of the population) and weighted by the factor score regression coefficient. Subject's scores on each factor were summed for a total allostatic load score, representing the extent to which dysregulation across all domains is manifest in each subject relative to each other. Subjects were grouped into quartiles of total allostatic load score and those in the top quartile were categorized *a priori* as having a high allostatic load. This categorization of the score was done in order to facilitate interpretation and compare individuals across levels of systemic dysregulation. Finally, log-linear modeling was used to estimate the predicted probability of high allostatic load at each age, and the relative risk of high allostatic load associated with age groups (25-34, >=35) and race in this sample, controlling for smoking and including a test for interaction between race and age.

We conducted sensitivity analyses in order to evaluate the robustness of our results. First, we used an alternate cut-point to define a high allostatic load score (above

or below the median). Second, we tested the traditional high-risk percentile summary score operationalization of allostatic load (one point for each of the 10 biological parameters measured in the top quartile of the sample's distribution) in a log-linear model including race and age, and a test for interaction. All analyses were performed using SAS v9.2 (SAS Institute, Cary, NC).

4.3 Results

Complete data for the 10 parameters of interest were available in 157 women. Table 1 contains the sample demographic characteristics and descriptive statistics for the biological indicators included in the analysis. The sample's racial distribution approximately mirrors the larger Bogalusa Heart Study population (one third African American, two thirds White). Subject's most recent exam year ranged from 1995 to 2002 at mean age of 34. Triglycerides, glucose, insulin and C-reactive protein were log-transformed to improve univariate normality.

The hypothesized measurement model was estimated using the maximum likelihood method. All manifest variables loaded significantly on their corresponding latent domain, indicating convergent validity of the biological parameters (Figure 1). With the exception of glucose and white blood cells, all of the biological parameters had relatively high loadings on their respective factors (>0.50). The strongest correlations between the latent factors or domains were between adiposity and insulin resistance, inflammation and insulin resistance, and adiposity and inflammation (0.81, 0.69, and 0.61, respectively; Figure 1.) The model fit indices for the hypothesized model suggested a good fit to the data and adequate description of the underlying structure (Table 2). Although the model χ^2 was statistically significant (50.45, 25 df), the χ^2/df ratio was 2,

and the CFI was 0.97 and NNFI = 0.94, both exceeding the 0.90 threshold for a reasonably good fit. Furthermore, the RMSEA was just over the 0.05 threshold at 0.08. This model fit the data significantly better than the uncorrelated null model in which the latent factors were not allowed to covary (improvement test difference in model χ^2 = 177.23), not a surprising result given the known relationships between allostatic domains. In supplementary analyses, a third model was developed consisting of a common second-order allostatic load factor representing the relationships between all of the individual allostatic domain factors (as opposed to the pairwise correlations in the hypothesized measurement model). Seeman et al.,[53] demonstrated the theoretical coherence of this "meta-factor" model of allostatic load using data from the Coronary Artery Risk Development in Young Adults study. The meta-factor model, however, fit our sample data poorly (CFI=.73, NNFI=.58, and RMSEA=.21), and therefore the pairwise correlated 5-factor measurement model was selected as the final model. Table 2 summarizes the fit statistics for all three models.

Contrary to the study hypothesis, White women in our sample had a higher estimated mean total allostatic load factor score compared to African American women ($P<0.05$, Table 3). African American women, however, had a significantly higher mean score on the blood pressure factor (0.02 vs. -0.01), and a higher, albeit non-significant mean score on the adiposity factor. Whites had a significantly higher mean score on the lipids factor, and there were no significant racial difference in mean scores for the insulin resistance and inflammation factors. Finally, there was some evidence of a trend in allostatic load increasing with age in both White and African American women. Moreover, the predicted probability of a high allostatic load score appeared to increase

more sharply by age among African American women, compared to Whites suggesting evidence of more rapid health deterioration, or weathering (Figure 2). However, while the adjusted log-linear relative risk of high allostatic load appeared to correspond to the hypothesized direction (increased risk among the older women compared to younger), the trend was not statistically significant, nor was the interaction between age and race. RR for high allostatic load in older women compared to younger women 1.24 (95% CI: 0.63, 2.46) for Whites, and RR= 3.23 (95% CI: 0.63, 16.69) in African Americans.

The results of our sensitivity analyses were consistent with our initial findings. By the alternate definition of a high total allostatic load factor score (above the median), White women still had a higher mean score compared to African Americans ($P<0.01$), and both race and age remained non-significant in the log-linear model. Finally, we repeated the above analyses using the traditional summary measure of allostatic load and found no difference in mean score by race in univariate analysis (mean score=2.4 for White women, 2.5 for African American women, P=.92), nor in the log-linear model including race and age. Age, however, was significant in this model (beta estimate = 0.0248, P=0.03).

4.4 Discussion

The intention of this analysis was to extend the work of Seeman et al.,[53] McCaffery et al.,[92] and others who have sought to develop a model of allostatic load that is both statistically sound and theoretically in line with the conceptual model of cumulative physiologic wear and tear as the price of chronic adaptation to stress. Consistent with their findings, our results provide supporting evidence for a latent factor model of allostatic load that captures the inter-relationships between the multiple

biological systems involved in physiologic regulation. Our correlated, five-factor model provided an adequate fit to the data, which was significantly better than the uncorrelated model.

There are several reasons why our data likely did not fit the second-order underlying allostatic load factor model as well as the five-factor model, including our relatively small sample size and our limited number of biological parameters representing each underlying regulatory system. Guidelines for minimum appropriate sample size (N) and number of measured indicators per latent factor in confirmatory factor analysis and structural equation modeling are inconsistent and occasionally contradictory.[98] Our study complies with the established rule of thumb for an absolute minimum N>100;[99] however our ratio of observations to parameter estimates (variances, covariances, and path coefficients) in the final model is lower than the suggested 5:1 at approximately 2:1.[94] This ratio would be considerably lower in the meta-factor model. Additionally, the availability of more biological indicators from each regulatory system may have provided a better fitting model;[98] however increasing the number of indicators per factor (from 2 per factor, in the current study) would have further decreased the N to parameter estimate ratio.

Despite our limited sample size, our theorized measurement model appeared to provide an adequate fit to the empirical data. We used this model to develop a novel metric of the co-occurrence of dysregulation across systems. Higher values of each of the biological parameters defined in the model indicate a greater degree of dysregulation in the corresponding subsystem or domain. Therefore, summing the standardized

regression-based factor scores for each domain allowed us to quantify each subject's degree of multisystemic dysregulation relative to each other.

By this measure, the White women in our sample had a higher mean allostatic load score overall, contrary to our hypothesis. Previous studies have shown consistently higher levels of allostatic load scores in African Americans compared to Whites and other ethnic minorities using US nationally-representative data.[46-50] Moreover, gender-specific patterns of allostatic load indicate that women exhibit higher cumulative burden of physiologic regulation than do men,[100] and African American women in particular have been shown to have the highest levels of allostatic load across race and gender.[53,101]

Reasons behind our contrary finding are difficult to explain. In contrast to the majority of previous studies that focus on urban populations or national samples, our study population arises from the unique context of the rural South, and the experiences of both the White and African American women we examined are inherently different from their urban counterparts. These rural women represent an understudied population, and though sparse, the literature on allostatic load in rural populations centers largely around shared cumulative socioeconomic stressors as opposed to race-based challenges. For example, Fuller-Rowell et al.[102] showed that the effect of poverty on allostatic load in a group of rural, predominantly White adolescents was mediated by experiences of socioeconomic position-related discrimination. Brody et al.[103] found that a supportive family environment buffered development of allostatic load in a sample of African American youth residing in rural Georgia. Evans[104] reported a dose-response relationship between exposure to cumulative risk (a metric which captured exposure to a number of social, socioeconomic and environmental risk factors) and allostatic load in rural White

children. It may be that one or many of the social and socioeconomic risk factors that characterize rural living – chronic poverty, lack of educational and employment opportunities, lack of availability and access to medical care, domestic violence, alcohol and drug use[103,105,106] – had a larger effect on the development of allostatic load than race alone (as proxy for experiences of interpersonal and institutionalized racism) in this small sample. Previous nationally-based research has demonstrated broader racial disparities in AL among non-poor women compared to impoverished women,[101] suggesting the significant and highly influential impact of poverty on allostatic load.[31] As measures of socioeconomic position were unavailable for analysis in our data, future research should address how interactions between socioeconomic factors, and race and gender act as contextual stressors in the rural South and may influence stress response processes and susceptibility.[107]

While the trend in allostatic load scores increasing with age appeared consistent with our hypothesis, our relatively small sample size is most likely the reason for our lack of a statistically significant finding. Our plot of the predicted probability of high allostatic load shows a striking racial difference in the pattern of allostatic load and age and mirrors that of Geronimus et al.[101] Their analysis included a broader range of ages and reported little difference in allostatic load scores among women younger than age 35 but significant and increasing racial gaps thereafter up to age 64. Likewise, the slope of the predicted probabilities among African American women in our sample appears to increase sharply in the mid-30s and eventually surpasses white women at age 40 and above (Figure 2). Applied to a larger sample of African American and white women, this pattern may provide further statistically significant evidence of weathering and the racial

disparities in clinical and subclinical health that develop in young adulthood and widen with age.

In addition to our limited sample size, the data available in these analyses are cross-sectional, which prohibits our drawing conclusions about the accumulation of multisystemic dysregulation in a single individual over time. A further limitation is our inability to investigate the impact of socioeconomic position in modifying the relationship between race and allostatic load given the data available. Finally, in these analyses we did not weight any of the factor scores in creating an allostatic load score; therefore, by simply summing scores across all five factors, lipids – the domain with scores of the highest magnitude for both Whites and African Americans – drove the total score. Whites in this population had significantly higher crude mean triglyceride (134.6 mg/dL vs. 85.1 mg/dL in African Americans, $P<0.01$) and total cholesterol levels (195.1 mg/dL vs. 173.7 mg/dL in African Americans, $P<0.01$). It follows that the mean lipids factor score – representing the underlying distribution of these two biomarkers – was significantly higher in Whites, as was the total allostatic load score which combined this factor score with all others of much less magnitude.

There are strengths to this analysis that contribute to the literature on chronic stress and racial disparities in health. Our operationalization of allostatic load overcomes the overly simplistic algorithms used in a majority of previous studies and accounts for the known relationship between allostatic mediators and the regulatory subsystems they comprise. As such, it represents a theoretically sound and statistically appropriate multisystemic measure of biological risk at pre-clinical levels. Further, our unique study population consisting of young women allowed for an examination of the origins of racial

gaps in allostatic load at early ages in contrast to the literature currently dominated by aging populations.

The allostatic load framework allows for a shift beyond individual-level analyses of health determinants towards examining how social, psychosocial, environmental, and biological stressors collectively contribute to differential rates of disease. As such, allostatic load has been repeatedly recognized as a potential contributor to racial disparities in health yet infrequently quantified empirically. Future studies should continue to develop models that capture the cumulative effects of stress on an array of interconnected biological systems. Longitudinal investigations on the accumulation of allostatic load over time may further elucidate the biological mechanisms by which experiences of social injustice lead to population-level disparities in health. Finally and perhaps most importantly, future work should begin to address the stressful life experiences that disproportionately burden African American women in the US.

Table 1. Descriptive Statistics of sample demographics and biological indicators (N=157).

	Mean or %	SD
Race		
African American (%)	30.6	
White (%)	69.4	
Age (year)	33.8	4.6
Systolic Blood Pressure (mmHg)	111.9	12.1
Diastolic Blood Pressure (mmHg)	75.4	9.6
Body mass index (kg/m^2)	28.4	7.3
Waist circumference (cm)	86.8	16.8
Total cholesterol (mg/dL)	188.5	39.5
Triglycerides (mg/dL)	119.5	81.7
Glucose (mg/dL)	81.4	17.8
Insulin(uU/mL)	12.3	8.0
White Blood Cells (1,000/μL)	6.6	1.9
C-Reactive Protein (mg/L)	3.4	3.7

Table 2. Model fit statistics.

	χ^2	df	χ^2/df	NNFI	CFI	RMSEA
Good fit reference:	*Non-significance*		*<2.0*	*>0.90*	*>0.90*	*<0.05*
Null model (uncorrelated factors)	227.68	35	6.51	0.66	0.74	0.18
Measurement model (5 factors, correlated)	50.45	25	2.02	0.94	0.97	0.08
Theoretical model (Second-order allostatic load factor)	227.68	29	7.85	0.58	0.73	0.21

Table 3. Mean total allostatic load score and individual factor scores by race

	Mean Score	
	African American	White
Factor		
Total Allostatic Load Score (sum of five factor scores)*	-0.82	0.36
Blood pressure*	0.02	-0.01
Adiposity	0.02	-0.01
Lipids**	-0.62	0.27
Insulin Resistance	-0.11	0.05
Inflammation	-0.12	0.05

*$P<0.05$

**$P<0.001$

Figure 1. Final measurement model results (χ^2/df ratio=2, CFI=0.97, RMSEA=0.08). White boxes represent measured biological parameters, shaded boxes represent latent factors (regulatory domains). All factor loadings are statistically significant. With the exception of the correlation between blood pressure and lipids, all correlations between latent factors are statistically significant. Estimates for error terms are not shown.

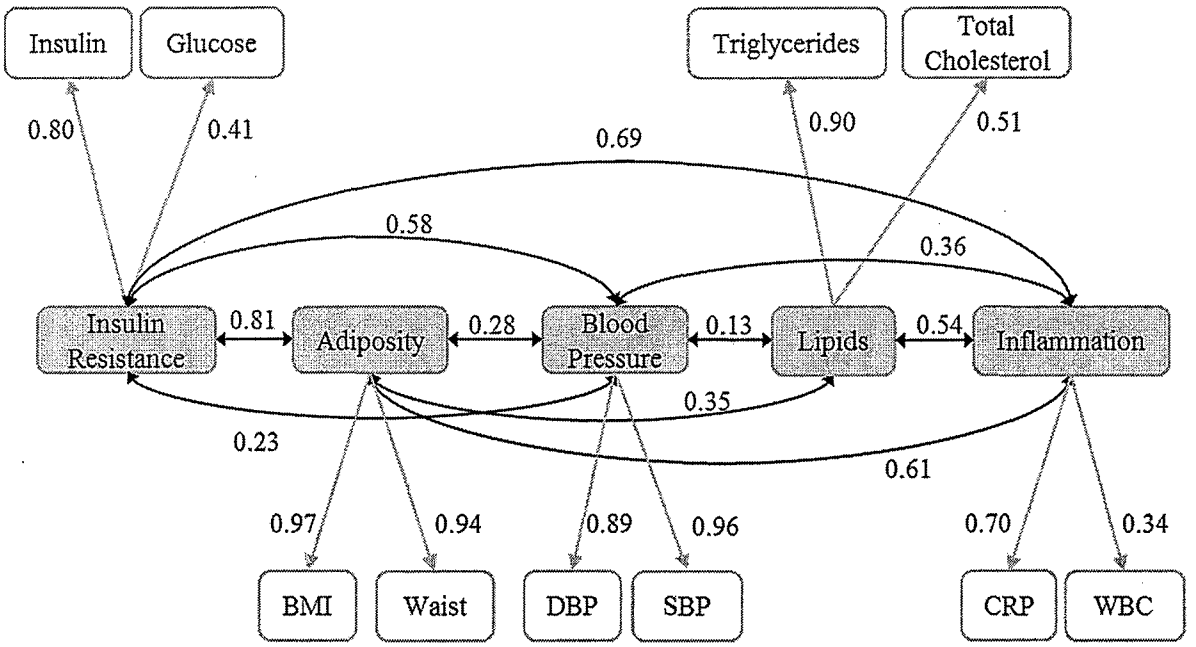
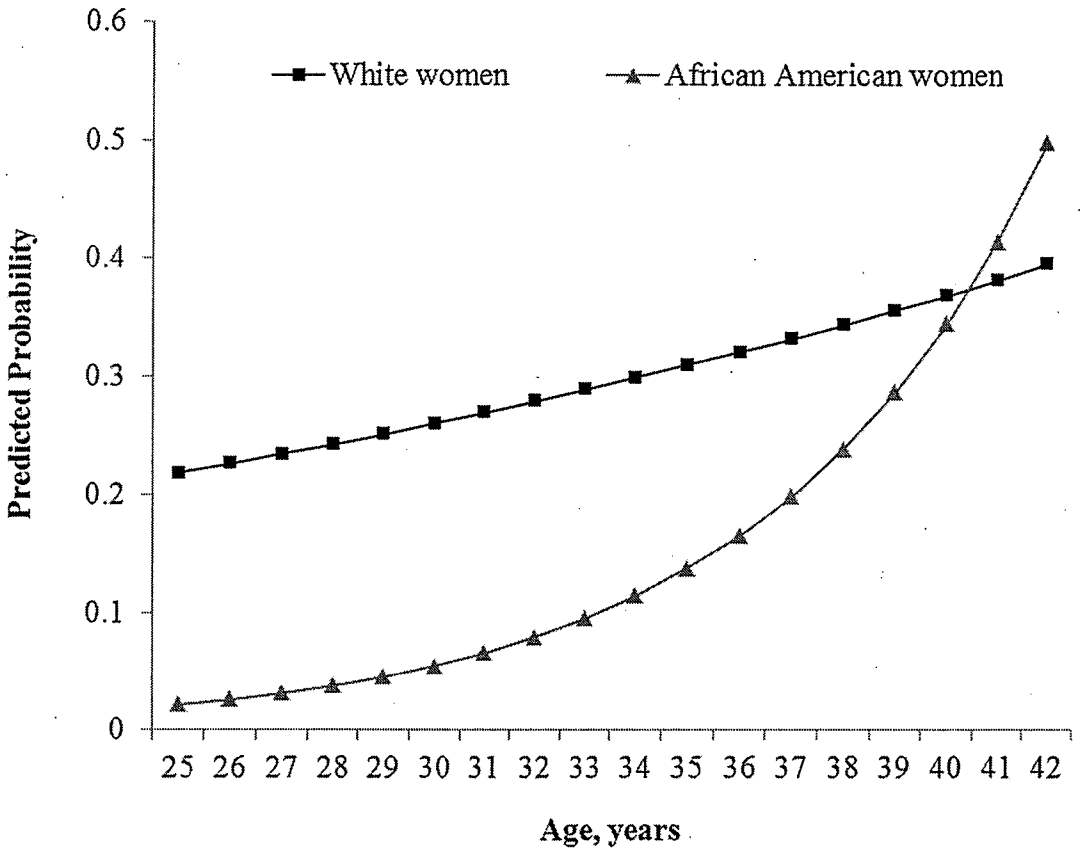


Figure 2. Predicted probability of high allostatic load (top quartile allostatic load score) by age and race.



CHAPTER 5. Preconception Allostatic Load and Racial Disparities in Adverse Birth Outcomes: the Bogalusa Heart Study (*Manuscript II*)

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5.1 Introduction

Infants born to African American women in the United States are more than two times as likely to die before age one than those born to non-Hispanic White women.[1] This disparity is driven largely by the disproportionately higher percentage of preterm births (PTB, defined as a birth at <37 weeks gestation) occurring to African American women; almost 20% of infants born to African American women are preterm, and their rate of death due to preterm-related causes is more than three times the rate among non-Hispanic White women.[1] Likewise, the rates of low birthweight (LBW, birthweight <2,500g) and very low birthweight (<1,500g) are 2 and 3 times higher, respectively, among African Americans compared to Whites.[2] These disparities continue to persist despite decades of research and intervention, and the causes behind them remain largely unexplained.[3] Previous investigations have focused on potentially differential exposures at or around the time of pregnancy.[3] However, studies that control for differences in maternal education,[4] socioeconomic position,[5,6] health behaviors such as smoking, alcohol, and drug use,[7,8] and access to prenatal care[9] continue to demonstrate evidence of residual racial disparities in birth outcomes.

The complexity of the mechanisms that drive these disparities necessitate new ways of conceptualizing reproductive health determinants. The life-course perspective adapted by Lu and Halfon[10] provides a structural re-framing of reproductive health in the

broader context of women's health: the life-course perspective posits that birth outcomes are a result not only of exposures during the 9 months of pregnancy but of exposure to risk and protective factors that occur and accumulate across the woman's life span, beginning even in her own time in utero. This accumulation refers to the "wear and tear" wrought on the body by persistent and prolonged exposure to stressful physical, psychological and sociocultural environments that impacts the health and functioning of the body over time.[11] Racial/ethnic disparities in reproductive health, therefore, may be at least in part a manifestation of the differential life experiences and exposures of White and African American women in the United States and the resulting disproportionate burden borne by the latter.[12]

The theoretical construct of allostatic load refers to the cumulative dysregulation of the body's physiologic domains involved in stress response and adaptation (e.g. cardiovascular, metabolic, immune, and endocrine).[16] It represents an indicator of physiologic "wear and tear" that results from chronic exposure to stress and has been studied as an antecedent to the onset of clinical disease.[14] Repeated or prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to a loss of effectiveness and efficiency in stress hormone feedback mechanisms.[20,22] As a result, exposure to chronically elevated levels of cortisol, epinephrine, norepinephrine, and dehydroepiandrosterone leads to increasingly poor regulation of cardiovascular, inflammatory, and metabolic systems.[108] Unsustainable over time, this cumulative physiologic burden can begin to manifest pathologically leading to allostatic load, which has been associated with declines in physical and cognitive function and increased risk

for cardiovascular diseases, cancers, autoimmune disorders, and other chronic diseases.[24,26,109]

An allostatic load framework has been increasingly used to conceptualize the physical consequences of the multi-level biological, environmental, and social factors that drive racial disparities in health, including reproductive health.[10,34,45,54] It represents an integration of the life-course perspective and the harmful physical health effects of social hierarchy.[45] Yet despite the theoretical plausibility of multisystemic dysregulation as a mediator of health over the life-course and precursor to clinical pathologies (including those that affect reproductive health), to our knowledge only one previous study has empirically measured allostatic load in pregnant women and analyzed its impact on adverse pregnancy outcomes.[79] The purpose of this analysis is to examine the relationship between allostatic load prior to conception and the occurrence of preterm birth, small-for-gestational age, and low birthweight infants, and to identify any differences in effect size by race.

5.2 Methods

Identification of Study Population

The women included in these analyses are participants of the Bogalusa Heart Study (BHS), a longitudinal investigation of cardiovascular disease risk began in 1973 by researchers now at Tulane University.[89] Bogalusa, Louisiana is a semi-rural town of approximately 45,000 residents. Surveys of the town's school children were repeated approximately every two years through 1994, enrolling new children as well as re-examining those previously enrolled. As children participants aged, they were eligible for re-examination in up to four of the ten surveys conducted among adults age 18-50

occurring between the years of 1997 and 2009.[91] Birth records available for the proposed analysis were those issued by the State of Louisiana between the years 1990 and 2009, inclusive. This includes a total of 1,354,951 births. A three-stage data linkage procedure was used to link women from the Bogalusa Heart Study to birth record of their firstborn child using LinkPro v3.0 (Figure 1). LinkPro v3.0 is an integrated SAS application system for both deterministic and probabilistic record linkage (InfoSoft, Inc., Winnipeg, MB). Stage I consisted of a deterministic linkage based on maternal social security number, available in a subset of Bogalusa Heart Study participants and missing in only 5% of birth records. An exact match of social security number was sought for each woman with a non-missing SSN and was categorized as follows: 1:1 match (women with only one birth), 1:N match (women with multiple births), and unmatched (including truly nulliparous women and women with missing or potentially typo-error SSN in the birth records). All SSN matches (1:1 and 1:N) were considered definite matches.

Stage II was a probabilistic linkage among women who were previously unmatched by SSN and those who were missing SSN in the BHS data. Linkage was based on maternal date of birth (day, month, year), first name, last name, and Soundex codes for first and last names for a total of seven variables. Records that matched on 4 or fewer variables were excluded as non-matches. Records with exact matches on all seven variables were be classified as true-matches. The remaining records (those matched on 5 or 6 of the 7 variables) were reviewed manually and classified as either true-matches or non-matches. Manual review entailed visual comparison of matching variables with alternate values for names and date of birth, as well as maternal race and address variables not used in the matching strategy.

Finally, Stage III of the linkage repeated Stage II this time using the child's last name (and Soundex code) from the birth record and maternal last name from the BHS dataset to identify any remaining possible matches. The same rules for minimum number of matching variables and manual review for classification of non-matches and true-matches were applied.

Combining true matches from all three stages resulted in a single dataset of 2,773 women matched to 5,227 infants. Limiting the dataset to singleton first births resulted in 2,743 mother-infant pairs. Of these, 1,497 (54.6%) had a BHS examination that occurred prior to the date of conception, 1,467 (98.0%) had data from that examination on at least one of the 8 allostatic load biomarkers and 431 (final sample size) had complete data on all 8 biomarkers (179 African American and 252 White).

Allostatic load measurement

Eight biomarkers were available for use in the measurement of preconception allostatic load: systolic and diastolic blood pressure (SBP and DBP) as markers of cardiovascular activity; total cholesterol, triglycerides, glucose, and insulin representing metabolic indicators; fibrinogen, a marker of systemic inflammation; and body mass index (BMI). An allostatic load index was computed for each individual based on a count of the number of biomarkers scoring in the highest risk quartile of the age-adjusted sample distribution. This high risk quartile summary measure is the most frequently employed operationalization of allostatic load and is based on the work of researchers from the MacArthur Study of Successful Aging. Seeman et al.,[24] were the first to examine the construct validity of this allostatic load index for the quantification of cumulative physiological burden across a range of regulatory systems. Since that time it

has been utilized in a large number of investigations, and shown to be associated with increased risks of adverse physical and mental health outcomes, including all-cause mortality, with differential impacts by race, gender, and socioeconomic position.[23,109]

Detailed descriptions of the BHS risk screening examinations have been published in greater detail elsewhere.[89] Briefly, the physical examination involved duplicate height and weight measurements, which were used in the calculation of body mass index (weight in kg/height m^2). Right arm blood pressure was measured in triplicate with mercury sphygmomanometers by each of 2 trained observers on subjects in a relaxed, seated position; means of 6 replicate blood pressure readings were used for both SBP and DBP. All subjects were instructed to fast for 12 hours prior to the examination and blood draw. Plasma glucose level was measured as part of a multiple chemistry profile (SMA20) with the multichannel Olympus Au-5000 analyzer (Olympus, Lake Success, NY). A radioimmunoassay kit was used to measure plasma insulin (Phadebas insulin kit, Pharmacia Diagnostics, Piscataway, NJ). Serum cholesterol and triglycerides levels were assayed enzymatically on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, Ind).[93] Fibrinogen data were determined using a Technicon H6000 (Technicon Instrument Corp. Tarrytown. NY). All laboratories responsible for processing BHS samples are rigorously monitored for quality control, precision and accuracy by independent institutions.

Birth outcomes

Birthweight and gestational age data were extracted from the birth records and used to classify infants with regard to the three adverse birth outcomes of interest: preterm birth (<37 weeks gestation), low birthweight (<2,500 grams), and small-for-

gestational age (SGA, <10th percentile birthweight for gestational age based on this sample distribution). For all birth records, gestational age estimation is based on the date of the last menstrual period. When such data are missing, gestational age is based on a clinical estimate (as estimated by attendant) for birth records from 1990-2002 and later replaced by an obstetric estimate (as estimated by attendant based on all perinatal factors including ultrasound) for records after 2003.[110]

Statistical Analysis

Basic descriptive statistics were computed for each allostatic load component. Variables that deviated from univariate normality were log-transformed. Racial differences in allostatic load components, total allostatic load index (the summary measure of components measured in the top quartile), maternal age, education, smoking status during pregnancy, and birth outcomes were assessed in bivariate analyses. Additionally, date of conception was estimated by subtracting the number of days of gestation from the child's date of birth. For women who completed multiple BHS examinations, the one closest and prior to the date of conception was used in computing allostatic load.

Log-linear modeling was used to examine relationships between race, allostatic load, and education (an indicator of socioeconomic position), and the three birth outcomes of interest. All models were controlled for maternal age, length of time between allostatic load measurement and date of conception, and smoking during pregnancy. Given the broad range of years in which the woman's last preconception BHS examination may have occurred, we also controlled for date of examination. A priori tests for two- and three-way interactions were considered for allostatic load, and

race, and maternal education at the time of birth. As a marker of socioeconomic position, we expected that a higher education level may buffer the effects of allostatic load on adverse birth outcomes among African American women.

To evaluate the robustness of our results, we conducted a sensitivity analysis by limiting the data to women with less than 5 years between the time of the allostatic load measurement and the date of conception. Given the inherently cumulative nature of physiologic dysregulation, allostatic load would be expected to increase with time as an individual ages.[24] Therefore, we expected to find that among women with a narrower window between allostatic load measurement and pregnancy – such that a greater accumulation of physiologic burden may be apparent – the effect size on birth outcomes would be greater. The log-linear modeling described above was repeated on the limited subset for all three birth outcomes.

5.3 Results

Mean age at the time of BHS exam from which the allostatic load index was derived was approximately 13 years for both African American and White participants (Table 1). All of the participants gave birth to their first child at a relatively young age although African American women had a slightly younger mean (20.4 years) compared to White women (21.6 years). Approximately one third of the women had continued education beyond high school at the time of their first child, while another third had not completed high school. Mean values for four of the eight biomarkers used in the operationalization of allostatic load differed significantly between African American and White women when examined alone. Both systolic and diastolic blood pressure were higher among African American women in addition to insulin, while White women had a

higher mean level of triglycerides (all $P<0.05$). Despite these differences, the mean allostatic load index appeared higher among African American women compared to White but was not statistically significant.

As expected, bivariate statistics indicated racial disparities in the three adverse birth outcomes of interest (Table 1). The rate of babies born at LBW was almost twice as high in African American women as in White women ($P<0.01$ and $P<0.05$, respectively). The rate of PTB among African American women was 14% compared to only 9.5% among White women but this difference was not statistically significant.

The relative risks for all three adverse birth outcomes appeared to increase with increasing allostatic load as hypothesized; however, none of the relationships between allostatic load and birth outcomes were statistically significant in the adjusted models (Table 2). For every one point increase in allostatic load, women were 1.08 times more likely to have PTB (95% CI 0.93, 1.26), 1.11 times more likely to have a LBW infant (95% CI 0.98, 1.26), and 1.09 times more likely to have an SGA infant (95% CI 0.93, 1.28). White women had a significantly decreased risk for having a low birthweight and small-for-gestational age baby compared to African American women, but there was no racial difference in the risk of PTB in the models including allostatic load, age, education, date of BHS exam, smoking during pregnancy, and years between allostatic load measurement and conception. Likewise there was no difference in risk for PTB, LBW, or SGA by maternal education level after adjustment. Finally, there was no evidence of any effect modification of the relationship between allostatic load and birth outcomes by race or maternal education level.

The results of the sensitivity analyses were consistent with the initial analyses (Table 3). Among the women with 5 or fewer years between the time of allostatic load measurement and conception of their first child the magnitude of the effect estimate of allostatic load was larger for all three outcomes, but remained nonsignificant.

5.4 Discussion

In the analyses presented here we attempted to provide some empirical evidence of the deleterious effect that an accumulation of physiologic dysregulation leading up to the time of pregnancy can have on a woman's birth outcome. Much of the literature on the health effects of stress on reproduction has relied on subjective measures of stress and questionnaires that, while validated, may not capture the complex and multilayered nature of stress from a physiological or biobehavioral perspective.[67] For example, Lu and Chen[68] found no association between stressful life events and racial disparities in preterm birth, but they acknowledge the inadequacy of their stress assessment which may have failed to capture the chronic stressors and unique contextual factors experienced by women of color on a daily basis. To this extent, allostatic load may be a more appropriate measurement of the broader accumulation of stress over the life-course.[67,69] While it is clear that individually the biological systems responsible for maintaining allostasis have direct impacts on fetal health,[111,112]less is known about the effect of their collective dysregulation. The theoretical construct of allostatic load acknowledges their interconnected nature and emphasizes a multisystems view of reproductive health risks and differentials.

In reproductive health literature, allostatic load is a frequently proposed hypothesis to explain the disproportionate occurrence of adverse outcomes experienced

by African American women.[10,72-75,113] However, to our knowledge no study has investigated the relationship between pre-pregnancy allostatic load and length of gestation and birthweight or racial differences in these outcomes. Our previous work in this area includes a small prospective study of allostatic load in pregnant women (measured at 26-28 weeks gestation) and its impact on number of pregnancy outcomes.[79] We found that higher allostatic load during pregnancy was associated with a shorter length of gestation, but the effect did not differ by race. Data available for the current study allowed us to measure women's allostatic load prior to her pregnancy. We believe that quantifying the relationship between a pre-pregnancy measure of allostatic load and adverse birth outcomes is important both for re-enforcing a life-course perspective and for minimizing any bias due to the inherently altered physiological state of pregnancy that occurs independent of allostatic load.

Although the estimates were nonsignificant, the trend appeared to suggest that women with a higher allostatic load were at increased risk for giving birth preterm, or to a low birthweight or small-for-gestational age infant. As a marker of essentially accelerated "aging", we expected that allostatic load would be associated with adverse outcomes that are known to increase with maternal age.[114]

The characteristics of our unique study population may be one reason behind our null findings. The relatively young age at first birth in this population (mean=21) and our requirement that allostatic load measurement occur prior to pregnancy implies an inherently shorter amount of time women in this sample may have experienced stress and accumulated physiologic wear and tear (mean age at allostatic load measurement=13). In an analysis of a nationally-representative sample of White and African American women,

Geronimus et al.[101]reported little difference in allostatic load scores among women younger than age 35 but significant and increasing racial gaps thereafter up to age 64. Second, the women included in our study represent an understudied population, given their unique location in the rural South. In a previous cross-sectional examination of allostatic load in this population we found higher allostatic load levels among White women compared to African Americans, a peculiar and unexplained finding that suggests additional factors (poverty, lack of access to resources) may be at play. Additional studies should investigate how women in a rural context experience and internalize chronic stressors and the extent to which it impacts their physical health.

There are limitations to the current study. First, as a secondary analysis, this project is limited to the data available in the two linked datasets. While the BHS provides data on an extensive number of physiological biomarkers, there are no measures of stress hormones in women (cortisol, catecholamines or their antagonists). The absence of stress hormones in a summary measure of allostatic load is arguably inadequate as it is their over- or under-production that mediate the pathological consequences of chronic stress. The proposed study, however, focused on the secondary effects that occur as a result of allostatic load and stress hormone dysregulation across multiple biological systems. As such it provides preliminary evidence of a frequently hypothesized relationship; to our knowledge, no previous study has estimated the effect of a preconception allostatic load measure – with or without stress hormones – on birth outcomes. Future studies should examine alternative biomarkers of allostatic load, including stress hormones, in order to capture a more complete measure of physiologic burden leading up to the time of pregnancy. Second, despite the sound reliability of

record linkage methodology for identifying mother-infant pairs,[115] quantifying the validity and reliability of probabilistic record linkage is problematic if not impossible in many cases – as in the current study – where there is no gold-standard of information to compare matches against. Incorrect linkage of mother-infant pairs is a small but unavoidable likelihood. However, stringent criteria for classifying true links, as well as verification with pregnancy-related variables available in the BHS data should have minimized this bias.

Furthermore, only birth records issued by the state of Louisiana from 1990-2009 were available for the data linkage. Therefore, the study population was limited to only those BHS participants who remained in (and gave birth in) the state of Louisiana. Moreover, since we limited the data to first births, any BHS participant who gave birth prior to 1990 was excluded. In order to investigate the possibility of selection bias given these conditions, we did a crude comparison of race and age of women whom we successfully matched to a birth record and those who we did not (which includes women who never gave birth, those who gave birth before 1990, and those who gave birth out of state). A greater proportion of women included in our analysis were African American (40.1% compared to 34.7% of those unmatched, $P<0.001$), and matched women were on average younger (35 compared to 42 years, $P<0.001$). We have no source of data to further describe the women that we were unable to match, nor any of the children they may have had and the direction of bias is unpredictable.

Finally, as the primary outcome variables are based on values from the birth certificate (gestational age and birthweight) it is likely that some subjects may be misclassified with regard to preterm birth, low birthweight, and small-for-gestational age.

In general, birthweight has shown to be a highly reliable variable from the birth record, whereas gestational age has only moderate reliability.[116] As the time frame of outcome measurement includes a span of twenty years' worth of birth records, it is likely that the quality of data changed over the course of the study years with improvements in fetal dating technology which should reduce misclassification bias in infants born most recently. Ideally, future studies of pre-conception allostatic load with prospective data collection of infant weight and gestational age would overcome this limitation.

Despite its limitations, this work contributes to the literature by providing an empirical test of a frequently proposed hypothesis. Our lack of significant findings compels further investigation of the biological mechanisms linking social inequities to racial disparities in adverse birth outcomes. The development of allostatic load over the life-course maybe one of many reasons why sub-groups of women experience adverse reproductive health outcomes with greater frequency than others. Furthering our understanding of the longitudinal and contextual determinants of reproductive health – including the physical impact of societal disadvantage – can help shape policy and interventions that promote health equity among all women and their infants.

Figure 1. Linkage process flowchart and identification of study population.

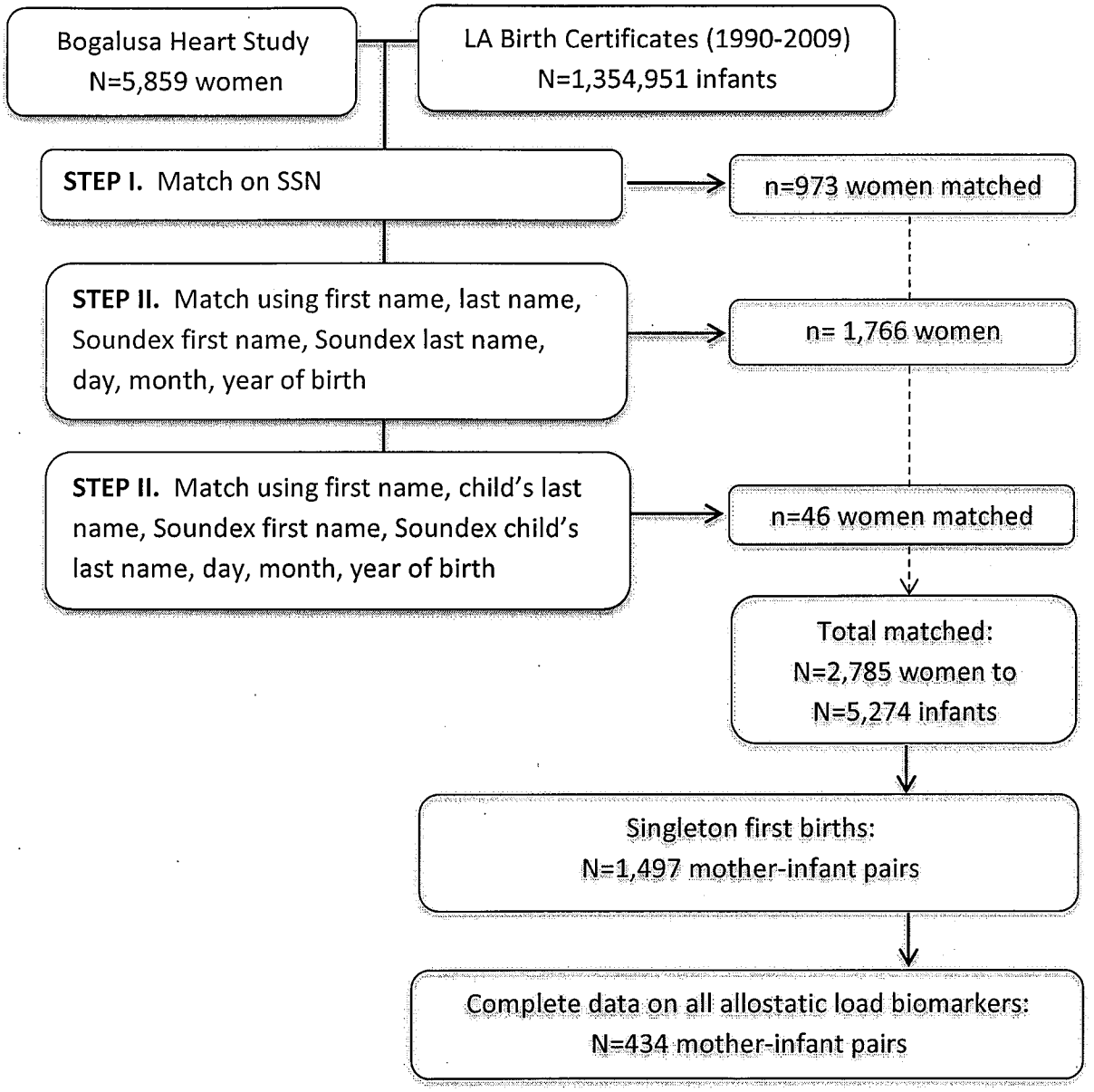

Table 1. Descriptive Statistics of sample demographics, biological indicators, and birth outcomes (N=431).

	African American (n=179)		White (n=252)	
	Mean	**SD**	**Mean**	**SD**
Age at time of exam	13.2	3.9	12.5	4.4
Age at first birth**	20.4	4.4	21.6	4.2
Allostatic load components				
*SBP (mmHg)***	104.3	10.1	101.7	9.3
*DBP (mmHg)**	64.8	10.2	62.7	9.1
Body mass index (kg/m^2)	21.5	5.8	21.0	5.2
*Total cholesterol (mg/dL)**	175.9	30.9	170.1	28.9
*Triglycerides (mg/dL)***	63.2	32.3	78.4	42.8
Glucose (mg/dL)	82.7	9.2	83.9	9.7
*Insulin (uU/mL)***	17.2	20.4	12.9	10.0
Fibrinogen (mg/dL)	264.0	80.6	258.3	80.2
Allostatic load score	2.2	1.7	1.9	1.7
Birthweight (g)**	2965.5	697.8	3230.9	595.3
Gestational age (wks)	38.4	3.4	38.7	2.1
	N	**%**	**N**	**%**
Education (at time of first birth)				
More than high school	54	30.2	85	33.7
High school	62	34.6	84	33.3
Less than high school	63	35.2	83	32.9
Smoked during pregnancy**	5	2.8	40	16.0
Preterm birth	25	14.0	24	9.5
Low birthweight**	32	17.9	23	9.1
Small-for-gestational age	27	15.2	44	17.5

*P0.05

**P0.01

Table 2. Adjusted relative risks and 95% confidence interval (CI) for adverse birth outcomes by maternal characteristics (N=431)[a]

	Preterm birth		Low birthweight		Small-for-gestational age	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Allostatic Load	1.08	0.93, 1.26	1.11	0.98, 1.26	1.09	0.93, 1.28
Race						
African American	Ref	--	--	--	--	--
White	0.65	0.37, 1.03	0.49	0.29, 0.83**	0.50	0.25, 0.99*
Education at time of first birth						
More than high school	Ref	--	--	--	--	--
High school	0.64	0.31, 1.34	0.74	0.37, 1.48	1.84	0.73, 4.61
Less than high school	0.72	0.35, 1.49	0.91	0.46, 1.80	2.37	0.84, 6.67

[a]Models adjusted for maternal age at first birth, smoking during pregnancy, date of BHS examination, and years between allostatic load measurement and conception.
*P0.05
**P0.01

Table 3. Sensitivity analysis results. Adjusted relative risks and 95% confidence interval (CI) for adverse birth outcomes by maternal characteristics where time between allostatic load measurement and conception ≤ 5 years (N=172)[a]

	Preterm birth		**Low birthweight**		**Small-for-gestational age**	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Allostatic Load	1.06	0.84, 1.35	1.09	0.91, 1.31	1.08	0.86, 1.37
Race						
African American	Ref	--	--	--	--	--
White	0.83	0.30, 2.28	0.39	0.15, 0.99*	0.33	0.10, 1.09
Education at time of first birth						
More than high school	Ref	--	--	--	--	--
High school	0.51	0.15, 1.69	0.63	0.22, 1.81	3.53	0.38, 32.99
Less than high school	0.39	0.13, 1.23	0.70	0.24, 2.09	3.13	0.37, 26.77

[a]Models adjusted for maternal age at first birth, smoking during pregnancy, and date of BHS examination.
*P<0.05

CHAPTER 6. Neighborhood Poverty, Allostatic Load, and Birth Outcomes in African American and White Women: Findings from the Bogalusa Heart Study (*Manuscript III*)

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6.1 Introduction

Decades of policy and public health intervention targeting reproductive health have done little to reduce the disproportionately high rates of adverse perinatal outcomes experienced by African American women compared to women of other racial and ethnic groups in the United States.[3,117] Moving beyond individual and interpersonal-level risk factors, a growing body of research has examined social and structural determinants of reproductive health in an effort to explain the persistence of racial disparities.[118] Evidence indicates that characteristics of the physical and social environment in which women reside – crime rates,[119,120] residential segregation,[121,122] neighborhood poverty and deprivation,[123-126] and income inequality,[127,128] for example – negatively impact their health and that of their infant. Differential exposure to such stressors that may be more common in racially or socioeconomically disadvantaged groups may lead to gradients in health outcomes along racial or socioeconomic lines.

Less is known about the biological mechanisms by which exposure to such stressors affect health and functioning.[124] Allostatic load is a theoretical construct that represents dysregulation across the body's multiple physiological systems responsible for maintaining equilibrium when faced with physical or social challenges.[16] It is the cumulative physiological wear and tear wrought on the body by over-activation of the physiologic stress response that places an individual at increased risk for onset of stress-related clinical diseases.[25,108] Measurements of allostatic load are typically derived from

biomarkers representing multiple physiologic domains (e.g. cardiovascular, metabolic, immune, and endocrine).[23] While studies vary considerably in their operationalization of allostatic load, including the constituent biomarkers used to measure it, results consistently implicate its role as a biologically-mediated pathway between adversity and negative health outcomes.[23,45] Allostatic load has been shown to be higher among individuals of lower socioeconomic position,[31] those living in impoverished or deprived neighborhoods,[129-132] non-Whites,[48-50,52] and those in situations of more directly observable daily, chronic stress (e.g. caregivers).[133] Moreover, it has been associated with increased risks for a number of stress-related chronic morbidities, declines in cognitive functioning, and all-cause mortality.[23,26,27,29,109,134]

As a model of biological risk patterned by chronic and repeated stressors over the life-course, it follows that allostatic load leading up to the time of pregnancy would be associated with negative birth outcomes.[10] Dysregulation of the hypothalamic-pituitary axis – the primary mediator of allostatic load – may result in higher outputs of stress hormones during pregnancy leading to preterm labor.[67] Furthermore, excess glucocorticoids may result in immune-suppression, placing the woman at risk for infections and subsequently a heightened pro-inflammatory response associated with preterm labor or premature rupture of membranes.[135] Given the plausibility of allostatic load as a biological mediator of the effect of class- or race-based stress on birth outcomes, it is frequently hypothesized as a contributor to disparities in reproductive health,[10,71-75] but empirical evidence is sparse.

In a previous manuscript based on the same population analyzed in the current study, we examined associations with low birthweight, preterm birth, and small-for-

gestational age and found no difference in risk by allostatic load level, race, or maternal education at time of birth. In the analyses presented here, we sought to examine more closely the relationships between allostatic load, race, and adverse birth outcomes within the context of neighborhood-level poverty. Applying a socioecological framework in this manner may provide valuable insight into the mechanisms behind stress and racial disparities in birth outcomes, particularly given the historical and contextual factors unique to African American women in the south.

6.2 Methods

Identification of Study Population

Women included in these secondary analyses are participants of the Bogalusa Heart Study (BHS), a biracial (African American/White) study that has been rigorously researching cardiovascular health in children and young adults since 1973.[89] Surveys of all school children in the semi-rural town of Bogalusa, Louisiana were repeated approximately every two years through 1994, enrolling new children each time and re-examining those previously enrolled. Examinations continued as participants aged into adulthood, the most recent completed in 2009.[91]

Birth records for the 1,354,951 births that occurred in the state of Louisiana between the years 1990 and 2009, inclusive, were provided by the Office of the State Registrar. A three-stage data linkage procedure was used to identify mother-infant pairs of women who had participated in at least one BHS examination prior to conception and her firstborn infant using LinkPro v3.0 (InfoSoft, Inc., Winnipeg, MB) (Figure 1). First, an exact match of social security number was sought for each woman with a non-missing SSN was categorized as follows: 1:1 match (women with only one birth), 1:N match

(women with multiple births), and unmatched (including truly nulliparous women and women with missing or potentially typo-error SSN in the birth records). All SSN matches (1:1 and 1:N) were considered definite matches (Stage I).

All women who remained unmatched to a birth record after Stage I were included in a probabilistic linkage based on maternal date of birth (day, month, year), first name, last name, and Soundex codes for first and last names (Stage II). Records with exact matches on all seven variables were be classified as true-matches. Records that matched on four or fewer variables were excluded as non-matches. The remaining records (those matched on five or six of the seven variables) were reviewed manually and classified as either true-matches or non-matches by comparison of matching variables with alternate values for names and date of birth, as well as maternal race and address variables not used in the matching strategy.

Finally, Stage III of the linkage repeated Stage II for all women who remained unmatched this time using the child's last name (and Soundex code) from the birth record and maternal last name from BHS. The same rules for minimum number of matching variables and manual review for classification of non-matches and true-matches were applied as in stage II.

Combining true matches from all three stages resulted in a single dataset of 2,773 women matched to 5,227 infants. Limiting the dataset to singleton first births resulted in 2,743 mother-infant pairs. Of these, 1,497 (54.6%) had a BHS examination that occurred prior to the date of conception, 1,467 (98.0%) had data from that examination on at least one of the 9 allostatic load biomarkers and 866 (final sample size) had complete data on all 9 biomarkers (352 African American, 514 White).

Individual-level measures

Preconception allostatic load was derived from the following nine biomarkers collected at BHS examinations: systolic and diastolic blood pressure (SBP and DBP), total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, glucose, insulin, and waist circumference. Allostatic load was measured in each individual as a count of the number of biomarkers scoring in the highest risk quartile of the age-adjusted sample distribution.

Detailed descriptions of the BHS risk screening examinations at which these biomarkers were collected have been published in greater detail elsewhere.[89] Briefly, the physical examination involved triplicate waist circumference measurement midway between the rib cage and the superior border of the iliac crest. Right arm blood pressure was measured in triplicate with mercury sphygmomanometers by each of 2 trained observers on subjects in a relaxed, seated position; means of 6 replicate blood pressure readings were used for both SBP and DBP. All subjects were instructed to fast for 12 hours prior to the examination and blood draw. Plasma glucose level was measured as part of a multiple chemistry profile (SMA20) with the multichannel Olympus Au-5000 analyzer (Olympus, Lake Success, NY). A radioimmunoassay kit was used to measure plasma insulin (Phadebas insulin kit, Pharmacia Diagnostics, Piscataway, NJ). Serum cholesterol and triglycerides levels were assayed enzymatically on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, Ind).[93] All laboratories responsible for processing BHS samples are rigorously monitored for quality control, precision and accuracy by independent institutions.

Additional individual-level variables included maternal race, age and education at time of first birth (less than high school, high school, greater than high school), smoking during pregnancy (yes/no), year of BHS examination at which allostatic load measure was derived, and years between that exam and date of last menstrual period (preconception years).

Neighborhood-level poverty

For the purposes of this study, "neighborhood" was defined as US Census block group, based on the Census 2000 TIGER Line/Shapefiles. Where available, participant's address number, street, city, state, and zip of residence at the time of the BHS examination from which the allostatic load measure was derived were geocoded into block group using ArcGIS (ESRI, Inc., Redlands, California). The final sample of 866 women resided in 55 census block groups, and the number of women per block group ranged from 1 to 151 (mean=6).

Neighborhood-level poverty was defined as the percentage of households living below the federal poverty level in a single block group. Given the broad range of years at which participant's preconception BHS examinations took place, data on neighborhood-level poverty were obtained from both Census 1990 and Census 2000. For women whose preconception BHS examination occurred between the years 1987-1993, block group poverty levels were obtained from Census 1990. For preconception examinations that occurred between 1998-2003, data were obtained from Census 2000. Finally, for women whose examination took place from 1994-1997, neighborhood poverty was estimated as the mean of Census 1990 and Census 2000 values. For the purposes of modeling, neighborhood poverty was categorized into high poverty (>27% of households below

poverty level, top quartile of the sample distribution) or low poverty (≤27% of households below poverty level). Individuals were then categorized by their race and poverty level of the neighborhood in which they resided (White, low poverty neighborhood; White, high poverty neighborhood; African American, low poverty neighborhood African American, high poverty neighborhood).

Birth outcomes

Birth weight and gestational age of infants born to women participants of BHS were extracted from the birth records. Gestational age on the birth record is an estimation based on the date of last menstrual period. When the date is unknown or missing, gestational age is based on a clinical estimate (as estimated by attendant) for birth records from 1990-2002 and later replaced by an obstetric estimate (as estimated by attendant based on all perinatal factors including ultrasound) for records issued after 2003.[110] Low birthweight was defined as a birth weight of less than 2,500 grams and births before 37 completed weeks gestation were classified as preterm.

Statistical Analyses

All individual-level predictors, potential confounders, and birth outcomes were examined in bivariate to assess differences by race. Descriptive analyses also included a crude comparison of difference in neighborhood poverty by race as well as the cross-distribution of participants by allostatic load quartile and neighborhood poverty quartile among White and African American women separately.

To address potential structural confounding, participants were frequency-matched based on their propensity for residing in a high-poverty neighborhood. Given the greater probability (propensity) for living in a high poverty neighborhood among women who

did so (Figure 1), propensity-score matching should reduce potential unmeasured structural confounding between women across poverty levels. Generalized estimating equations were used to estimate racial disparities in low birthweight and preterm birth associated with allostatic load and race in the context of neighborhood poverty level and individual-level socioeconomic position (education). Models accounted for matched individuals and clustering within neighborhood and were adjusted for maternal, age, smoking during pregnancy, year of BHS examination and years between examination and conception.

6.3 Results

Allostatic load was derived from biomarkers measured at a BHS examination that occurred an average of 6.8 years prior to conception. African American women were significantly younger at the time of their first birth and had significantly higher mean preconception allostatic load score compared to Whites (Table 1). African American women, on average, lived in neighborhoods with a greater proportion of households below the federal poverty level compared to White women (31.7% vs. 17.7%). The racial disparity in low birthweight was apparent in this sample, and although the rate of preterm birth appeared higher in African American women compared to Whites (12.5% vs. 9.1%), this difference was not statistically significant.

The greatest proportion of African American women included in these analyses (26.1%) had high allostatic load scores and lived in high-poverty neighborhoods (Table 2). Conversely, only 3.7% of White women had high allostatic load scores and lived in high-poverty neighborhoods.

Table 3 presents the odds ratios and 95% confidence intervals from generalized estimating equations for associations with low birthweight and preterm birth. In fully adjusted models, allostatic load was not associated with either low birthweight or preterm birth in this sample. Compared to White women living in a lower poverty neighborhood, White women living in higher poverty and African American women in either a low or high poverty neighborhood were more likely to have a low birthweight infant. The association was strongest for African American women in lower poverty, who were more than 5 times as likely to have a low birthweight infant than White women in lower poverty (OR: 5.23, 95% CI: 2.26, 12.10). Likewise, women in this group – African Americans in low poverty – were more likely to have given birth preterm compared to White women in the same lower poverty neighborhoods. There was no statistical difference in the likelihood of preterm birth for African American women in high poverty or White women in high poverty compared to White women in low poverty. Maternal education, as an indicator of individual-level socioeconomic position, was not associated with either preterm birth or low birth weight in the fully adjusted models that included allostatic load and the grouped race/neighborhood poverty variable.

Table 3a contains the results of a supplemental analysis in which the effects of allostatic load, race, neighborhood-level poverty and individual-level education on gestational age and birthweight are stratified by race as opposed to using a single combined race and neighborhood-poverty level variable. As show in Table 3a there is no association between allostatic load and either gestational age or birthweight for White or African American women. This is consistent with the original analyses (Table 3). Furthermore, poverty was significantly associated with gestational age among African

American women such that as neighborhood poverty increases, gestational age likewise increases. This unusual finding is also consistent with the original analysis in which African Americans in areas of higher poverty were at less risk for preterm birth than African American s in wealthier areas compared to White women in wealthier areas. There is no effect of neighborhood poverty level on either gestational age or birthweight for White women. Finally, education was protective for White women such that a higher education resulted in increased birthweight, but not for African American women.

6.4 Discussion

Our aim in the present analysis was to examine a potential mechanism by which chronic stress accumulates in the body over time with implications for preconception health and racial disparities in adverse birth outcomes. Consistent with previous literature, we found that mean allostatic load score was higher among African American women compared to whites, and that African American women were more likely to reside in a higher-poverty neighborhood.[48,53,132] We also found a higher percentage of low birthweight infants and a higher albeit nonsignificant rate of preterm birth among African American women compared to White, trends supported by our state and national birth outcomes data.[1,2]

Contrary to our hypothesis, however, we did not find that allostatic load predicted low birthweight or preterm birth in the models that included race and neighborhood poverty level. Nor was there a significant association between neighborhood poverty level and allostatic load in this sample with adjustment for race (data not shown). In a study based in Detroit, Schulz, et al.[129] reported a positive association between neighborhood poverty and allostatic load with residents of higher-poverty neighborhoods

(> 20% of households below the poverty line) had an average 10% higher allostatic load score. Moreover, they found that the relationship between neighborhood poverty and allostatic load was mediated through perceived psychosocial stress and not by health-related behaviors.[129] It may be that in the absence of psychosocial stress measures we were unable to disentangle the pathways through which poverty and allostatic load together impact women's health and pregnancy outcomes. Furthermore, tests of potential mediating pathways between poverty, allostatic load, and birth outcomes may require additional structural and psychosocial indicators given the unique cultural context of this sample of young, semi-rural women in the southern US.[123]

An additional finding from these analyses is that among the groupings that considered both the individual's race and the level of poverty in the neighborhood in which they resided, African American women in areas of lower poverty appeared to fare worst relative to Whites in the same low-poverty neighborhoods, compared with both White and African American women from impoverished neighborhoods, independent of individual socioeconomic position.

Messer et al.[136] found that compared to a low-poverty neighborhood, living in a higher poverty neighborhood increased the odds of preterm birth among White women, but the association was non-significant for black women with adjustment for maternal age and education. Similarly, O'Campo et al.,[137] reported greater effect estimates of the relationship between neighborhood poverty and preterm birth among White women compared to those estimated among non-Hispanic Black women in race-stratified models, a difference that may be partially explained by the narrower range of depravation distribution among the Black women in their sample. Conversely, the distribution of

neighborhood poverty percentage was broader among African American women in our sample compared to Whites.

Taken together, this evidence suggests that while poverty has deleterious effects on reproductive health for all women regardless of race, higher neighborhood socioeconomic position does not necessarily eliminate the disproportionate burden of adverse outcomes among African American women compared to Whites, and in this instance, appears to exacerbate the disparity. Reasons for our finding are unclear, but suggest additional factors such as racial segregation,[121,122] institutionalized racism,[138] or perceived discrimination[126] may be influencing the relationship between neighborhood environment and adverse birth outcomes among African American women in areas of lower poverty. It may be that responses to racial discrimination – which vary by socioeconomic position in the degree of socialization parents impart on families – may be more protective in neighborhoods characterized by high levels of poverty disorder.[139]

There are limitations to these analyses for consideration. First, our definition of "neighborhood" as census block group undoubtedly mischaracterized neighborhood or community as would be perceived by the individuals living within them. This problem of neighborhood definition is not new to social epidemiology,[136] and it both limits comparison across studies and prohibits causal inference regarding neighborhood-level effects. Ideally, future studies can incorporate more carefully considered groupings of individuals within salient, community-based geographical areas that capture the stressors and stress buffers experienced by residents on a daily basis. Further, we had no information on the amount of time these women lived in the neighborhood prior to the time of allostatic load measurement or for the period of time between the allostatic load

measurement and conception of their first born child. However, given the relatively young age of this sample and the school-based nature of recruitment for the Bogalusa Heart Study, it is reasonable to assume that most if not all of these women had spent a majority a of their young lives in the neighborhood in which we classified them. Our measure of allostatic load therefore should have captured the physiologic effects of cumulative exposure to the neighborhood environment occurring though childhood and into adolescence.[140]

Despite its limitations, this analysis does contribute to the literature by being one of the first to empirically measure the effect of allostatic load on adverse birth outcomes, taking into account individual- and neighborhood-level stressors. In prior work we estimated the effect of allostatic load on African American and White women in New Orleans, a very different cultural, structural, and social context from that of Bogalusa.[79] In that study, which was limited in sample size and number of allostatic load biomarkers, we found a small positive association between allostatic load and gestational age, such that higher maternal allostatic load decreased gestational age at birth. We found no racial difference in the magnitude of effect of allostatic load on gestational age or birth weight. In addition to a larger sample size and a greater number of allostatic load biomarkers, data available for the current study allowed us to examine a measure allostatic load prior to pregnancy, an important improvement given the known physiologic changes that occur during pregnancy independent of preexisting physiologic dysregulation.[74] Further, the life-course perspective suggests that birth outcomes are not only the result of exposures that occur during the weeks of gestation, but are influenced by the accumulation of

exposures leading up to the time of pregnancy.[10] As such, we examined maternal allostatic load an index of stress accumulation in the years leading up to pregnancy.

The persistence of racial disparities in perinatal outcomes implicates the deeply pervasive nature of political, economic, and social processes that drive health inequity above and beyond the effects of demographics, health behaviors, and individual-level resources. Describing the biologic pathways by which theses process get "under the skin" to affect the health of women and their children will require a great deal of future work and research that is both relevant to social policy and amenable to individual-level intervention.

Table 1. Descriptive Statistics of individual-level demographics, biological indicators and pregnancy outcomes and neighborhood-level poverty by race (N=866).

	African American (n=352)		White (n=514)	
	Mean	**SD**	**Mean**	**SD**
Age at time of exam**	13.4	5.7	15.8	6.5
Age at first birth**	20.9	4.8	23.3	5.1
Years between allostatic load measurement and conception (preconception years)	6.7	4.3	6.9	4.3
Allostatic load biomarkers				
SBP, mmHg	103.7	9.7	103.8	9.1
DBP, mmHg	64.3	9.7	65.4	8.0
Waist circumference, cm	69.9	14.6	69.3	12.6
Total cholesterol, mg/dL	174.5	30.5	171.2	32.0
*High Density Lipoprotein, mg/dL**	57.2	13.1	50.8	11.3
Low Density Lipoprotein, mg/dL	106.3	27.0	105.2	27.3
*Triglycerides, mg/dL**	67.8	30.5	93.3	94.5
Glucose, mg/dL	79.9	15.0	80.4	17.9
*Insulin, uU/mL**	13.9	9.5	11.5	7.0
Allostatic load score**	2.6	1.7	2.1	1.9
Neighborhood poverty, %**	31.7	17.2	17.7	10.5
	N	**%**	**N**	**%**
Low birthweight**	49	13.9	37	7.2
Preterm birth	44	12.5	47	9.1
Education (at time of first birth)**				
More than high school	94	26.7	220	42.8
High school	146	41.5	188	36.6
Less than high school	112	31.8	106	20.6
Smoked during pregnancy**	11	3.1	92	17.9

*P<0.05

**P<0.01

Table 2. Percentage of individuals by level of allostatic load and neighborhood poverty among White and African American study participants (N=866).

Quartile of allostatic load score by race		Quartile of neighborhood poverty			
		1 (low)	2	3	4 (high)
African American (n=352)					
	1 (low)	2.0	3.1	0.3	6.0
	2	1.7	4.8	3.4	9.4
	3	0.6	7.1	4.8	10.8
	4 (high)	4.0	10.2	5.7	26.1
White (n=514)					
	1 (low)	4.5	8.6	6.6	1.6
	2	3.3	14.0	6.6	2.1
	3	2.3	7.6	5.5	2.0
	4 (high)	5.6	14.2	11.9	3.7

Table 3. Odds Ratios of low birthweight and preterm birth associated with maternal race and neighborhood poverty level and allostatic load.[a]

	Low birthweight			Preterm Birth		
	OR	95% CI		OR	95% CI	
Allostatic load	1.10	0.93	1.31	1.01	0.85	1.19
Race and Neighborhood Poverty Level[b]						
White, low poverty	Referent	.	.	Referent	.	.
White, higher poverty	3.39**	1.42	8.11	2.11	0.98	4.52
African American, low poverty	5.23**	2.26	12.10	2.56*	1.19	5.49
African American, higher poverty	3.51*	1.01	12.19	2.37	0.80	7.05
Education						
More than high school	Referent	.	.	Referent	.	.
High school	1.52	0.63	3.67	0.77	0.35	1.72
Less than high school	1.07	0.34	3.31	0.82	0.30	2.29

[a]Model controlled for maternal, age, smoking during pregnancy, year of BHS examination and years between examination and conception

[b]High poverty defined as top quartile of neighborhood poverty distribution (>27.0% of families below federal poverty level)

*<0.05

**<0.001

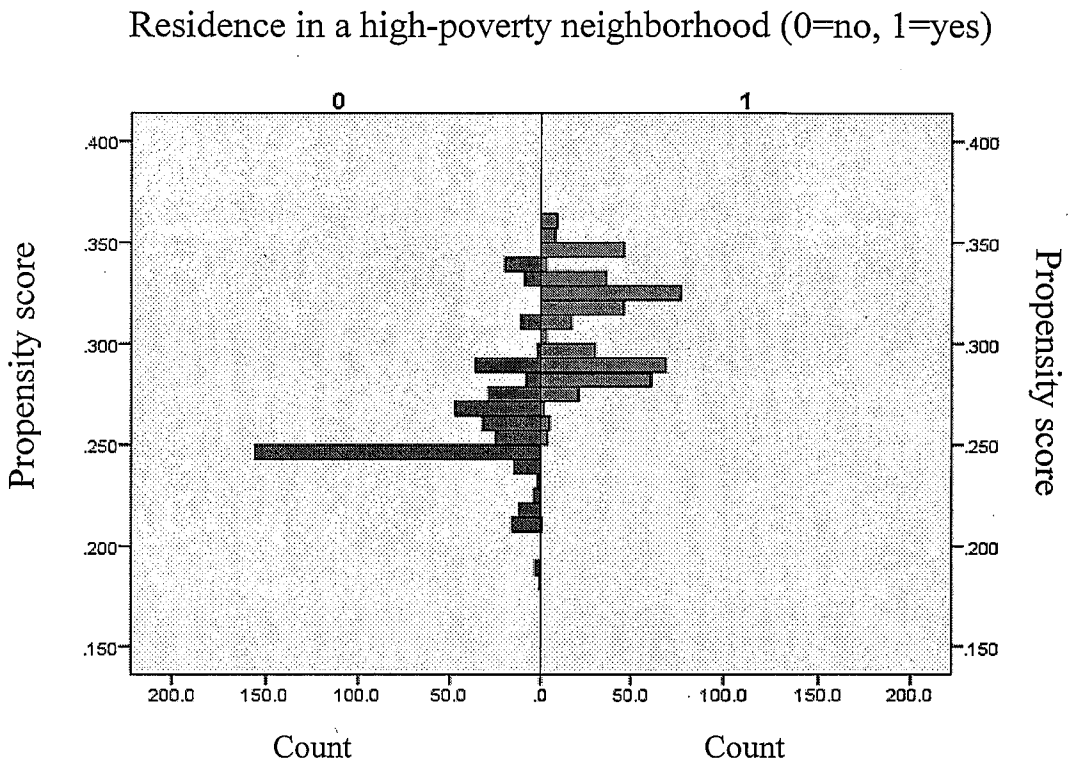
Table 3a. Supplementary race-stratified analysis of the effects of individual-level allostatic load and education and neighborhood-level poverty on gestational age and birth weight.[a,b]

	Gestational age				Birthweight			
	White		African American		White		African American	
	Beta	P	Beta	P	Beta	P	Beta	P
Allostatic load	-0.07	0.14	-0.01	0.92	-7.48	0.58	3.61	0.83
Poverty (block group)	-0.17	0.83	1.16	<0.001	-3.83	0.99	-87.93	0.42
Education								
> High School	Referent	.						
High School	-0.21	0.37	0.15	0.76	-144.60	0.04	-90.43	0.34
<High School	-0.35	0.13	0.03	0.95	-132.14	0.07	-123.94	0.25

[a]Model controlled for maternal age, smoking during pregnancy, year of BHS examination and years between examination and conception

[b]Stratified models will not converge with binary outcomes

Figure 1. Propensity score matching. Propensity for living in a high-poverty neighborhood by actual residence in a high-poverty neighborhood (1) vs. a low-poverty neighborhood (0).



CHAPTER 7. Strengths and Limitations

7.1 Strengths

With an increasing focus on social determinants of health, public health researchers are beginning to understand the social, political, and economic processes that drive health inequities. Theoretical constructs – including allostatic load – and hypotheses about the biologically-mediated pathways by which these processes impact physical health abound. However, to our knowledge, the analyses presented here are the first to empirically measure preconception allostatic load in a cohort of young women and estimate its potential role as a contributor to the racial inequity in adverse birth outcomes. Manuscript I adds to the small amount of existing literature about how best to measure allostatic load using theoretically sound and statistically coherent models, taking a more comprehensive, multisystemic view of pathophysiology and health potential that extends beyond single system risk-factor epidemiology. By linking two large datasets for Manuscript II, we were able to quantify without temporal ambiguity the association between the accumulation of physiological stress in the years of life leading up to conception and the outcomes of pregnancy. Finally, Manuscript III is the first study to consider how place within a social hierarchy engenders wear and tear on the body and places women at risk for delivering a preterm or low birthweight infant.

7.2 Limitations

All three of the individual studies included in this investigation are subject to their own limitations, as outlined in each discussion section. However, there are also broader, overarching limitations that warrant mention. Unmeasured confounding is one of the

most important threats to the internal validity of these results. Propensity score matching was used in Manuscript III as an effort to address the potential for unmeasured structural confounding between women classified by their neighborhood poverty level (high or low). An unmatched analysis did not differ in significance of effect estimates between allostatic load and preterm birth or low birthweight. Nonetheless, given the greater propensity for living in poverty among women who were actually living in poverty, matching by propensity score was both appropriate and justified.

All of the analyses were adjusted for variables available from either the birth record or BHS dataset that are known to be associated with adverse birth outcomes. However, this was a small number given the range of factors that influence pregnancy health. Ideally, our final models should have included a greater variety of variables that captured health behaviors both during and prior to pregnancy, as well as other potential medical risk factors or underlying conditions that may be masking the effects of allostatic load on birthweight and gestational age.

Likewise, while the BHS provides data on an extensive number of physiological biomarkers, there are no measures of stress hormones in women (cortisol, catecholamines or their antagonists). The absence of stress hormones in an empirical measure of allostatic load is arguably incomplete as it is their over- or under-production that mediate the pathological effects of chronic stress. However, despite the unavailability of the primary mediators, the measures of allostatic load used in these analyses included a variety of secondary effect indicators from the metabolic, cardiovascular, and immune systems. Similarly, to date at least 12 publications based on the National Health and Nutrition Examination Survey (NHANES) have utilized measures of allostatic load that

include only secondary effect indicators from these physiologic domains as the survey data does not include stress hormones.[109] This includes Geronimus' formative work on the *weathering* hypothesis, which compared allostatic load between White and Black participants across the US based on biomarkers from the cardiovascular, metabolic, and immune systems only.[52] A recent publication in the *American Journal of Public Health* on associations between neighborhood poverty and allostatic load utilized only waist circumference, systolic and diastolic blood pressure, glucose, total cholesterol, tryglycerides, and low- and high-density lipoproteins in their operationalization of allostatic load.[129] The measure of allostatic load used in Manuscript II improved upon this by including fibrinogen in addition to these metabolic and cardiovascular indicators in order to capture immune system functioning. A previous study that provided the initial evidence of a meta-factor model of allostatic load demonstrated that the core domains of an allostatic load meta-factor were metabolism and inflammation as these latent factors had the highest loadings.[53] Moreover, the inclusion of inflammatory biomarkers is an important distinction between allostatic load and metabolic syndrome (the latter typically captured by blood pressure, lipid profiles, and anthropometric measures). McCaffery[92] et al., used confirmatory factor analysis to distinguish allostatic load from metabolic syndrome by including an inflammation factor (as measured by C-reactive protein and Interleukin 6) and vagal tone variables. Finally, Juster et al.,[23] suggest that the pathways leading to metabolic syndrome differ from allostatic load and that more work on the temporal sequencing of neuroendocrine dysregulation will further illuminate its effects on both of these subclinical conditions.

Perhaps the greatest limitation to these analyses is sample size and power. Manuscript I had included the smallest number of participants (N=157) and barely met the minimum suggested size for latent variable modeling. However, it was important to include relevant markers of inflammation – C-reactive protein and white blood cells, which were only available from a BHS sub-study – in the structural equation model in order to measure a latent inflammation domain. Not utilizing inflammation markers in our allostatic load model may have increased our sample size and possibly have improved our measurement model fit statistics, but the resulting allostatic load scores would have captured an incomplete picture of multisystemic physiologic dysregulation.

Manuscripts II and III were also limited in sample size by the requirements that women were successfully matched to a birth record and that allostatic load data were available from an examination that occurred prior to conception. Preconception C-reactive protein and white blood cells – the inflammation markers used in Manuscript I – were available in less than 20 women. As such, fibrinogen was used as an alternate indicator of inflammation. However, the structural equation model could not be fit to the data using fibrinogen as the only marker of a latent inflammation domain. Therefore, the operationalization of allostatic load most frequently used in the literature (summary measure of highest risk quartiles) was employed instead. These data were complete for a larger sample than Manuscript I (N=431), however, it is likely that the analyses estimating the associations between allostatic load and birth outcomes were underpowered. A post hoc power calculation suggests that the minimum detectable relative risks for preterm birth and low birthweight by allostatic load score were 1.98 and 1.97, respectfully, with 1-beta=80% and alpha=0.05. The actual estimates appeared in

the right direction (increased risk for higher allostatic load), but were of considerably less magnitude and were statistically nonsignificant.

Finally, in Manuscript III the much larger sample size (N=866) was enabled by not including inflammation biomarkers in our allostatic load index. Although these indicators should ideally be incorporated in a comprehensive allostatic load measure as discussed above, they are absent in nearly all of the literature examining allostatic load in neighborhood- or structural-level contexts. This may be an artifact of methodological requirements outweighing the theoretical justification of their inclusion: multilevel and marginal models both require a large absolute sample size in addition to a large number of clusters and large cluster sizes. Even with over 800 women, the limited number of block groups in which these women resided prohibited multilevel modeling and as such we were unable to estimate the between and within group variances. Instead, generalized estimating equations (marginal models) were used to make population-averaged interpretations of the effect of neighborhood poverty level on allostatic load and birth outcomes. These effect estimates had fairly wide confidence intervals, indicative of a lack of precision due to the limited sample size, but were highly significant nonetheless.

A related threat to internal validity is selection bias, which likely occurred as a result of the data linkage aspect of this study design. Women included in the analyses were only those BHS participants who remained in Louisiana and gave birth to their first born child between 1990 and 2009. Furthermore, only those women for whom a matching birth certificate was identified during the data linkage were included in Manuscripts II and III. A comparison between matched and unmatched women indicated that women who were matched were more frequently African American (40.1%

compared to 34.7% of those unmatched, P<0.001) and younger (35 compared to 42 years, P<0.001). With regard to age, it is likely that the older women had given birth to their first child prior to 1990 and were therefore unmatched because of unavailability of birth records prior to 1990. Additionally, it may be that lower-risk women who moved out of the state for career or educational pursuits were underrepresented. On the other hand, it may be that higher-risk women who were not in contact with prenatal care and gave birth outside of the healthcare system were underrepresented. Given all of these possible scenarios, it is difficult to predict the direction of bias our sample selection through data linkage had on the estimates of effects. A future study based on data from a single source, such as a longitudinal cohort following women for both allostatic load and pregnancy data, may yield less biased results.

Selection bias may also have occurred as a result of the requirement that women included in the allostatic load and birth outcomes analyses (those who were matched to a birth record) also have complete biomarker data available from a BHS exam that took place prior to conception. This issue is complicated by the panel-study design of BHS and the fact that particular biomarkers were only collected during sub-studies such that the measures are only available for participants who were present for that year's examination. While blood pressure, lipid profiles, and anthropometric measures are consistently collected at every BHS examination, collection of inflammation markers varies across exam years. Of the 1,497 women who were successfully matched to the birth record of their singleton first born child, 431 had attended either the 1987 or 1998 examinations when fibrinogen was measured and therefore had complete allostatic load biomarker data for analysis in Manuscript II. The mean age of these women was

approximately 13. Therefore, in order to investigate how the women who attended these exams may have differed from all other women who ever attended a BHS exam, Table 1 compares biologic characteristics measured at age 13 (or at the closest age within the range 11-14) between these two groups. Women included in the analysis had significantly higher levels of cholesterol and body mass index. Blood pressure and triglyceride levels did not differ and there was no difference in the racial distribution between the two groups. Both the BHS participants who were included in this analysis and those who were not attended at average approximately 4 exams to date (mean=3.9 vs. 3.6, respectively, $P<0.01$).

Table 2 repeats this comparison for the women included in Manuscript III. Of the 866 women included in that analysis, 519 had a BHS examination that occurred between the ages of 11-14. Compared to all other women who had a BHS examination in the same age range, these women had significantly lower blood pressure, but higher body mass index and cholesterol. Again, there was no difference in the racial distribution of these two groups. As above, both groups attended an average of about 4 exams to date (mean=3.9 for women not included and 3.6 for women included in analysis, $P<0.01$).

There is no clear distinction in the risk profiles of those selected for analyses compared to those who were not included that would allow for prediction of the effect this bias may have had on the measures of association between allostatic load and birth outcomes. Given the availability of repeated measures on many of the BHS participants, future work on this dataset might consider utilizing imputation techniques to increase the number of women with complete biomarker data for derivation of an allostatic load

measure. This would both increase sample size and power and may address some of the selection bias in only analyzing women with non-missing data.

Table 1. Descriptive Statistics of biological indicators measured at age 13 or the closest age to 13 within the range 11-14 among women analyzed in Manuscript II and all other women who participated in a BHS examination within the same age range.

	Included in Manuscript II (n=280)		Not included in Manuscript II (n=3,112)	
	Mean	SD	Mean	SD
SBP (mmHg)	105.2	8.9	105.8	9.0
DBP (mmHg)	65.7	8.1	66.5	7.9
Body mass index (kg/m^2)**	21.4	4.4	20.7	4.5
Total cholesterol (mg/dL)**	171.6	31.2	162.3	28.6
Triglycerides (mg/dL)	77.7	38.2	75.6	39.1

[a] Manuscript II included a total of 431 women with a mean age of 13 (ranging from 5 to 29).
**P<0.01

Table 2. Descriptive Statistics of biological indicators measured at age 13 or the closest age to 13 within the range 11-14 among women analyzed in Manuscript III and all other women who participated in a BHS examination within the same age range.

	Included in Manuscript III (n=519)		Not included in Manuscript III (n=2,873)	
	Mean	SD	Mean	SD
SBP (mmHg)*	104.9	8.7	106.0	9.1
DBP (mmHg)**	65.4	7.5	66.6	8.0
Body mass index (kg/m^2)*	21.1	4.9	20.7	4.4
Total cholesterol (mg/dL)**	167.4	29.9	162.3	28.7
Triglycerides (mg/dL)	78.6	42.9	75.2	38.2

[a] Manuscript II included a total of 866 women with a mean age of 14.8 (ranging from 4 to 35).
*P<0.05
**P<0.01

CHAPTER 8. Conclusion

The theoretical plausibility of allostatic load as a metric of risk for adverse birth outcomes and the biologic mediator of racial disparities is strong. However, in these first attempts to empirically quantify its relationship to preterm birth, low birthweight, and small-for-gestational age, it was not associated with an increased risk. It should not be concluded definitively that the cumulative physiological stress represented by allostatic load makes no contribution to the occurrence of these outcomes. Rather, these results underscore the need for further refinement of measures that capture holistically the way in which stressful conditions and experiences encountered across the life-course shape the functioning and health of our bodies over time. This requires that future studies that include prospective collection of a range of biologic indicators measured in women longitudinally across critical periods of development prior to, during, and after pregnancy. Concurrently, measures of the social and physical environment in which women are born, live, and work must be collected and used to examine the stress biology in context. Use of latent variable modeling and other advanced analytic techniques should be applied with careful consideration and sound theoretical support from psychology and physiology in operationalizing measures of chronic stress. Finally, exploration of emerging theories of stress effects on development – such as those that focus on stress responsivity and adaptive calibration of stress mediators[141] – may provide superior explanations for how harmful exposures in the physical and social environment are internalized and can manifest in adverse pregnancy outcomes.

Perhaps one of the most critical implications to be drawn from the analyses presented here is the amount of work yet to be done in achieving health equity among all

women and children in this country. This will require addressing the root causes of health disparities with translational research that is directly relevant to intervention and policy. Moreover, evidence from the study population examined in this project indicates that health determinants in the social and structural environment are not necessarily analogous between urban and rural women. Much of the existing literature on stress, race, and reproductive health is derived from urban populations and is not readily generalizable to women in rural contexts. These women represent an understudied population and more evidence is needed to inform context-specific programs and policies designed to eliminate disparities in access to and quality of health care, educational and employment opportunities, and to create healthy, equitable living conditions in their small communities.

It is clear, however, that across both urban and rural contexts interpersonal and structural racism influences the distribution of these factors such that African Americans suffer worse health outcomes than White individuals. The disproportionate frequency at which African American women experience the death of a child before its first birthday is an unquantifiable burden. It is the legacy of historical and current subjugation embodied in the young women born more than a hundred years since the end of slavery and only a generation since civil rights, and in the bodies of their infants, born too early or too small. This is an issue whose concern is broader than public health. It is a matter of social justice, and human rights.

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