

Understanding Relationships Between Early Life Toxic Stress, Childhood Socioeconomic Disadvantage, and Allostatic Load in Adolescence

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UNDERSTANDING RELATIONSHIPS BETWEEN EARLY LIFE
TOXIC STRESS, CHILDHOOD SOCIOECONOMIC
DISADVANTAGE, AND ALLOSTATIC
LOAD IN ADOLESCENCE

By
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ABSTRACT
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Chronic disease prevalence among children and adolescents is rising, which is thought to result in part from elevations in allostatic load (AL). AL is the cumulative physiological dysregulation that results from exposure to biological, social and environmental stressors over time. Socioeconomic disparities in chronic disease and AL have been well-documented in adult populations, including links between childhood socioeconomic disadvantage (CSD) and AL, yet little is known as to whether CSD may begin to impact AL earlier in life. Differential exposure and vulnerability to stress among racial/ethnic minorities may increase risk for elevated AL among those experiencing CSD. Framed by the Life Course Perspective and the Allostatic Load Framework, the purpose of this dissertation was to determine the best measurement approach for AL, examine direct and indirect pathways between CSD and AL through several environmental and behavioral mediators, and determine whether these relationships varied across race/ethnicity.

This was a cross-sectional, correlational study of 1900 adolescents (aged 12 to 18) from four waves (2003 to 2010) of the National Health and Nutrition Examination Survey (NHANES). We constructed latent variables for AL and CSD, based upon biologic and self-reported indicators. Smoking and lead exposure were measured with biomarkers, while nutrition, physical activity, and race/ethnicity were self-reported. Structural equation modeling (SEM) was used to examine relationships between latent construct variables and measured mediating variables across three race/ethnicity groups.

The data best supported a unidimensional AL factor structure, with the highest factor loadings found for metabolic indicators. The only significant total effects pathway for CSD on AL was for Whites, indicating the model best explained AL variance for this group. There were small, positive direct effects pathways significant for African Americans (AAs) and Whites, indicating higher CSD predicted higher AL for those groups. A single indirect pathway between CSD and AL mediated by lead was significant for AA adolescents, though the reversed directionality suggests a need for a different measurement approach for cumulative lead exposure. These findings highlight the importance of exposure to CSD as a predictor for development of AL for adolescents, while also elucidating different mechanisms at play across different racial/ethnic populations.

DEDICATION

Amanda L. King, PhD(c), MSN, RN, APNP-BC

This dissertation is dedicated to my mother, Lin Elizabeth King, who instilled in me a strong sense of self-belief, determination, and an endless curiosity about the world, all of which have been instrumental in my success. You inspired everyone around you with your strength, kindness and empathy for others throughout your life, which I strive to emulate in mine each day. Though you are not here to celebrate this accomplishment with me, you have been with me in spirit every step of the way. Thank you for cultivating everything that is good in me, you are missed.

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Amanda L. King, PhD(c), MSN, RN, APNP-BC

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CHAPTER I: INTRODUCTION

Chronic diseases are one of the most significant health and development challenges of the 21st century, both in terms of the human suffering they cause as well as the socioeconomic impact they have on countries burdened by them (World Health Organization, 2014). Chronic diseases, also commonly referred to as noncommunicable diseases (NCDs), can be defined as medical diseases or conditions that are not caused by infectious agents, implying they are non-transmissible between individuals (Kim & Oh, 2013). While four major chronic diseases (cardiovascular disease, cancer, diabetes, and chronic respiratory disease) are responsible for over 80% of all chronic disease deaths worldwide (WHO, 2014), there are several other important chronic diseases that are associated with significant morbidity and mortality, including obesity, stroke, and chronic kidney disease. As the leading cause of death globally, chronic diseases were responsible for 38 million of the world's 56 million deaths in 2012, with a projected increase to 52 million deaths by the year 2030 (WHO, 2014).

The global economic ramifications of chronic diseases are enormous due to the combined burden of health care costs to manage them as well as the lost economic productivity due to morbidity and premature mortality (Hunter & Reddy, 2013). The authors of a study conducted by the World Economic Forum determined that chronic diseases could result in a cumulative productivity loss of \$47 trillion between 2011 and 2030 (Bloom, Cafiero, Jane-Llopis, & al., 2011). In the absence of evidence-driven actions, the human, social, and economic costs of chronic diseases

will continue to grow and will overwhelm the ability of countries to effectively respond to them (WHO, 2014).

In the United States (US), more than half of all individuals suffer from one or more chronic diseases, affecting over 117 million people (Centers for Disease Control and Prevention, 2017; Ward, Schiller, & Goodman, 2014). Chronic diseases are the leading cause of death and disability in this country, with just two of them (heart disease and cancer) accounting for nearly 46% of all deaths in the US (CDC, 2016b). Not only are these the most common health problems in this country, they are also the costliest, with an estimated \$1.3 trillion annual impact on the US economy (CDC, 2016b; Healthy People 2020, 2016; Hunter & Reddy, 2013). While the prevalence of chronic diseases continues to rise as people are living to older age, the distribution of these diseases continues to be unequal with minority and low socioeconomic individuals often experiencing higher prevalence of chronic disease (Loi, Del Savio, & Stupka, 2013). Due to the societal racism and discrimination that persists in the US, the distribution of social determinants of health have played a large role in creating these health inequities for certain minority populations (Bailey et al., 2017). The overarching goals of the Healthy People 2020 framework are to promote high-quality, longer lives that are free of preventable chronic disease by creating social and physical environments that promote health for all groups, which will eliminate health disparities (Halfon, Larson, Lu, Tullis, & Russ, 2014; Healthy People 2020, 2016). However, in order to achieve these goals, it is important to seek a broader understanding about the determinants of chronic disease that

includes biological, environmental, social, and behavioral factors and how they interact to shape health.

The following section will be an introduction of the key concepts that are essential for understanding the importance of stress and its implications for health, both in adolescence and across the life course. Following these conceptual introductions is a discussion of the significance of this research to vulnerable populations and to the nursing discipline in order to establish the importance of this study. Finally, this chapter will close with the purpose of this study and the aims it will accomplish.

Introduction of Key Concepts

In order to fully understand and appreciate the complex relationships that were explored in this study, it is important to define the key concepts that will be foundational in this research. The significance of these concepts for child and adolescent health are also discussed, with a more in-depth discussion found in chapter two.

Toxic stress. The concept of stress was initially coined by Hans Selye in the 1930s, who described it as a generalized response of the body to any demand for a change in homeostasis (Selye, 1973). Although the terms “stress” and “stressor” commonly carry negative connotations, they can either be adaptive or maladaptive, and even similar responses can vary in their adaptive value based on timing, duration, and the environmental context in which they occur (Zannas & West, 2014). There is a spectrum of the stress response in the body, which includes positive, tolerable, and toxic stress, depending on the nature of the stressors and

any buffering influences that might be protective from their effects (Bucci, Marques, Oh, & Harris, 2016; Shonkoff & Garner, 2012). A positive or tolerable stress response is associated with acute, short-lived stressors and is characterized by a successful return to homeostasis once the body has adapted to the stressor. In contrast, a toxic stress response is characterized by prolonged or frequent activation of the stress response in the body, which leads to systemic dysregulation across multiple body systems (Bucci et al., 2016), ultimately increasing risk for a variety of chronic diseases. When toxic stress occurs during sensitive periods of development, such as during fetal or childhood development, the effects of that stress have the potential become programmed into long-term pathophysiological processes, thus increasing vulnerability to developmental, biological, and psychological adverse outcomes across the life course (Johnson, Riley, Granger, & Riis, 2013).

Childhood socioeconomic disadvantage. There is compelling evidence that early life exposure to socioeconomic disadvantage can contribute to toxic stress with potential for lifelong health consequences through biological embedding, defined as altered biological functioning as a result of the exposure (Slopen, Goodman, Koenen, & Kubzansky, 2013). Childhood socioeconomic disadvantage (CSD) refers to the comparative deprivation that a child experiences related to their position within a hierarchical social structure, which is often based upon a combination of variables indicative of their access to financial and social resources (i.e. parental education, occupation, and income, as well as the family residence and food security) (Meier et al., 2016). Previous research suggests that the toxic stress

experienced by children from a disadvantaged socioeconomic environment can have permanent effects on the parts of the brain that are involved with stress adaptation, which can have lifelong implications for their health trajectories (Hanson, Chandra, Wolfe, & Pollak, 2011; Noble, Houston, Kan, & Sowell, 2012). Whether the CSD serves as a critical or sensitive period exposure during which risk for chronic disease in adulthood becomes embedded, remains unclear.

Allostatic load. Allostatic load (AL) is a marker of cumulative biological risk that has been theorized to capture the biological pathways through which stressful experiences across the lifespan lead to chronic disease later in life (Barboza Solís et al., 2015; Friedman, Karlamangla, Gruenewald, Koretz, & Seeman, 2015). This term was initially conceptualized by (McEwen (1998), who expanded upon the concept of allostasis – the ability to achieve stability through adaptation – hypothesizing that the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems protect the body by mounting adaptive responses to stressors. The price we pay for our body’s ability to adapt to stress is what he termed AL, which is the biological result of chronic overactivity of our stress management systems (Hux & Roberts, 2015). The concept of AL provides multidisciplinary researchers an integrative framework for studying the protective effects of stress mediators during acute stress experiences, as well as the maladaptive effects of chronic or repeated stress exposures over time (Beckie, 2012). AL has been widely found to be associated with early life toxic stress and later life chronic disease (Barboza Solis et al., 2015; Beckie, Duffy, & Groer, 2016; Berg, Simons, Barr, Beach, & Philibert, 2017), but it is unknown how early in life this

phenomenon emerges and what the ideal points for intervention are in order to improve health trajectories for those experiencing CSD.

Significance to Vulnerable Populations

Vulnerability has traditionally been viewed with a negative connotation, one that implies individuals or groups being at risk for harm or susceptibility to developing negative health outcomes (Engle, Castle, & Menon, 1996; Glass & Davis, 2004; Spiers, 2000). Though vulnerability is a fundamental concept that shapes how patients experience health, its theoretical origin lies within the field of epidemiology, rather than nursing (Spiers, 2000). Vulnerable populations have traditionally been defined as individuals and groups who are at risk of developing poor physical, psychological, or social health outcomes within a given period of time (Aday, 2001). The populations that have classically been identified as at increased risk include: pregnant women, infants, children and adolescents, the elderly, those with chronic illnesses, minority populations, incarcerated individuals, and those of lower socioeconomic backgrounds (Spiers, 2000). However, in recent years the perception that only certain groups of people are vulnerable has transitioned towards a view that *all* human beings are vulnerable, to some extent, depending on their individual context and experiences. This modern conceptualization of vulnerability views it as part of the human condition, a self-evident truth where a person is never entirely free from possible physical or psychological harm (Sellman, 2005).

For an individual or group, vulnerability can be assessed holistically from both etic and emic perspectives, which each contribute a different aspect of

vulnerability. The etic perspective of vulnerability is used to describe the phenomena as viewed by someone outside of the vulnerability experience and identifies individuals or groups who are at increased risk for adverse health outcomes, based on normative standards that are determined by society (Spiers, 2000). This etic perspective is often from the viewpoint of the researcher and makes the assumption that the risks are quantitative in nature and fall on some sort of numerical scale that can be measured. Using this approach, the quantitative information can then be used to target interventions for the vulnerable individual or group in order to reduce their risk factors and hopefully improve their health outcomes.

In contrast, the emic perspective of vulnerability is a description of the phenomena understood by the individual that is at risk, thus is more experiential and qualitative in nature (Spiers, 2000). This viewpoint is based on the individual subjective experiences of exposure to harm through violations or challenges to their identity and integrity. The emic perspective places vulnerability in a psycho-social-cultural context, which allows for a much broader perspective than the etic perspective and focuses more on the vulnerability one experiences in everyday life (Spiers, 2000). This viewpoint aligns with the assumption that vulnerability is a universal experience, given that the potential for danger or risk to some aspect of one's health is essentially a part of the human condition. Taken together, the etic and emic perspectives combine the concepts of risk and experience in order to better understand the vulnerability of an individual or population, which can aid efforts to develop more effective interventions to improve their health.

Vulnerability of children and adolescents. Children and adolescents are unique vulnerable populations, considering that their experiences are entirely dependent upon the circumstances they are born into. They exist in a social context with their parents or caregivers and rely on them to provide them the necessities in their lives (i.e. food, shelter, clothing, medical care, etc.). Additionally, these caregivers serve as important sources of social support for children and adolescents, as well as positive role modeling for healthy behaviors, such as healthy eating and being physically active (Non et al., 2016). Some of most vulnerable and marginalized children that have been recognized in the literature are those born into poverty or socioeconomic disadvantage (Blair & Raver, 2016; Razack, 2009), as well as those who experience abuse, neglect, or other household dysfunction (Bucci et al., 2016). All of these vulnerability risk factors impact children and adolescents when the interactions between the individual and their environment produce toxic stress, which presents new threats to homeostasis and successful adaptation, thus predisposing them to poor physical and psychological health over time.

While the child's social environment clearly is a potential source for vulnerability, they also have vulnerability at the biologic level that plays a role in determining their health risk. Children are unique in that their brain and body systems are not fully developed until they approach adulthood, which leaves them increasingly vulnerable to adverse exposures (Bucci et al., 2016). This is the basis for the critical and sensitive periods model within the life course perspective, which proposes that there are specific time windows within fetal and child development where an exposure can have lifelong effects on disease risk (Ben-Shlomo, Cooper, &

Kuh, 2016). Early childhood and adolescence are thought to be sensitive periods of development where biological systems are particularly shaped by external influences and experiences (Bucci et al., 2016), thus increasing the vulnerability of the individual during this time frame. Therefore, when it comes to toxic stress and AL, the timing of the stressful exposure for the child or adolescent is critically important when determining the long-term impact it can have on the child's lifelong health trajectory.

Significance to Nursing

The metaparadigm of a discipline identifies the relevant phenomena or central concepts of interest for a particular branch of knowledge. The metaparadigm of nursing defines the foundations of the profession as being focused on the person, environment, and health and understanding how nurses can interact with these spheres in order to promote health for our patients (Fawcett, 1984). This type of holistic approach to patient care is engrained in nurses from the beginning of their training and is a key distinguishing factor about their practice, compared to other health care professionals. Nursing science is unique in that it transcends the boundaries of disease and other research disciplines in order to promote health and well-being for individuals at all stages of life, and across diverse populations and settings (National Institute of Nursing Research, 2016).

It is the mission of the National Institute of Nursing Research (NINR) to promote and improve the health and quality of life for individuals, families, and communities (NINR, 2016). This organization supports and conducts research that integrates biological and behavioral science in order to develop the scientific

foundations for clinical practice. A major area of scientific focus for the NINR is that of wellness, which aims to promote health and prevent chronic disease. Research supported in this area focuses on the key biological, behavioral, social, and environmental factors that promote long-term health in order to prevent the development of chronic disease across the life course (NINR, 2016). This study aligned very closely with the NINR wellness focus by exploring the relationship between early life toxic stress, childhood socioeconomic disadvantage, and allostatic load during adolescence, thus focusing on an important developmental time period that potentially has significant lifelong health implications for adolescents.

Nursing research has the potential to be significantly enhanced by the AL framework, which provides a mechanism for assessment of the impact of toxic stress on the health of children and adolescents without having to wait for the long-term adverse health outcomes that sometimes don't emerge until adulthood (Rosemberg, Li, & Seng, 2017). Therefore, the results of this study could provide important information about important stressful exposures during childhood, how they shape AL development in adolescence, and could highlight potential mediating pathways that are intervenable in order to mitigate chronic disease risk in this population. Additionally, there are potential policy implications from this study, which could support the allocation of more resources to individuals earlier in the life course (i.e. during childhood and adolescence), rather than later in life where the majority of the country's health care resources are currently spent (DeVol, Bedroussian, Charuworn, & Chatterjee, 2007; Hunter & Reddy, 2013). Given our well-earned scientific expertise and public respect, nurses are in an excellent

position to exert considerable influence on health care policy through participation and dissemination of research about the impact of toxic stress across the life course.

Purpose of the Study

A vast body of literature supports the notion that our earliest exposures during childhood and adolescence play a significant role in programming our health status later in life. While the relationships between toxic stress, CSD, and AL have been consistently demonstrated in adult populations, it is unclear whether elevated AL is present earlier in life, as this construct has rarely been measured in pediatric populations. As such, there is also a need to develop a robust AL measure for adolescents that captures dysregulation across the stress response systems. Additionally, there is a need to identify the extent to which environmental and behavioral factors may explain socioeconomic disparities in AL and whether these associations vary across race/ethnicity groups, which could help identify targeted interventions that are more likely to promote health equity.

Therefore, the overall purpose of this study is to develop a latent AL measure, examine the relationship between CSD and AL in adolescence, assess environmental and behavioral mediating pathways, and explore the role that race/ethnicity has on these relationships. As a result, we will attain a broader understanding of the mechanisms by which stressful exposures become biologically embedded and affect health trajectories for adolescents. There are three aims of this study. The first aim was to develop an AL latent construct for an adolescent population. The second aim was to examine total, direct, indirect effects of CSD on AL in adolescence, assessing smoking, lead, nutrition and physical activity as

potential mediators between CSD and AL. And the final aim was to determine the extent that the total, direct, and indirect effects between CSD and AL in adolescence vary across race/ethnicity.

This study was consistent with the recommendations from goals of the Healthy People 2020 framework, which focuses on health promotion across the life course through examination of biological, social, environmental, and behavioral risk factors for chronic disease (Halfon et al., 2014; Healthy People 2020, 2016). While there is extensive research suggesting that early life exposure to toxic stress and socioeconomic disadvantage leads to AL in adults, there are few studies that determine if AL can be measured, or intervened upon, in childhood and adolescence. Given that chronic disease interventions earlier in the life course have the potential to be much more beneficial than waiting until adulthood (Hanson & Gluckman, 2014), there is a greater potential to mitigate chronic disease risk for individuals if we are able to screen for AL and intervene during these early years of development. Therefore, this study will lay the groundwork for building a program of research that focuses on identifying the biological, social, environmental, and behavioral risk factors that contribute to AL in children and adolescents, which will inform future stress interventions to improve pediatric health trajectories.

CHAPTER II: THEORY AND REVIEW OF LITERATURE

In chapter two, I build upon the introductory content about the significance of toxic stress and AL to child and adolescent health that was presented in chapter one. This chapter begins with a discussion of the two theoretical models that together formed the underlying theoretical framework guiding this study. The philosophical underpinnings for this study are also presented in order to illustrate the rationale for the proposed methodological approach in chapter three. A review and critical analysis of the existing literature then follows, including definitions for all key concepts, as well as the strengths and weaknesses of existing research in this area. This then leads to a discussion of the gaps in the existing literature and how this study proposed to fill those gaps. The chapter concludes with a presentation of the proposed aims, research questions, and hypotheses, as well as the assumptions of the study.

Theoretical Framework

Life course perspective. Also referred to as the life course approach or life course theory, the life course perspective provides an interdisciplinary framework for guiding research on health and human development, and has been promoted by epidemiologists, psychologists, sociologists, anthropologists, and biologists for decades (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). This framework has been utilized to evaluate and predict the long-term effects of biological, environmental, and social exposures during gestation, childhood, and adolescence on health outcomes in adulthood (Ben-Shlomo et al., 2016; Halfon et al., 2014). It

has commonly been used as a guiding framework in studies focusing on chronic disease outcomes, such as cardiovascular disease, metabolic disorders (including obesity and diabetes), and cancer, although it is also often utilized to evaluate how socioeconomic and environmental factors influence health throughout the life of an individual (Ben-Shlomo et al., 2016; Braveman, 2014). The ultimate goal with this approach is to elucidate biological, behavioral, environmental, and psychosocial processes that occur across the life course of an individual, or across generations, which influence their risk for development of physiological and psychological disease (Green & Benzeval, 2013; Kuh et al., 2003). Ben-Shlomo and Kuh (2002) proposed several conceptual models that are widely used within the life course perspective, which describe how exposures across the lifespan can affect health in different ways. These models include accumulation of risk, birth cohort effects, chains of risk, and critical or sensitive periods models, each of which will be explained below.

Accumulation of risk. An accumulation of risk model proposes that life course exposures gradually accumulate over time through illness, injury, adverse environments, or health-damaging behaviors (Ben-Shlomo & Kuh, 2002; Kuh et al., 2003). This type of model tests the extent of cumulative damage affecting an individual's biological systems as the adverse exposure increases over time, which renders the body's repair mechanisms less able to cope with the repeated insults. Evidence suggests that the majority of individuals can successfully cope with a single adverse stressor, but problems can arise when stressors accumulate over time (Masters Pedersen et al., 2015). Therefore, accumulation of risk models focus

on the individual's total burden of adverse exposures, including the number, duration, or severity of a variety of environmental, socioeconomic, and behavioral factors that negatively impact health (Ben-Shlomo et al., 2016; Power, Kuh, & Morton, 2013). This accumulation of risk model is conceptually similar to the AL framework (to be discussed in more detail shortly), which proposes that as the number and/or duration of stressful exposures increases for an individual, there is increased cumulative damage that occurs to the biological systems responsible for adapting to those stressors (Ben-Shlomo & Kuh, 2002).

There are two kinds of accumulation of risk models: independent risk factor and cluster risk factor models. In the independent risk factor model, each exposure risk factor has a direct and independent effect on the outcome measure. Each independent risk factor exerts its effects on the outcome measure over time. By contrast, the cluster risk factor model has a risk factor exposure (exposure A) that has only indirect effect on the outcome measure because it is mediated through exposure to intermediary risk factors (exposures B and C), which also accumulate over time. Thus, exposure A increases risk to exposures B and C, which ultimately increases risk for the outcome measure of interest.

Birth cohort effects. A birth cohort can be defined as a group of individuals who were born at a common point in historical time (Kuh et al., 2003). Cohort members can experience differences in environment, social change, health behavior, and history, each of which can impact long-term health outcomes. Cohort differences in environmental living standards, childbearing habits, and prevalence of risky health behaviors, such as smoking or alcohol use, can significantly impact

the health of individuals born during a particular time period, thus affecting the health trajectory of that group as a whole. Studies using birth cohort effects models can be quite powerful when utilizing repeated measures of both biological and psychological exposures, and can highlight secular trends of exposure-disease associations, as well as trends in health care practices, across longer periods of time (Ben-Shlomo & Kuh, 2002; Kinlaw et al., 2017; Kuh et al., 2003).

Chains of risk. A chains of risk life course model proposes a sequence of adverse exposures that are linked, meaning that one adverse experience or exposure leads to another adverse exposure, and so on (Goosby, Cheadle, & McDade, 2016; Kuh et al., 2003). These models are based on the notion that an initial exposure can set into motion a chain of reactions that leads to further exposures, which will either increase or decrease the risk of a particular health outcome. Some disciplines have refer to chains of risk models as pathway models (Power et al., 2013), which can also involve mediation and modification factors that influence particular exposures in the chain that ultimately determine the risk for developing the outcome of interest (Kuh et al., 2003). There are two different types of chains of risk models, including independent effect and trigger effect models. In the independent effect chains of risk model, each exposure increases the risk of the subsequent exposure in the pathway, but also has its own independent effect on the outcome measure. Trigger effect models occur when each subsequent exposure has no direct effect on the outcome measure, but instead only affects the next link in the chain. Ultimately, the earliest exposures in the chain will not affect the outcome of

interest without the final exposure in the chain of risks being present (Kuh et al., 2003; Power et al., 2013).

Critical or sensitive periods. Also known as biological programming or latency models, critical period models refer to exposures that act during a critical window of development, which irreversibly affects the structure or function of organs, tissues, or body systems, and in turn impacts disease risk later across the life course (Halfon et al., 2014; Kuh et al., 2003; Power et al., 2013). This model serves as the theoretical foundation for the Developmental Origins of Health and Disease (DOHaD) hypothesis, which was originally founded by Dr. David Barker in the 1980s. In Barker's seminal epidemiological work (1986), he discovered an association between low birth weight and increased risks for several adulthood chronic diseases, including diabetes, hypertension, and cardiovascular disease (Barker, 2012; Chavatte-Palmer, Tarrade, & Rousseau-Ralliard, 2016). His theory was based on the premise that adverse influences during intrauterine life can result in permanent maladaptive changes in fetal physiology and metabolism, which increased risk for disease in adulthood (Roberts & Wood, 2014; Smith et al., 2016), hence suggesting a critical period effect. This biological programming can occur through direct changes to the structure and functions of the organs affected by the adverse exposure, or through alterations in the expression of genes that are affected by environmental interactions (Gluckman, Hanson, Cooper, & Thornburg, 2008; Halfon, Larson, & Russ, 2010), known as gene-environment interactions.

Sensitive period models are similar to critical period models, in which adverse exposures are thought to have a more significant impact on health

outcomes when they occur during specific developmental periods (i.e. times of rapid physical and psychological development), compared to later life stages (Ben-Shlomo et al., 2016; Power et al., 2013). As a result, there can still be a biological programming effect, but it is thought to be more amenable to later life intervention than if it occurred during a more critical period (Halfon et al., 2014). Critical and sensitive periods models are a departure from the classic biomedical model of health where a person's health trajectory is solely based on a combination of their genetic endowment and adult lifestyle choices, instead highlighting the importance of social, psychological, and environmental exposures exerting profound influence at the earliest developmental periods in the life course (Ben-Shlomo et al., 2016; Halfon et al., 2014).

Early childhood and adolescence are thought to be sensitive periods of development where biological systems are readily shaped by either positive or negative influences and experiences (Bucci et al., 2016), which can significantly alter health trajectories for children and adolescents. Adolescence is a particularly sensitive time, given that it is marked by rapid physiological changes with pubertal development, as well as dramatic social changes as the children gain more independence and prepare themselves for adulthood (Crosnoe, 2011; Goosby et al., 2016). Therefore, the sensitive periods life course model served as one of the theoretical foundations for this study, proposing that development of AL during childhood and adolescence could potentially program for ill health later in life.

Allostatic load framework. The AL framework was developed in order to explain how mammalian physiological responses to stressors in the environment

evolved in order to maximize their chances for survival, while limiting the amount of damage to the body (Edes & Crews, 2017; Korte, Koolhaas, Wingfield, & McEwen, 2005; McEwen & Wingfield, 2003; McEwen & Stellar, 1993; Sterling, 2004).

However, these adaptive responses to repeated exposures to stress come at a cost, when over time repeated activity of the stress response systems results in systemic physiological dysregulation (Edes & Crews, 2017). The damage that accumulates is known as AL, which is the result of the chronic “wear and tear” on the body as a result of repeated adaptive responses to stressors (McEwen, 1998). AL can be estimated using multisystem biomarker construct variables that are representative of the key stress mediating body systems, including the neuroendocrine, cardiovascular, metabolic, and immune systems (Beckie, 2012). While the AL framework originated within the biology discipline, it has been adopted and utilized by numerous other fields, including epidemiology, psychology, sociology, and medicine, as an integrative approach to examine the maladaptive physiologic effects of toxic stress exposures over time (Beckie, 2012), and its contribution to social disparities in health (Edes & Crews, 2017). While this framework has not been extensively utilized within the nursing discipline to date, it is ideally suited for health promotion and risk reduction intervention science (Rosemberg et al., 2017), which aligns well with the central goals of nursing.

The AL framework first emerged with Dr. Bruce McEwen’s seminal work (1998), which conceptualized the biological pathways through which stressful exposures could contribute to chronic disease burden over time. Sterling and Eyer (1988) initially defined the term “allostasis” as the ability to achieve stability

through change, which is essential for an organism in order to maintain homeostasis. There are two factors that are largely responsible for individuals' responses to stressful exposures or situations: (1) the way an individual perceives a particular stressful situation (Lazarus & Folkman, 1984), and (2) that individual's general physical health, which is determined by genetic and lifestyle factors, as shown in the AL framework (see Figure 1). According to McEwen's AL model, the perception of stress is also influenced by an individual's previous life experiences, as well as their environmental exposures (McEwen, 1998). When the brain perceives an exposure or situation to be stressful, it initiates a cascade of physiologic and behavioral responses, which leads to the process of allostasis and adaptation to the stressor. Over time, AL can accumulate from repeated physiological attempts at adaptation, which results in overexposure to stress mediators, with eventual damage to allostatic organ systems and development of chronic disease phenotypes (McEwen, 1998).

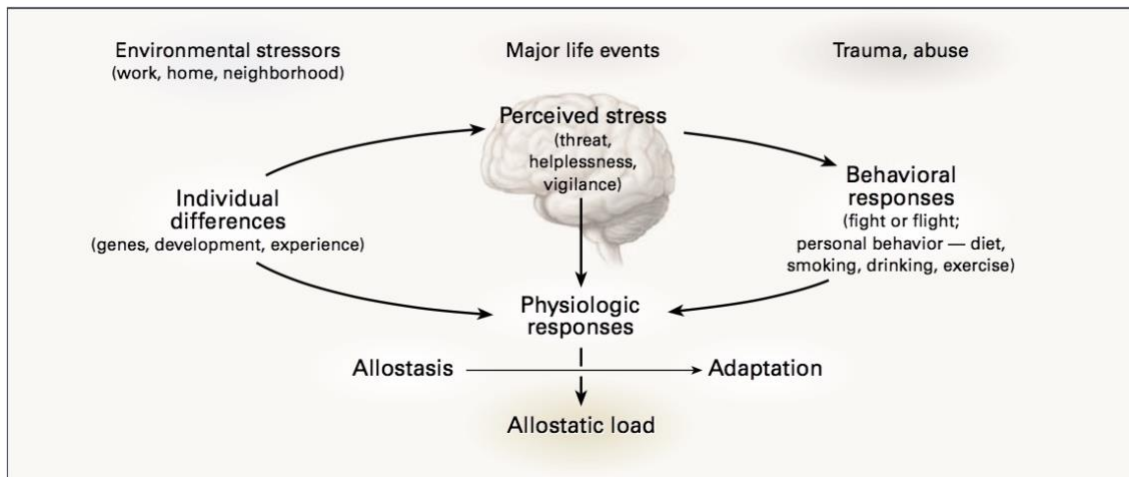


Figure 1. Allostatic Load Theoretical Framework

From [*The New England Journal of Medicine*, McEwen, B. S., Protective and damaging effects of stress mediators, 338(3), 171-9]. Copyright © (1998) Massachusetts Medical Society. Reprinted with permission.

Biological premise for AL. Because the neuroendocrine, immune, and cardiometabolic systems are highly integrated in the body, stimulation of one of these allostatic systems commonly triggers physiologic responses in the others (Danese & McEwen, 2012). When a stressful exposure or experience is perceived by the brain, the sympathetic-adrenal-medullary (SAM) axis immediately releases hormones known as catecholamines (i.e. epinephrine and norepinephrine) from the adrenal medulla (Juster, Russell, Almeida, & Picard, 2016; McEwen & Wingfield, 2003). This process is shortly followed by activation of the hypothalamus-pituitary-adrenal (HPA) axis, which is responsible for a physiological cascade that produces the key stress hormones within the neuroendocrine system, the glucocorticoids. The paraventricular nucleus within the hypothalamus activates the HPA axis during the stress response by stimulating a hormone called corticotropin-releasing factor

(CRF), which then signals the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary gland (Juster et al., 2016; McVicar, Ravalier, & Greenwood, 2014). ACTH then enters the bloodstream and travels to the adrenal cortex, where it is involved in the production of cortisol, an important glucocorticoid in humans that is central in the systemic stress response (McVicar et al., 2014; Sapolsky, Romero, & Munck, 2000). The SAM and HPA axes are very efficient at mobilizing the necessary energy resources necessary for stress adaptation, but this also initiates physiological compensatory mechanisms elsewhere in the body (McEwen & Wingfield, 2003). Compensatory alterations that occur during times of stress include suppressed digestion, cellular growth/repair mechanisms, and reproductive functioning, all of which are sacrificed in order to accommodate the increased neurological, cardiovascular, respiratory, and immune activities that require significant metabolic resources (Juster et al., 2016).

The primary job of the brain during a stressful experience is to detect the threat and promote adaptive mechanisms in order to improve survival odds for the organism. Apart from the pituitary and hypothalamic control over the SAM and HPA axes, there are other important brain regions that are involved in identification and management of potential threats for survival (Danese & McEwen, 2012; Edes & Crews, 2017). The hippocampus has been found to be important for memory and cognition, and is a key part of negative feedback regulation for the HPA axis, which turns off the stress response system (Juster et al., 2016; Shih, 2016). The amygdala is a portion of the brain that has been implicated in fear and emotional processing and also has an important role in memory of previous experiences, including those

that are stressful (Danese & McEwen, 2012; Juster et al., 2016). Finally, the prefrontal cortex is also important for neural stress regulation, as it is involved in cognition, coping, and exerting executive control over the functions of subcortical brain structures (Danese & McEwen, 2012; Juster et al., 2016; Shih, 2016).

When the above neurobiological stress network (i.e. the pituitary, hypothalamus, hippocampus, amygdala, and prefrontal cortex) detects threats or stressors, the amygdala is triggered to increase the body's alertness and attention to its surroundings through activation of sympathetic nervous system (SNS) in what is commonly known as the "fight or flight response" (Danese & McEwen, 2012; Suresh, Latha, Nair, & Radhika, 2014). This is a multisystem response to stress where changes in organ and tissue function are highly coordinated in order to increase the delivery of well-oxygenated, nutrient-rich blood to the vital organs that have increased metabolic needs during stressful situations (Herman et al., 2016). Within the cardiovascular system, heart rate and myocardial contractility increase in order to increase cardiac output to skeletal muscles, while there is also widespread vasoconstriction of the smooth muscles in certain blood vessels (such as those in the kidneys and mesentery) and vasodilation in others (such as skeletal muscles) in order to divert blood to the most metabolically active organs (Herman et al., 2016; McCorry, 2007). The metabolic responses during the "fight or flight" response include an increased rate of glyconeolysis (the breakdown of glycogen into glucose) and gluconeogenesis (the formation of new glucose from non-carbohydrate energy sources) in the liver, which serves to increase serum glucose availability in order to fuel the brain and body tissues (McCorry, 2007). There is also a widespread

inflammatory response elicited by the immune system during the “fight or flight” response, which involves the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor, as well as other inflammatory proteins, such as C-reactive protein, all of which prepare the body for potential cellular injury and infection (Adamo, 2014; Herman et al., 2016). Ultimately, the stress response is intended to mobilize energy reserves to allow an individual to successfully respond and adapt to a potential threat, but a dysregulated or inappropriately prolonged HPA axis response is maladaptive, and is thus linked with numerous pathological conditions and disease states (Herman et al., 2016).

Antecedents of AL. Antecedents refer to the events or attributes that must precede the occurrence of a particular concept (Walker & Avant, 2005), also known as predisposing or risk factors for a health outcome. Numerous antecedents have been identified for AL, including psychological factors (i.e. stressful life events, trauma, abuse, neglect), social or environmental factors (i.e. low socioeconomic status, neighborhood quality, environmental toxins, workplace conditions), and individual factors (i.e. genetic/epigenetic predisposition, race/ethnicity, health behaviors, and resilience) (Beckie, 2012; Rosemberg et al., 2017), though the specific mechanisms that underlie these relationships require further empiric clarification. These antecedents can either serve as sources for toxic stress or can affect the way an individual perceives stress, thus affecting the way their HPA axis functions and ultimately, their risk for developing AL. Primary literature investigating the relationship between some of these antecedents and AL will be discussed in more detail in the critical review of literature section.

Primary mediators and secondary outcomes of AL. The process of allostasis begins when the brain perceives a stressor of some kind, resulting in the release of hormones known as the primary mediators of AL. These hormones, including norepinephrine, epinephrine, cortisol, and dehydroepiandrosterone sulfate (DHEA), are rapidly mobilized in response to the stressor, which is adaptive in the short-term, but deleterious in the long-term (Beckie, 2012; McEwen, 1998). If there are chronic or frequent demands for adaptation to stress, or if there is inefficient production or suppression of these hormones, there is increased risk for development of systemic organ dysfunction and eventual chronic disease (McEwen & Gianaros, 2011).

There are numerous secondary outcomes of AL that result from prolonged exposure to the primary stress mediators, which entail systemic dysregulation of cardiometabolic and inflammatory biomarkers in an attempt to compensate for dysregulated stress hormones over a sustained period of time (Beckie, 2012; Juster, McEwen, & Lupien, 2010). These secondary outcomes of AL include dysregulation of blood pressure, heart rate, cholesterol levels, glucose and insulin metabolism, body mass index, creatinine and albumin levels, and other inflammatory proteins (Beckie, 2012; Edes & Crews, 2017). Should the stress persist, as is the case with toxic stress, tertiary outcomes of AL emerge with clinical manifestations of a variety of adverse health outcomes, including cardiovascular disease, diabetes, obesity, various psychological diseases, and all-cause mortality (Beckie, 2012; McEwen, 1998). Specific outcomes of AL that have been identified in previous research will be elaborated on further in the review and critical appraisal of literature section.

Philosophical underpinnings of this study and how they shape the methodological approach proposed follow next.

Philosophical Underpinnings

The present study utilized a systematic approach aided by use of a guiding philosophical paradigm (Houghton, Hunter, & Meskell, 2012). A paradigm is a pattern of beliefs and practices with guiding principles that provide a lens through which investigation is accomplished (Guba, 1990b; Weaver & Olson, 2006). Egon Guba, a pioneer in the field of paradigm expansion in research, outlined several classic paradigms that guide scholarly inquiry. These paradigms can be characterized by the way proponents respond to three basic questions: ontological, epistemological, and methodological (Guba, 1990a). Ontological questions relate to what is the nature of reality, or what is knowable. Epistemological questions are about what the nature of the relationship is between the knower (the researcher) and the knowledge that they are seeking. Finally, methodological questions refer to how the researcher approaches discovering that knowledge. These answers to ontological, epistemological, and methodological questions together formulate a basic belief system that serves as a starting point in research and helps determine what kind of methodological approach the researcher will take in their scientific inquiry (Guba, 1990a; Houghton et al., 2012).

The existence of several different paradigms poses a challenge in research because there are always multiple ways to approach a research topic, resulting in some debate about the ideal approach to scientific inquiry in order to find truth. The positivist paradigm has served as the classic paradigm underpinning scientific

research, which utilizes the scientific method with well-defined concepts and variables, highly controlled experimental conditions, and deductive, empiric hypothesis testing (Houghton et al., 2012; Weaver & Olson, 2006). However, for the purposes of this study, the postpositivist paradigm served as the underlying philosophical framework, which is presented next, highlighting its central tenets, as well as how it differs from the traditional, positivist approach to scientific research.

Postpositivism. Postpositivism can be best characterized as a modified version of the positivist paradigm, which has many similar attributes also some key differences, in order to address some of the shortcomings identified within the positivist approach (Houghton et al., 2012). Positivism is based on a *realist* ontology, where the truth is out there and available for discovery, which is the sole purpose of science and research (Guba, 1990a; Weaver & Olson, 2006). In contrast, with postpositivism, the paradigm moves from an ontology of *realism* to one of *critical realism*, which acknowledges that while the real world is driven by immutable truth, it is impossible for humans to truly perceive it or fully discover it, given our intellectual and sensory imperfections (Guba, 1990b; Houghton et al., 2012). As a result of this *critical realism*, postpositivists must be critical of their own scholarly work, given that we can never be sure that we have really uncovered the truth, rather than our own preconceived notions about it. Despite these doubts, the postpositivist ontology still remains grounded in realism, and believes that reality is out there for us to discover through careful research design.

Epistemologically, postpositivism acknowledges the flaw in assuming that it is possible for a researcher to maintain a distant and non-interactive relationship

with the knowledge they seek, as is the belief in positivism (Guba, 1990b). While positivists purport an *objectivist* epistemology, postpositivists subscribe to a *modified objectivist* epistemology, where they view objectivity as an ideal goal, but also recognize that it cannot be achieved in an absolute sense (Guba, 1990b; Houghton et al., 2012). Reality is constructed to an extent, given that the research is influenced by the values of the researcher (Onwuegbuzie, 2002). Additionally, postpositivist epistemology emphasizes relying on critical tradition (i.e. the process of disseminating knowledge) and the critical community (i.e. journal editors, peers, and readers) in order to ensure that all findings are legitimate, widely available, and consistent with the existing scholarly traditions in the field (Guba, 1990b; Weaver & Olson, 2006).

Methodologically, the positivist paradigm is rooted in *empirical experimentalism*, which prizes well-designed, carefully controlled experimentation that is entirely objective and widely reproducible (Guba, 1990a). However, because postpositivism recognizes the unreliability of human minds, this paradigm places emphasis on *critical multiplism*, which is an elaborated form of triangulation where the findings of an inquiry are based on as many sources as possible (Guba, 1990b). In addition to seeking out multiple data sources, postpositivism also relies on objective knowledge being ascertained through replication of findings in order to further establish the validity of results (Weaver & Olson, 2006). Postpositivism tends to rely on deductive logic, with much of the research grounded in this paradigm being influenced by theory and hypothesis testing (Onwuegbuzie, 2002). As a result, while true objectivity may not be ultimately attainable, strong study

design based on theory and empirical research, as well as strong methodological rigor, will ultimately decrease the likelihood that biased or distorted interpretations will be made in the analysis of findings.

Since the 1980s, the postpositivist paradigm has been found to be an appropriate philosophical framework for the study of nursing questions that require systematically gathered and analyzed data from representative samples (Bunkers, Petardi, Pilkington, & Wells, 1996), as well as those utilizing predictive theories for at-risk individuals and populations (Norbeck, 1987). Given the theoretical framework that informs the current study, as well as its quantitative methodological approach, postpositivism seemed an appropriate choice for the philosophical paradigm to guide this study.

Comprehensive Review & Critical Analysis of Literature

The literature review that follows provides the foundation for the necessity of this study in order to understand the relationships between early life toxic stress, CSD, and AL. Toxic stress is described first through discussion of the conceptual definitions of different kinds of stress, as well as the historical development of the concept. Additionally, pertinent literature related to the association between toxic stress and adverse childhood experiences and HPA axis dysregulation is also presented. The review then shifts to discussion of the CSD literature, which focuses on the conceptual definition of CSD, associated health outcomes, its effects on developing brain structures in children, as well as the different proposed pathways by which CSD exerts its negative influence on health. With a fuller understanding of the detrimental effects of toxic stress and CSD on long-term health trajectories, the

review then presents the AL literature, focusing on its conceptual and theoretical origins, early seminal work that first proposed and utilized the AL construct, important physical and psychological health outcomes, the impact of childhood adversity and socioeconomic and environmental factors, as well as past operationalization of AL.

Next, the review discusses environmental and behavioral mediators that link CSD exposure with development of AL, including review of smoking, lead, nutrition, and physical activity. Lastly, the concept of race/ethnicity is discussed, focusing on how this term was conceptualized for this study, as well as how differential exposure and vulnerability to stress, as well as societal racism and discrimination, can determine the effects that stressful exposures have on certain racial/ethnic populations. Racial/ethnic disparities that have been found in the AL literature are also discussed, with potential explanations offered. This chapter concludes with identification and discussion of the gaps in the literature, which shaped the direction of the current study.

Toxic stress. The earliest phases in the life course are some of the most important and sensitive periods during mammalian development (Lupien, McEwen, Gunnar, & Heim, 2009; Provencal & Binder, 2014). Adverse experiences, such as stress, that occur during these early years represent one of the most powerful influences on health and disease development, particularly if they are chronic in nature (Metz, Ng, Kovalchuk, & Olson, 2015). Dr. Hans Selye (1973) was an endocrinologist who is credited with coining the term “stress”, which he described as a generalized response of the body to any demand for a change in homeostasis.

Through extensive laboratory experimentation with mammalian species, he found that although they were exposed to differing noxious physical and psychological stimuli (i.e. blaring lights, deafening noise, temperature extremes, perpetual frustration, maternal separation), they all exhibited strikingly similar pathophysiological changes, including enlarged adrenals, stomach ulcers, and immune system dysfunction, thus giving rise to his generalized adaptation syndrome (GAS) theory of stress (Selye, 1973). What those varying stressors all had in common was that they all placed an increased demand on the body to adapt to the adverse exposure, which triggered the adaptive mechanisms that was proposed in his GAS stress theory (Selye, 1973).

Selye later demonstrated that exposure to persistent stressors caused animals to develop several chronic diseases, similar to those found in humans, including cardiovascular disease, myocardial infarctions, stroke, and immunological diseases (Selye, 1973). These findings have been replicated in human studies, with exposure to early life stress found to be associated with a wide range of adverse health outcomes, including heart disease, diabetes, obesity, cancer, as well as several psychological and behavioral disorders (Bourke et al., 2013; Heim & Binder, 2012; Mueller & Bale, 2007; Provencal & Binder, 2014). Thus, early life stress research continues to be an area with significant interest, which aims to delineate the specific mechanisms by which toxic stress exerts its negative influence on health across the life course.

However, not all humans and animals respond to early life stressors in the same way. Genetic makeup can modify the way stressful conditions are perceived,

as well as how the allostatic systems respond to them (Buschdorf & Meaney, 2016) through epigenetic regulation of key genes involved in the stress response (Vaiserman, 2015; Zannas & West, 2014). Additionally, an individual's social and physical environment can also have a significant impact on not only the quantity and duration of certain stressors, but also the perceived severity of those stressors, with potential downstream effects on health behaviors (Robinette, Charles, Almeida, & Gruenewald, 2016; Williams & Mohammed, 2013). As such, when conceptualizing the effects of toxic stress in individuals, we must take into account not only genetic and behavioral factors that shape their chronic disease risk, but also the contextual social and environmental factors that can have a profound impact on their cumulative stress burden.

There is a common misperception that stress is always a negative experience, which is not the case. Stress can either be adaptive or maladaptive, and even similar responses can vary in their adaptive value based on the context they occur in and for that particular individual (Zannas & West, 2014). As previously defined, there are positive and tolerable stress responses, which are associated with more acute, short-lived stressors and result in a successful return to homeostasis once the stressor has passed. Such experiences can actually be beneficial for the individual by building resilience and a sense of mastery, which will aid them in addressing future stressors that are presented. In contrast, a toxic stress response is defined as a prolonged or frequent activation of the stress response, which can increase risk for a variety of chronic diseases, particularly if it occurs during sensitive periods of development (Johnson et al., 2013). These types of stressors tend to be of much

longer duration and/or of higher severity than stressors associated with positive or tolerable stress responses, which is why toxic stress is much more likely to lead to development of AL.

Adverse childhood experiences. There are many ways to refer to stressful or traumatic events that are experienced during childhood, including early life stress, early life adversity, early life trauma, or more commonly, adverse childhood experiences (ACEs) (Bucci et al., 2016). While there is a long history in studying the relationships between early life adversity, toxic stress, and long-term physical and mental outcomes, the Adverse Childhood Experience Study (ACE Study) was one of the first to utilize a large sample size in order to test these relationships (Bucci et al., 2016). In the seminal study by Felitti et al. (1998), done in collaboration with the Centers for Disease Control and Prevention (Bucci et al., 2016), with a prospective, descriptive methodological approach ($N = 9,508$) they sought to describe the association between childhood emotional, physical, or sexual abuse, as well as early life household dysfunction, to adulthood health risk behaviors and chronic disease outcomes. An ACE Study questionnaire was developed, based on previously published surveys, which measured seven categories of ACEs, including: psychological, physical, or sexual abuse, violence against the mother, or living with household members who were substance abusers, mentally ill or suicidal, or ever imprisoned (Felitti et al., 1998). These categories were then compared to adulthood measures of health risk behaviors, also assessed via a questionnaire developed by the researchers, including the following risk metrics: smoking, severe obesity, physical inactivity, depressed mood, suicide attempts, alcoholism, any drug abuse,

parenteral drug abuse, a high lifetime number of sexual partners (≥ 50), and a history of sexually transmitted diseases (Felitti et al., 1998). Additionally, they assessed the relationship between ACEs and the chronic diseases that accounted for the highest mortality in the US at the time (the mid-1990s), including the following: ischemic heart disease, cancer, stroke, chronic bronchitis, emphysema, diabetes, hepatitis or jaundice, and any skeletal fractures (i.e. a proxy for unintentional injury) (Felitti et al., 1998). Results from the ACE Study suggested a strong a dose-response (or cumulative) relationship between the number of ACEs an individual experiences and multiple risk factors for several of the leading adult causes of death, as well as with 6 of the 10 of the adulthood chronic diseases studied (Felitti et al., 1998). This study contributed significantly to the ACEs literature by highlighting the prevalence of a variety of potential stressors during childhood, helping delineate the cumulative nature of the negative effects of ACEs, and linking them to a variety of important health outcomes (and the risk factors that predict them).

HPA axis dysregulation. Since the first ACEs study, the majority of research focusing on the effects of early life adversity and physiological and psychological health outcomes have utilized adult sample populations, which are limited by retrospective assessment of childhood events, but have the advantage of being able to assess health outcomes that often take years to manifest in adulthood (Bucci et al., 2016). Several recent studies have evaluated the relationship between childhood toxic stress and HPA axis dysregulation (Calhoun et al., 2014; Kaplan, Madden, Mijanovich, & Purcaro, 2013), which as previously discussed is a key determinant of AL and chronic disease development. In a study by Calhoun et al.

(2014), they evaluated the effects of adolescent toxic stress with dysregulation of the HPA axis through peer relational victimization, which was characterized by behaviors that threaten an individual's dyadic relationships or social reputation amongst their peers (Calhoun et al., 2014). This was a prospective descriptive study design with a sample of 62 female adolescents, ages 12-16 years old, who presented with a wide range of life stressors and adjustment difficulties. The participants completed two surveys (the Peer Experiences Questionnaire and the Network of Relationships Inventory) in order to assess their subjective experiences of stress with relational victimization from their peers (Calhoun et al., 2014). The study design was strengthened by the addition of objective, biologic measures of stress through measurement of salivary cortisol before and after a laboratory-based social stressor task (Trier Social Stress Task), which intended to provide measures of HPA baseline, reactivity, and recovery (Calhoun et al., 2014). The results of this study demonstrated that higher levels of adolescent toxic stress (via peer relational victimization) was associated with blunted cortisol reactivity (i.e. an HPA axis that is not responding effectively to the stressor), despite controlling for other factors that can affect HPA axis functioning (Calhoun et al., 2014). Additionally, high levels of friend responsiveness were found to be associated with greater HPA axis regulation (Calhoun et al., 2014), suggesting that social support can be protective for optimal stress regulatory processes, similar to findings in other stress research (Brooks et al., 2014; Horan & Widom, 2015; Sheikh, Abelsen, & Olsen, 2016).

Childhood socioeconomic disadvantage. There is compelling evidence that early life exposure to socioeconomic disadvantage in childhood can contribute

to toxic stress, with the potential for lifelong health consequences for the individual. An adverse or disadvantaged social environment is thought to affect physiological health through a process called biological embedding, which allows this social stress to “get under the skin” and alter biological functioning as a result (Slopen et al., 2013). Children and adolescents from socioeconomically disadvantaged environments might be particularly vulnerable to biological embedding by virtue of being exposed to a multitude of stressful influences that these kinds of environment tend to have (Shonkoff, Boyce, & McEwen, 2009), in addition to the sensitive developmental timeframe of the exposure. As previously defined, CSD can be conceptualized as the deprivation that a child experiences related to their position within a hierarchical social structure, which tends to be based on a combination of variables indicative of the child’s access to resources and social support (Meier et al., 2016), including parental factors such as education, occupation, and income, as well as household factors such as crowding, food security, and social dynamics between family members (Chaffee, Abrams, Cohen, & Rehkopf, 2015; Non et al., 2014; Wickrama, O’Neal, & Oshri, 2014). These factors have the potential to contribute to the stress experienced by the child if the degree of disadvantage deprives them of their basic needs in order to grow, succeed, and fully participate in society (Chaudry & Wimer, 2016).

Health outcomes associated with CSD. The reason CSD is so important when determining risk for chronic disease is due to its negative health effects across the life course, spanning from the early childhood years well into adulthood (Chaudry & Wimer, 2016). Previous research has demonstrated numerous adverse

health effects for children from disadvantaged socioeconomic environments, including toxic stress (Blair & Raver, 2016; Wickrama, Lee, O'Neal, & Kwon, 2015), dysregulation of the HPA axis (Fischer et al., 2017; Ursache, Noble, & Blair, 2015), allostatic load (Barboza Solís et al., 2016; Turner, Thomas, & Brown, 2016), early puberty (Sun, Mensah, Azzopardi, Patton, & Wake, 2017) structural changes in the brain (Lawson et al., 2017; Noble et al., 2015), cognitive delays (Pac, Nam, Waldfogel, & Wimer, 2017), increased asthma exacerbations (DePriest & Butz, 2017; Yakubovich, Cluver, & Gie, 2016), and increased exposure to environmental pollutants and toxins (Aizer & Currie, 2014; Etchevers et al., 2015).

Previous research has also linked CSD with several adulthood chronic conditions, including cardiovascular disease (Savelieva et al., 2017; Slopen et al., 2013), obesity (Bush et al., 2017; Pavea, 2017), diabetes (Tsenkova, Pudrovska, & Karlamangla, 2014), cancer (Masseti, Thomas, & Ragan, 2016), and several psychological disorders (Bjorkenstam et al., 2015; Lindstrom, Fridh, & Rosvall, 2014). The majority of these studies make use of data from large, longitudinal cohort studies, which can be prospective or retrospective, and have a greater ability to predict causality of distant adulthood health outcomes from a childhood exposure. I will now highlight a few areas of particular interest that relate to the effects of CSD on childhood and adolescent neurological development, as well as discuss proposed life course pathways that underlie the numerous health ramifications associated with CSD.

Effects on brain structures. An intriguing area of CSD research focuses on how socioeconomic deprivation biologically affects the structure of the developing

brain in children, which explains why CSD is so detrimental when experienced during our earliest years. The two structures that research has demonstrated to be most affected by CSD are the hippocampus and amygdala, which play key roles in regulating stress and emotional responses (Lawson et al., 2017; Luby et al., 2013). Much of the earlier research assessing these structures was based on mammalian animal models, where the animals exposed to supportive environments high in stimulation were found to have a larger hippocampus, compared to those experiencing deprivation (Van Praag, Kempermann, & Gage, 2000). Human studies have mirrored these findings, where children from more disadvantaged backgrounds have smaller hippocampus and amygdala volumes, compared to children living in more affluent social environments (Brody et al., 2017; Luby et al., 2013; Noble et al., 2015; Noble et al., 2012). In two studies by Noble et al. (2015); Noble et al. (2012), they focused on the association between low childhood socioeconomic environments and brain volumes in the hippocampal and amygdala brain regions. They utilized both prospective (2015) and cross-sectional (2012) study designs, with varying sample sizes ($N = 60$ in 2012 and $N = 1,099$ in 2015), with similar findings of decreased brain volume and surface area in those two regions, with income most strongly associated with brain structure for the most disadvantaged individuals. These findings (decrease in brain structure volumes with increasing CSD) have been mirrored in several other studies (Brody et al., 2017; Lawson et al., 2017; Luby et al., 2013), thus lending further credibility to the validity of their results. Ultimately, these findings suggest that the toxic stress experienced by children and adolescents from socially disadvantaged environments

can have permanent effects on the brain structures involved in stress adaptation, which can have lifelong implications for their cognitive functioning and vulnerability to the adverse effects of stress.

Life course pathways by which CSD influences health. While CSD has consistently been linked with poor individual health outcomes across the life course, there are several proposed pathways by which CSD exerts its negative influence on health. There is a body of epidemiological research that has focused on utilizing life course models, including critical periods, accumulation of risk, and chains of risk models, in order to determine what kind of pathway this CSD exposure follows when contributing to poor health outcomes over time. For example, in a study by Meier et al. (2016), they examined the association between socioeconomic position (SEP) at three different life course stages (early life, midlife, and late life) and their association with immune system response to persistent infections. Comparing critical periods and chains of risk models, they found that early life SEP was not independently associated with immune response in older age, but rather exerted its effects indirectly through its influence on SEP in subsequent life stages (Meier et al., 2016). Thus, their findings supported a chains of risk model, with early life socioeconomic disadvantage acting indirectly on later life disadvantage, ultimately affecting health outcomes.

Findings from the Meier et al. study have been mirrored in other research evaluating the influence of CSD on adult health outcomes (Friedman et al., 2015; Jonsson, San Sebastian, Strömsten, Hammarström, & Gustafsson, 2016; Pavela, 2017), however other studies found support for accumulation of risk models (Ng-

Knight & Schoon, 2016) critical periods models (McCrory, Dooley, Layte, & Kenny, 2015), or a combination of the two (Tsenkova et al., 2014). This variance in findings likely represents differences in study design (i.e. longitudinal with multiple life course measurements of SES vs. cross-sectional) as well as different conceptualization and operationalization of socioeconomic disadvantage variables. Ultimately, while the debate is ongoing as to specifically how CSD becomes biologically embedded in children, it is clear that its effects are detrimental for health and persist well into adulthood.

Allostatic load. As previously described, AL represents the cumulative, multisystem physiological dysregulation that results from repeated episodes of adaptation in response to stressful life demands across the life course of an individual (Beckie, 2012). While Sterling and Eyer (1988) and McEwen (1998) were responsible for the conceptual and theoretical foundations of the AL framework, nearly two decades of empirical research have focused on operationalizing the AL construct by examining both its antecedents and its associated health outcomes (Friedman et al., 2015; Widom, Horan, & Brzustowicz, 2015). Presented below is early work in this field, as well as literature that has both outcomes and antecedents of AL.

MacArthur study of successful aging. The first research study to operationalize the AL construct was conducted by Seeman, Singer, Rowe, Horwitz, and McEwen (1997), and is known as the MacArthur Study of Successful Aging. In this study, they had a cohort of 70- to 79-year old primarily high-functioning, mostly White Americans from whom they were able to repeatedly collect a wide range of

physiological biomarkers from over time, thus allowing assessment of numerous antecedents and long-term health outcomes of AL (Beckie, 2012; Seeman et al., 1997). Given the longitudinal study design, they were able to infer causal associations between AL and its health outcomes, as well as how it progressed over time as the participants gradually developed morbidity and mortality from chronic disease. Their original AL construct variable was comprised of 10 markers of multisystem biological dysregulation, which was intended to be merely an initial attempt at operationalization, and included the following (Seeman et al., 1997): four neuroendocrine primary mediators (DHEA, urinary cortisol, epinephrine, and norepinephrine) and six cardiometabolic secondary outcomes (systolic and diastolic blood pressure, waist-hip ratio, high-density lipoprotein cholesterol, the ratio of total cholesterol to high-density cholesterol, and glycated hemoglobin). Using this AL construct outcome variable, they found that higher AL was associated with cardiovascular disease, cognitive and physical decline, and all-cause mortality in the 12-year follow-up period, with the strongest predictive value found in the metabolic biomarkers for AL (Seeman et al., 1997). Ultimately, the findings from the MacArthur Study for Successful Aging have contributed significantly to our understanding of adulthood chronic disease by examining biologic risk from a cumulative, multisystem view that centers on toxic stress as the common threat linking a variety of chronic disease phenotypes, rather than focusing on organ- or disease-specific risk factors.

Childhood adversity. One of the most robust areas of AL research relates to the investigation of the predictors, or antecedents, to AL in the form of ACEs, as

defined and discussed extensively in the CSD literature review section. Childhood adversity, or ACEs, have consistently been found to contribute to toxic stress and predict development of AL, as well as numerous chronic diseases later in life (Barboza Solís et al., 2015; Friedman et al., 2015; Horan & Widom, 2015; Widom et al., 2015). While the exact definition of ACEs varies across the literature, they typically are identified as adverse childhood exposures such as trauma (Turner, Thomas, & Brown, 2016), neglect (Horan & Widom, 2015), abuse (Groër et al., 2016; Widom et al., 2015), poverty or socioeconomic disadvantage (Barboza Solís et al., 2016; Evans, 2016; Friedman et al., 2015; Turner et al., 2016), or other early life stressors (Dich et al., 2015), which have all consistently predicted increased AL in adulthood. The association between ACEs and AL is often cited as a dose-dependent relationship, with longer periods of adversity (or a more severe type of adversity) associated with higher AL, which aligns with the AL cumulative stress exposure theoretical framework. However, it is likely that it is a combination of both the timing of the childhood adversity, as well as its duration and specific pathway of influence, that work in concert to determine development of AL in children and adolescence.

Environmental and socioeconomic factors. Another important area in recent AL research focuses on the link between environmental and socioeconomic stressors as antecedents to AL development across the life course. In the last several years, there have been multiple studies that examined neighborhood factors that contribute to AL, proposing that certain stressors within the living environment can become biologically embedded, thus predisposing individuals to physical and

psychological disease. The majority of these studies have focused on neighborhood socioeconomic status or disadvantage as the source for the toxic stress, with nearly universal findings of increased AL with higher levels of neighborhood poverty or socioeconomic disadvantage (Chen, Miller, Brody, & Lei, 2015; Gustafsson et al., 2014; Jiménez, Osypuk, Arevalo, Tucker, & Falcon, 2015; Robinette et al., 2016; Schulz et al., 2012), despite a variety of study designs used (mostly retrospective longitudinal cohort studies and cross-sectional correlation studies). Some research has also attempted to differentiate between neighborhood-level stressors and individual- or household-level stressors, and identify which contribute most to development of AL (Theall, Drury, & Shirtcliff, 2012).

In a cross-sectional correlation study by Theall et al. (2012), they utilized data from the National Health and Nutrition Examination Survey (NHANES), which is a nation-wide population health survey, in order to assess environmental stress at the individual level (measured with AL [cardiometabolic and immune biomarkers], age, sex, education level, race/ethnicity, diet quality), the household level (measured with poverty-to-income ratio, AL of head of the household, parental education level and marital status, duration of residence there, and household crowding), and the neighborhood level (measured with percentage of people living below poverty line, in vacant homes, with female head of households, who are working class, have a college degree or higher, and have an education index of concentration at the extremes in that census tract). They utilized a pediatric study population ($N = 11,886$ individuals, $N = 6,696$ households, $N = 2,191$ census tracts) in order to examine the contextual effect of cumulative exposure to stress for those children.

Findings from this study demonstrated that neighborhood risk resulted in a higher AL for the adolescents living there, which was over and above the household level risks they had (Theall et al., 2012), which is consistent with other research (Mair, Cutchin, & Kristen Peek, 2011; Schulz et al., 2012). These results further confirm previous AL research findings, which proposes a dose-response relationship between cumulative stress exposures and development of AL, in this case with social and environmental exposures.

While decreased socioeconomic status (SES) has been consistently associated with increased rates of morbidity and mortality for an individual, toxic stress and AL provides a potential explanatory mechanism for how low SES (i.e. a social stressor) is translated into increased biologic risk (i.e. AL) for development of chronic disease. Individuals with lower SES are hypothesized to have both increased exposure to stressful life events, experiences, and environments, as well as fewer social and material resources which can serve as buffers for those stressors (Dowd, Simanek, & Aiello, 2009; Pearlin, Schieman, Fazio, & Meersman, 2005). Research has examined if factors representative of low SES, including low education levels (Nicod et al., 2014), receiving welfare (Nicod et al., 2014), household crowding (Riva et al., 2014), and cumulative socioeconomic disadvantage (Gustafsson, Janlert, Theorell, Westerlund, & Hammarström, 2011) are predictive of AL in adulthood, with some evaluating SES at multiple points in the life course (Gruenewald et al., 2012; Stein Merkin, Karlamangla, Diez Roux, Shrager, & Seeman, 2014). Low SES consistently was found to predict development of AL in later life, even after accounting for adulthood health behaviors and lifestyle factors

(Gruenewald et al., 2012; Gustafsson et al., 2011). While behavioral and lifestyle factors have the potential to mitigate risk for developing AL and chronic disease, the ability of socioeconomic disadvantage to independently predict poor health outcomes, regardless of such protective factors, is further evidence of its importance in shaping health for all individuals across the life course.

Physical and psychological outcomes of AL. There are decades of research that have focused on the physical and psychological outcomes of elevated AL in response to chronic, toxic stress. Several studies have found that adults with higher AL are more likely to suffer from psychological disorders, such as schizophrenia (Chiappelli et al., 2017; Nugent, Chiappelli, Rowland, & Hong, 2015), anxiety (Kuhn et al., 2016), depression (Beckie et al., 2016; Kobrosly, Seplaki, Cory-Slechta, Moynihan, & van Wijngaarden, 2013; Kobrosly, van Wijngaarden, Seplaki, Cory-Slechta, & Moynihan, 2014; Kuhn et al., 2016), and posttraumatic stress and chronic pain (Beckie et al., 2016), likely due to a combination of structural changes in the brain (as previously discussed in the CSD literature review) and the long-term effects of dysregulated circulating stress hormones. Of recent interest has been the link between AL and anxiety or depression, which was the focus of a retrospective cohort study by Kuhn et al. (2016), where they evaluated the impact of the timing of both childhood and adulthood adversities on adult anxiety and depression levels, as well as changes in brain morphology. These participants ($N = 833$) were adults who were free from psychological disorders upon recruitment for the parent study (in 1998), and were dichotomized into those with and without a history of child maltreatment (based on the Childhood Trauma Questionnaire), as well as those with

and without recent stressful life events (based on a list of threatening events). Anxiety and depression were measured with the Spielberger Trait Anxiety Scales and the German General Depression Scale, respectively, while structural brain changes were assessed with magnetic resonance imaging (MRI). The findings of this study showed that childhood and more recent adulthood stressful exposures had a pronounced impact on anxious and depressive temperament in an additive manner, with changes in brain morphology in key regions associated with stress and emotion (Kuhn et al., 2016). These results (higher AL predicting higher levels of depression and other psychological disorders) have also been reported in several other recent prospective and cross-sectional studies (Beckie et al., 2016; Kobrosly et al., 2013; Kobrosly et al., 2014), lending further support to these findings.

AL has also been studied in the context of pregnancy, given the long-standing interest in the effects of toxic maternal stress on the long-term health outcomes for the developing fetus. High maternal AL during pregnancy has been implicated in a variety of pregnancy outcomes, including preeclampsia (Hux & Roberts, 2015), low birth weight (Hux, Catov, & Roberts, 2014), and well as decreased gestational age (Wallace & Harville, 2013), all of which have long-term health implications for the child. In a prospective longitudinal cohort study done by Hux and Roberts (2015), they aimed to determine whether maternal AL measured early in pregnancy was associated with higher odds of developing preeclampsia, which is a multisystem disorder of pregnancy associated with significant maternal and fetal complications (Hux & Roberts, 2015). Data was prospectively collected from women ($N = 113$) enrolled at less than 15 weeks' gestation, who were 1:2 matched with case controls

(38 preeclamptic women matched with 75 uncomplicated, term deliveries, matched on age, parity, and lifetime smoking status) (Hux & Roberts, 2015). AL was operationalized with nine biomarkers of cardiometabolic and inflammatory function. Ultimately, they found that early pregnancy AL had 2.91 increased odds of developing preeclampsia, hypothesizing that increased damage or premature aging of organ systems adversely affected by AL in these women could predispose them to adverse pregnancy outcomes, such as preeclampsia (Hux & Roberts, 2015), as well as low birth weight (Hux et al., 2014) or decreased gestational age (Wallace & Harville, 2013).

There has been some concern with the validity of associations between AL and pregnancy outcomes due to the unique physiology during pregnancy involving some of the hormones involved in AL measurement, particularly with cortisol (Morrison, Shenassa, Mendola, Wu, & Schoendorf, 2013). Further work is needed in this area to definitively determine the specific biological mechanisms through which AL adversely affects the maternal and intrauterine environments, which could improve pregnancy outcomes and long-term health outcomes for the child.

Operationalization of AL construct. AL is a construct based on theoretical and empirical evidence that toxic stress contributes to systemic physiological dysregulation over time, ultimately increasing risk for chronic disease, as has been extensively discussed thus far through review of the toxic stress, CSD, and AL literature. Given that this is a theoretical, indirect measure of exposure to toxic stress, the latent AL construct must be derived from a number of measured, biological indicators that represent the effects on the allostatic body systems

(ideally including the neuroendocrine, cardiometabolic, and immune systems) (Howard & Sparks, 2016). One of the more common areas for criticism of the AL framework and body of literature is the lack of consistency in how it is operationalized and scored across studies, which makes the comparison and validity of findings in this field challenging (Beckie, 2012). A key driver that seems to determine how AL is operationalized in research is the availability of and logistical access to the numerous biomarkers that comprise the AL construct. For example, within many population-based studies, they tend to focus on the cardiovascular, metabolic, and inflammatory indicators of AL in order to create their AL constructs (Kobrosly et al., 2013; Masterson & Sabbah, 2015; Theall et al., 2012), likely reflective of the difficulty in accurately assessing neuroendocrine function at the population level. In contrast, studies using smaller, clinical sample populations have been more likely to include assessment of neuroendocrine function within their AL constructs, given they are better able to measure those variables in a meaningful way (Chen et al., 2015; Howard & Sparks, 2016). Consensus is yet to emerge on which indicators of AL are necessary to include in the construct in order to remain consistent with its theoretical biological premise and predictive utility in health outcomes for all age groups.

Calculation methods for AL also vary across the literature, with the most common approach being a summative count method using risk quartiles based on AL psychometrics established in the MacArthur Studies of Successful Aging (Seeman et al., 1997). However, using this approach requires that the AL biomarkers be dichotomized in order to sum each indicator score into a total AL score, which leads

to a loss of precision and explanatory power for each of those indicator variables. Additionally, when assessing AL in populations other than older adults (which was the population in which AL construct was initially validated), using those high-risk quartiles is less practical, and likely less meaningful, particularly for pediatric populations. As a result of these potential limitations in scoring AL, other more statistically complex methods have been proposed over the years, including summative scores based on clinical cutoffs (rather than risk quartiles), recursive partitioning, canonical correlation, and latent variable modeling with factor analysis (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; McCaffery, Marsland, Strohacker, Muldoon, & Manuck, 2012; Seplaki, Goldman, Weinstein, & Lin, 2006). While each approach has their advantages and limitations, there remains no consensus on which statistical approach best aligns with the theoretical underpinnings of AL, as well how to best measure this construct in children and adolescents. Further evidence is needed to support the performance of these more complex scoring methods in order to determine their utility and validity in AL research moving forward.

Environmental and behavioral mediators linking CSD to AL. After review of literature in the key areas underpinning the main concepts of this dissertation (i.e. toxic stress, childhood socioeconomic disadvantage, AL, and race/ethnicity), it is important to briefly discuss potential risk or protective factors that might serve as important mediating pathways between CSD and AL for adolescents in this study. Both environmental and behavioral factors are discussed, including smoking, lead, nutrition, and physical activity.

Smoking. Despite significant declines during the past two decades, the prevalence of children and adolescents in the US exposed to both passive smoking (the involuntary inhalation of other people's exhaled cigarette smoke) and active smoking remains high (Orton, Jones, Cooper, Lewis, & Coleman, 2014; Shenassa, Rossen, Cohen, Morello-Frosch, & Payne-Sturges, 2016). Smoke exposure has been causally linked to a number of chronic conditions, both in childhood and adulthood, including respiratory infections, several types of cancer, cardiovascular disease, and sudden unexplained death in infancy (Orton et al., 2014; Raghuveer et al., 2016; Royal College of Physicians, 2010). Nicotine has also been shown to be a potent activator of the HPA axis (Mendelson, Goletiani, Sholar, Siegel, & Mello, 2008), which could contribute to development of AL and chronic disease through chronic overstimulation of the neuroendocrine system.

Additionally, smoking can also be associated with socioeconomic disadvantage, with higher rates of household smoking reported in African American and low SES households (Raghuveer et al., 2016; Shenassa et al., 2016) and higher rates of active smoking reported in White adolescents and in more rural areas (US Department of Health and Human Services, 2016). The implementation of policies that prohibit smoking in public places has significantly reduced passive smoke exposure for children and adolescents in the US, however such policies do not extend to private homes, where some young individuals continue to be exposed and accrue negative health risks (Marano, Schober, Brody, & Zhang, 2009). Additionally, adolescents, particularly those in less affluent neighborhoods, continue to be targeted by the tobacco industry through advertising, which increases their

exposure and awareness about cigarettes, thus contributing to more active smoking in this population.

Lead. Lead is an environmental toxin that has been shown to adversely affect numerous physiological systems in the body, including the nervous, cardiovascular, hematopoietic, endocrine, renal, and reproductive systems (NCHS, 2016), particularly when the lead exposure occurs early in life. For infants and young children, lead exposure is particularly hazardous because these individuals are undergoing rapid physiological development, particularly in the brain (Aelion, Davis, Lawson, Cai, & McDermott, 2013). There is also emerging evidence that lead exposure can have direct biological effects on the HPA axis, which has the potential to predispose the individual for higher vulnerability to the adverse effects of stress (Souza-Talarico et al., 2017), though the exact mechanisms are not clear.

Common environmental sources for lead contamination in children and adolescents include lead-based paint in older housing, soil contamination from historical widespread use of leaded-gasoline, water contamination from leaded pipes, and air contamination related to industrial pollution (Aelion et al., 2013; Brink et al., 2013). An additional lead source is from the gradual release of this toxin from bones, which serve as a long-term repository for lead, thus allowing it to leach back into the bloodstream long after the exposure has ceased (Zota, Shenassa, & Morello-Frosch, 2013).

Risk for lead exposure has been found to be highest for young individuals living in low-quality housing and neighborhoods, as such there tends to be higher lead levels in children who experience socioeconomic disadvantage, are African

American, live in large metropolitan areas, or live in older housing (CDC, 2012). Lead is a particularly important environmental stressor with regards to health disparities due to the historical residential segregation into poor, low-quality neighborhoods that African Americans in the US have experienced for decades (Aelion et al., 2013; Etchevers et al., 2015), thus providing a potential mediating pathway between CSD and AL for children and adolescents.

Nutrition. Nutrition can be defined as the intake of the food necessary for optimal health and growth, which is particularly important for children and adolescents with rapidly developing bodies. Childhood and adolescence are key windows for shaping lifelong food preferences and healthy eating behaviors that can, in turn, affect dietary behaviors and risk for chronic disease in adulthood (Gu & Tucker, 2017). A higher quality diet has been associated with lower levels of obesity and inflammation (Beydoun et al., 2008; Gao et al., 2015), and lower risk for developing diabetes, cardiovascular disease, and several types of cancer (Chiuve et al., 2012). Diet quality has been extensively measured in past research using the Healthy Eating Index (HEI), which is based on The Dietary Guidelines for Americans and provides nutritional advice to promote health and reduce disease risk (Chiuve et al., 2012). A higher score on the HEI, which is based on intake of important food groups and nutrients, suggests higher guideline adherence and an overall higher-quality diet.

Some research has reported that certain minority populations and those of lower socioeconomic disadvantage tend to make poorer diet choices (Yu et al., 2015), which is likely due to a combination of higher incidence of toxic stress for

these groups, a lack of material resources to purchase healthier foods due to higher disadvantage, and a lack of access to stores that offer fresh food choices in the lower-quality neighborhoods they are segregated into (Bailey et al., 2017; Williams & Mohammed, 2013). Thus, when examining difference in eating behaviors across racial/ethnic groups, we must be aware that their choices are directly shaped by structural inequalities that ultimately determine what foods they are able to access and consume.

Physical activity. Physical activity, defined as any bodily movement produced by skeletal muscles that requires energy expenditure, is a behavioral risk factor for a wide array of chronic diseases, including cardiovascular disease, diabetes mellitus, obesity, hypertension, cancer, and all-cause mortality (Boone-Heinonen et al., 2011; Warburton, Nicol, & Bredin, 2006; WHO, 2003). While attention to adulthood physical activity has been prevalent in chronic disease prevention literature for decades, there is increasing attention being paid to this behavior during childhood in adolescence in order to potentially cultivate this protective factor early in life.

Similar to nutrition, physical activity levels in children and adolescents has been reported to be lower among minority and socioeconomically disadvantaged individuals, who are often reported to lead typically more sedentary lifestyles (Andersen et al., 2016; Kimbro, Brooks-Gunn, & McLanahan, 2011; Matthews et al., 2014). However, physical inactivity is likely due to a combination of social and environmental factors that are outside of the individual choice for the child/adolescent, including the safety of their neighborhood, a lack of access to

opportunities for physical activity, neighborhoods with poorer air quality or other environmental contamination, or is a direct result of higher toxic stress experienced by these populations (Aelion et al., 2013; Cox, Boyle, Davey, Feng, & Morris, 2007; Non et al., 2016). Health behaviors, such as physical activity, are considered to be imprinted during childhood and can have lifelong health implications if unhealthy behaviors are learned and adopted during this time (Non et al., 2016). Therefore, we need a better understanding about how toxic stress and socioeconomic disadvantage during childhood and adolescence can directly shape health behaviors, such as nutrition quality and physical activity, both of which have the potential to impact long-term risk for disease development across the life course.

Variation in effects across racial/ethnic groups. It has been long established that not everyone who has the same stressful exposures or experiences will have the same health outcomes (Bailey et al., 2017; Pearlin et al., 2005; Williams & Mohammed, 2013). Decades of medical and epidemiological research have demonstrated differences in chronic disease prevalence between certain racial/ethnic groups, including cardiovascular disease, diabetes, renal failure, cancer, stroke, and birth outcomes, as well as all-cause mortality (Gravlee, 2009; Hicken et al., 2013; Hux et al., 2014; Kershaw et al., 2016; Thorpe et al., 2016), with these effects often persisting after socioeconomic, genetic predisposition, and health behaviors are accounted for. While some research has attribute race/ethnic disparities in health to biological differences between different populations or differences in lifestyle choices, race/ethnicity should be conceptualized as a social, rather than biological, phenomenon, where groups of individuals that share a

particular cultural heritage and/or possess similar arbitrary physical characteristics (i.e. skin color, hair texture) are forged into racial/ethnic categories that are determined for them by societal systems of race relations (Krieger, 2001, 2012).

There has been a tendency in past literature to attribute higher chronic disease prevalence in minority populations as a reflection of genetic predisposition and poor health behaviors, with less attention paid to the sociocultural and environmental factors unique to these populations that have a significant impact on their cumulative stress burden and overall health (Himmelstein, Young, Sanchez, & Jackson, 2015; Krieger, 2014). However, structural racism, which is the societal fostering of racial discrimination and reinforcing inequitable resources (i.e. housing, education, employment, health care), is an upstream factor that likely plays a much more significant role in shaping the distribution of social determinants of health for minority populations (Bailey et al., 2017; Feagin & Bennefield, 2014). Therefore, structural racism ultimately can affect not only the degree of stress that minorities experience, but also their lifestyle and behavioral factors that contribute to adverse health outcomes.

Nancy Krieger, a well-renowned social epidemiologist, has proposed an ecosocial theory of disease distribution theory, where differences in the social environments and exposures experienced by externally defined racial/ethnic groups may become biologically embodied within an individual, thus directly influencing their biological processes, and ultimately, their lifelong health trajectory (Krieger, 2012). Differential exposure to stressors, which can be physical, social, and psychosocial in nature, tend to be more prevalent amongst certain racial/ethnic

populations, which places them at higher risk for developing toxic stress and AL, given the cumulative nature of how AL develops over time. Differential vulnerability to stress, which has been explained by the lower levels of social and psychological support, as well as material resources, that can exist for certain minority populations (Brody, Lei, Chae, et al., 2014; Umberson, Williams, Thomas, Liu, & Thomeer, 2014), can further contribute to toxic stress and reduce any stress buffering that more socioeconomic advantage provides. Therefore, the purpose of examining race/ethnicity as a potential moderating variable in this study was to explore potential mechanisms that might explain differences in how CSD effects AL in adolescents, based on differential exposure and vulnerability to stress, as well as downstream effects on their environmental and behavioral risk factors.

Racial discrimination. There is a well-established relationship between perceived racial discrimination and toxic stress, which is likely a significant contributing factor to the health disparities seen amongst certain populations (O'Brien, Tronick, & Moore, 2013). Several studies have shown that experiences of discrimination have been associated with dysregulated activity of the HPA axis, as shown through dysregulated cortisol functioning (Busse, Yim, & Campos, 2017; O'Brien et al., 2013; Tackett, Herzhoff, Smack, Reardon, & Adam, 2017). In a prospective descriptive study by O'Brien et al. (2013), 180 young adults from diverse racial/ethnic backgrounds were recruited in order to explore the association between lifetime discrimination and chronic stress, measured both subjectively and objectively. Lifetime discrimination was measured with a 12-item scale assessing the lifetime frequency of discrimination experiences across several

domains, including work, school, receiving services, and public life, while perceived stress was measured with the Perceived Stress Scale (O'Brien et al., 2013). They also included a biologic measure of chronic stress through measurement of hair cortisol (utilizing the proximal 3 cm of hair from the scalp to reflect the last 3 months of time) (O'Brien et al., 2013). The results of this study showed that experiences of lifetime discrimination significantly predicted hair cortisol concentrations (O'Brien et al., 2013), which supports other similar research proposing that discrimination stress adversely impacts the neuroendocrine system (Busse, Yim, & Campos, 2017; Tackett et al., 2017).

Anticipating prejudice or discrimination because of one's racial or social identity has also been shown to be associated with increased vigilance or a hyperawareness (Hicken, Lee, Morenoff, House, & Williams, 2014), which not only predisposes individuals to experiencing toxic stress (and the associated effects on their HPA axis), but it can also impact the stress responses of future generations through transmission of stress vulnerability phenotypes to their offspring (Sawyer, Major, Casad, Townsend, & Mendes, 2012). Therefore, if individuals are experiencing this kind of discriminatory stress on a frequent basis, it is plausible that they might have a higher degree of systemic physiological dysregulation, and thus higher risk for disease, when compared to their White peers.

Racial disparities in AL. Several studies have examined disparities in toxic stress and how that affects distribution of AL across certain racial/ethnic and socioeconomic groups (Brody, Yu, Chen, Kogan, et al., 2013; Hux & Roberts, 2015; Rainisch & Upchurch, 2013; Theall et al., 2012). A common finding across the

literature is that African Americans have the highest AL compared to Whites, or any other minority population (Rainisch & Upchurch, 2013; Theall et al., 2012), even when controlling for socioeconomic factors (Hux & Roberts, 2015). In a prospective, longitudinal study by Brody, Yu, Chen, Kogan, et al. (2013), with a sample of 443 African American youths (ages 11-13 years), they sought to test the relationships between cumulative SES stress, AL, and adjustment problems, in order to construct two profiles: a vulnerability to stress profile and a resiliency to stress profile. Interestingly, they found that the vulnerability profile was comprised of individuals who were exposed to high levels of cumulative SES risk with resultant higher AL, but had low levels of adjustment problems, while the resilience profile included those who again were exposed to high levels of cumulative SES risk, but instead had low AL and adjustment problems (Brody, Yu, Chen, Kogan, et al., 2013). These findings (higher AL and poor health outcomes in disadvantaged, vulnerable individuals) are congruent with other research in this field (Brody, Lei, Chen, & Miller, 2014; Rainisch & Upchurch, 2013). Ultimately, being of a certain race/ethnicity can shape exposure to additional stressors, such as perceived racism and discrimination, that other populations might be comparatively shielded from (Krieger, 2014; Priest et al., 2013), thus contributing to health disparities.

Gaps in the Literature

Despite extensive literature examining the long-term health effects of CSD, there is still much that is unknown regarding the underlying mechanisms and potential mediating pathways to AL and adulthood chronic disease. However, there is substantial empirical support for the notion that CSD can be a source for toxic

stress in adolescence, which over time contributes to physiological dysregulation, poor mental and physical health, and chronic disease, most especially in vulnerable or disadvantaged populations (Beckie, 2012; Juster et al., 2016; Turner et al., 2016). There are several gaps in the literature that this study hoped to fill. First, there are few studies that have measured biomarkers of AL within child or adolescent populations and there remains a lack of consensus about the ideal biomarkers to include in AL constructs among pediatric populations. In addition, there are very few studies who have used structural equation modeling to construct and score the AL latent measure, which makes this study's population and analytical approach both innovative and potentially beneficial for the ongoing AL measurement debate. Second, while there is a wide body of literature that incorporates study of effects of early life adversity and toxic stress on AL, the majority of studies measure the AL biomarkers in adult populations, and have assessed childhood factors that contribute to AL retrospectively. For this reason, it is unclear how early in the life course elevations in AL can emerge, and what factors contribute to its development in children. Lastly, given the relatively few studies that have measured AL and its antecedents in a pediatric population, it is unclear where potential interventions might be for health care providers when attempting to mitigate the long-term effects of toxic stress for their patients. As such, by inclusion of several pertinent mediating pathways between CSD and AL in this study, we hope to highlight environmental and behavioral pathways that could shape future intervention science in this field.

Given these gaps in the literature, there is a definite need to explore AL further within childhood and adolescence in order to determine whether or not it can be effectively measured in this population, given the physiological changes that occur between childhood and adulthood. Additionally, there is a need to utilize rigorous statistical approaches to best model the AL construct among adolescent populations. Furthermore, by conceptualizing CSD as a source for toxic stress and AL, as well as potentially increasing exposure to other environmental and behavioral risk factors, this study proposes a more ecological approach to health promotion and risk reduction by targeting interventions along multiple pathways, as called for by the Healthy People 2020 framework (Healthy People 2020, 2016). Therefore, the results of this study could provide important information about ideal intervention points to mitigate adverse health outcomes related to toxic stress, while also providing insight into differences in how CSD affects AL across different racial/ethnic populations. This will hopefully allow us to design future research interventions that are more likely to improve health equity for all groups. Moreover, these findings could identify larger structural implications for policies in this country relating to poverty, housing conditions, environmental quality, and health behaviors, which play a substantial role in shaping the health of the US population, particularly for groups who are more disadvantaged.

Study Aims, Research Questions, and Hypotheses

1. The first aim of this study was to develop an AL latent construct measure specific to an adolescent population.

- a. Research question 1: What factor structure best represents the AL construct in an adolescent study population?
 - i. *Hypothesis 1*: A unidimensional AL factor structure will have the best fit indices and be theoretically consistent with the underlying premise of AL in this population.
2. The second aim of this study was to examine the total, direct, and indirect effects of CSD on AL in an adolescent population. The following research questions and hypotheses will address this aim:
 - a. Research question 2: To what extent is CSD associated with AL in adolescence?
 - i. *Hypothesis 2*: Higher CSD will be associated with higher AL in adolescence.
 - b. Research question 3: To what extent do smoking, lead exposure, nutrition, and physical activity mediate the effect of CSD on AL in adolescence?
 - i. *Hypothesis 3a*: Higher CSD will be associated with exposure to higher exposure to smoking, which will be associated with higher AL in adolescence.
 - ii. *Hypothesis 3b*: Higher CSD will be associated with higher lead exposure, which will be associated with higher AL in adolescence.

- iii. *Hypothesis 3c*: Higher CSD will be associated with poorer nutrition, which will be associated with higher AL in adolescence.
 - iv. *Hypothesis 3d*: Higher CSD will be associated with less physical activity, which will be associated with higher AL in adolescence.
3. The third aim of this study is to determine the extent that the total, direct, and indirect effects between CSD and AL in adolescence vary across race/ethnicity. The following research question and hypothesis will address this aim:
- a. Research question 4: To what extent does race/ethnicity serve as a moderator of the association between CSD and AL, as well as between CSD and smoking, lead exposure, nutrition, and physical activity, for adolescents?
 - i. *Hypothesis 4a*: There will be a larger total effect of CSD on AL in adolescence for African-American and Hispanic children than there will be for Caucasian children.
 - ii. *Hypothesis 4b*: There will be a larger direct effect of CSD on AL in adolescence for African-American and Hispanic children than there will be for Caucasian children.
 - iii. *Hypothesis 4c*: There will be a larger indirect effect of CSD on AL in adolescence for African-American and Hispanic children

than there will be for Caucasian children through each of the mediating variables.

Study Assumptions

The current study was designed based on several assumptions. Through a postpositivist approach with a quantitative methodology, there was an assumption that the adolescents and adults who participated in NHANES were both willing and able to share accurate, honest responses with the interviewers administering the questionnaires. Additionally, there were numerous biological variables that were included in this study, which originated from the physical examination and laboratory testing portions of NHANES. There was an assumption that these physiological biomarkers were measured precisely and accurately by trained personnel, and that they were analyzed and recorded accurately. In total, it was assumed that representations about the nature of reality can be made from both the survey responses and the physiologic biomarkers, which will allow the relationships between the exposure, mediating, moderating, and outcome variables to be discernable with the given study design. Another key assumption was that AL was measurable in an adolescent population using similar variables that have been previously utilized in adult AL studies. Further, it was assumed that the measured indicator variables that represented both of the latent constructs (CSD and AL) (allostatic load) were truly representative of those concepts.

CHAPTER III: RESEARCH DESIGN AND METHODS

Study Design

This study utilized a cross-sectional correlational design using secondary data from the National Health and Nutrition Examination Survey (NHANES). NHANES is a major program of the National Center for Health Statistics (NCHS) that is designed to assess the health and nutritional status of children, adolescents, and adults in the United States each year (NCHS, 2016). NHANES utilizes a complex, multistage cluster probability sampling design in order to select participants representative of the population across all ages, with oversampling of persons 60 years and older, African Americans, and Hispanics (NCHS, 2016). Data were collected via in-home surveys conducted by trained interviewers and with a physical examination and laboratory testing completed by trained health care professionals in the NHANES mobile examination centers (MECs) (NCHS, 2016). Survey items were asked to the designated head of the household for children under the age of 16 years (typically a parent), while children 16 years and older answered questions independently. The public-use data are free, de-identified, and publicly available on the NHANES website at <http://www.cdc.gov/NCHS/nhanes.htm>.

Sample and Setting

Given that this was a secondary data analysis, the setting of this study reflected that of the parent NHANES study. NHANES surveys a nationally representative sample of about 5,000 persons each year, located in counties across the United States. The specific years of data that were used in this study were from

2003 to 2010, based on the availability of the specific variables of interest in an adolescent population. The sample population was thus a subset of adolescents who participated in NHANES during those years across four waves of NHANES data collection.

Inclusion and exclusion criteria. The sole inclusion criterion for the participants in this study was being 12 to 18 years of age, which reflected the interest in focusing on an adolescent population. Adolescence was selected for this study due to the importance of this life course period in shaping future health, with previous research identifying adolescence as a sensitive developmental period. While it would have been advantageous to include younger children in the sample as well, this was not feasible for the current study, given that many of the desired AL biomarkers were not collected from NHANES participants until the age of 12. The sole exclusion criterion for this study was having complete data for the race/ethnicity variable, which was needed for multi-group comparison in statistical analysis. Therefore, any participants who had missing data or answered “Other” to the race/ethnicity interview question were excluded from the study sample. All participants that met inclusion and exclusion criteria were retained in the final study sample, given that NHANES data are intended to be used in their entirety, rather than selecting random, smaller subsamples. The final sample size for this study was 1900 adolescents.

Protection of Human Subjects

The parent NHANES study was approved by the National Center for Health Statistics Research Ethics Review Board (NCHS, 2016). This current study reviewed

by the Marquette University Institutional Review Board and was declared exempt, given this study utilized secondary data with de-identified information, thus posing no risk to the participants. The primary investigator had also completed Collaborative Institutional Training Initiative (CITI) training according to the Marquette University research protocol.

Procedure

The variables of interest in this study were downloaded from the NHANES public website <http://www.cdc.gov/NCHS/nhanes.htm>. Each variable was downloaded separately for the years of interest (2003 to 2010), after which they were merged across years and compiled into a single dataset. There were extensive resources on the NHANES website that helped guide this process, as well as several experienced mentors on the committee that were familiar with this particular dataset and provided their expertise.

Study Measures

Childhood socioeconomic disadvantage. The sole predictor variable in this study was CSD, which was a unidimensional latent construct that was created using six measured variables (i.e. indicators) found in NHANES that are representative of material and social deprivation that can contribute to toxic stress for children and adolescents. Each of these measured variables have been used in past research to reflect socioeconomic disadvantage (Barrington & James, 2017; Elliot & Chapman, 2016; Meier et al., 2016; Ursache et al., 2015; Wimer, Nam, Waldfogel, & Fox, 2016), though this precise combination of variables for CSD had

not been previously utilized. The combination of variables used in in the CSD construct intended to capture the various social, material, and environmental factors that can contribute to toxic stress for children and adolescents and ultimately shape their health risks. The following indicators made up the CSD latent construct (see Figure 2), all of which were obtained through in-person interviews in NHANES: family poverty-income ratio (PIR), parent education level, family structure, food security, household crowding, and health insurance.

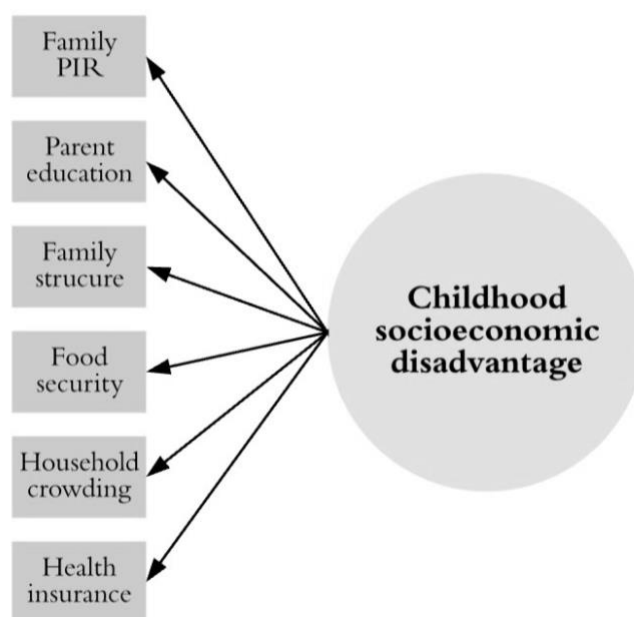


Figure 2. Childhood Socioeconomic Disadvantage Latent Indicators

Family PIR. The family PIR variable was calculated based on the Department of Health and Human Services' (HHS) poverty guidelines, which are issued on an annual basis (NCHS, 2016). The PIR was calculated by dividing the family's income

by the poverty guidelines, specific to the size of the family, and also taking into account the year and state where the data was collected (NCHS, 2016). This was a continuous variable in NHANES with a range from 0 to 5, with higher values indicating a higher family income relative to the poverty guidelines.

Parent education level. The parent education level variable measured the highest degree of education that the individual had completed at the time of NHANES data collection (NCHS, 2016). This education variable was a categorical ordinal variable with the following categories in NHANES: less than 9th grade, 9th-11th grade (includes 12th grade with no diploma), high school graduate/GED or equivalent, some college or AA degree, or college graduate or above. This was recoded for the purposes of this study into a dichotomous nominal variable, with the following categories: less than college education or college graduate or above.

Family structure. The family structure variable was created from the Marital Status variable in NHANES in order to capture if the adolescent resided within a 1-parent or 2-parent household. This was a categorical nominal variable with the following categories in NHANES: married, widowed, divorced, separated, never married, or living with partner. For the purposes of this study, this variable was recoded into a dichotomous nominal variable with the following categories: married/living with partner (2-parent household) or unmarried (1-parent household).

Food security. Household food security reflected the degree to which the quality and quantity of the household members' diets in the previous year were affected by the availability of food (NCHS, 2016). Several questions were asked of

participants during the Food Security questionnaire, including how often the following occurred: (1) worried they would run out of food, (2) food didn't last, (3) couldn't afford balanced meals, (4) relied on low-cost food for the child, (5) couldn't feed the child balanced meals, (6) child was not eating enough, (7) adults cut the size of or (8) skipped meals and frequency of this occurrence, (9) ate less than they should, (10) hungry but didn't eat, (11) lost weight and (12) had no money for food, (13) adults didn't eat for a whole day and frequency of this occurrence, (14) cut the size of child's meals, (15) child skipped meals and (16) frequency of this occurrence, (17) child was hungry in last 12 months, (18) and child did not eat for a whole day. Affirmative responses to any of these 18 questions were counted in order to derive a summative food security score. Food security was a continuous variable with a range from 0 to 18, with higher values indicating higher food insecurity.

Household crowding. Household crowding was determined by the total number of people and rooms in the household, with crowding typically defined as > 1 person per room (Riva et al., 2014; Solari & Mare, 2012). This variable was constructed from two variables in NHANES: (1) the total number of people in the household and (2) the number of rooms in the home. The total number of people in the home was obtained from the Demographics questionnaire in NHANES and was a continuous variable, ranging from 1 to 7 (NCHS, 2016). The number of rooms in the home was obtained from the Housing Characteristics questionnaire in NHANES and was also a continuous variable, ranging from 1 to 13 (NCHS, 2016). The total number of people in the household was then divided by the total number of rooms

in the household, thus yielding a household crowding variable that was continuous, with higher values indicating a higher degree of household crowding.

Health insurance. Health insurance status for the child was a categorical nominal variable that was obtained from the Health Insurance questionnaire in NHANES in response to the following question: Is the child covered by health insurance or some other kind of health plan? There were two options in response to this question in NHANES: yes or no.

Allostatic load. The sole outcome variable, AL, was a latent construct that was created using several measured variables found in NHANES that are representative of systemic dysregulation across the key physiological systems involved in the stress response. The vast majority of these indicators are biomarkers that have been used extensively in previous AL research (Beckie, 2012; Howard & Sparks, 2016; Juster et al., 2016; Mair et al., 2011; Worthman & Panter-Brick, 2008) in order to capture the systemic physiological dysregulation that occurs as a result of toxic stress. However, there is no research to date with the precise combination of biomarkers for AL in an adolescent study population (see Figure 3 for AL indicator variables). Physical measurements included systolic blood pressure (SBP), body mass index (BMI), and waist circumference, which were measured in MECs by a trained health care professional. The laboratory biomarkers were measured from serum (blood) samples and included creatinine, insulin, fasting glucose, glycated hemoglobin (HA1C), high-density and low-density lipoproteins (HDL and LDL) cholesterol, triglycerides, albumin, C-reactive protein (CRP), white blood cell count (WBC), and Epstein-Barr viral load (EBV). The biomarkers were all

continuous variables in NHANES, which had varying ranges and metrics, thus they were standardized for statistical analysis in order to have all the indicators in the same metric.

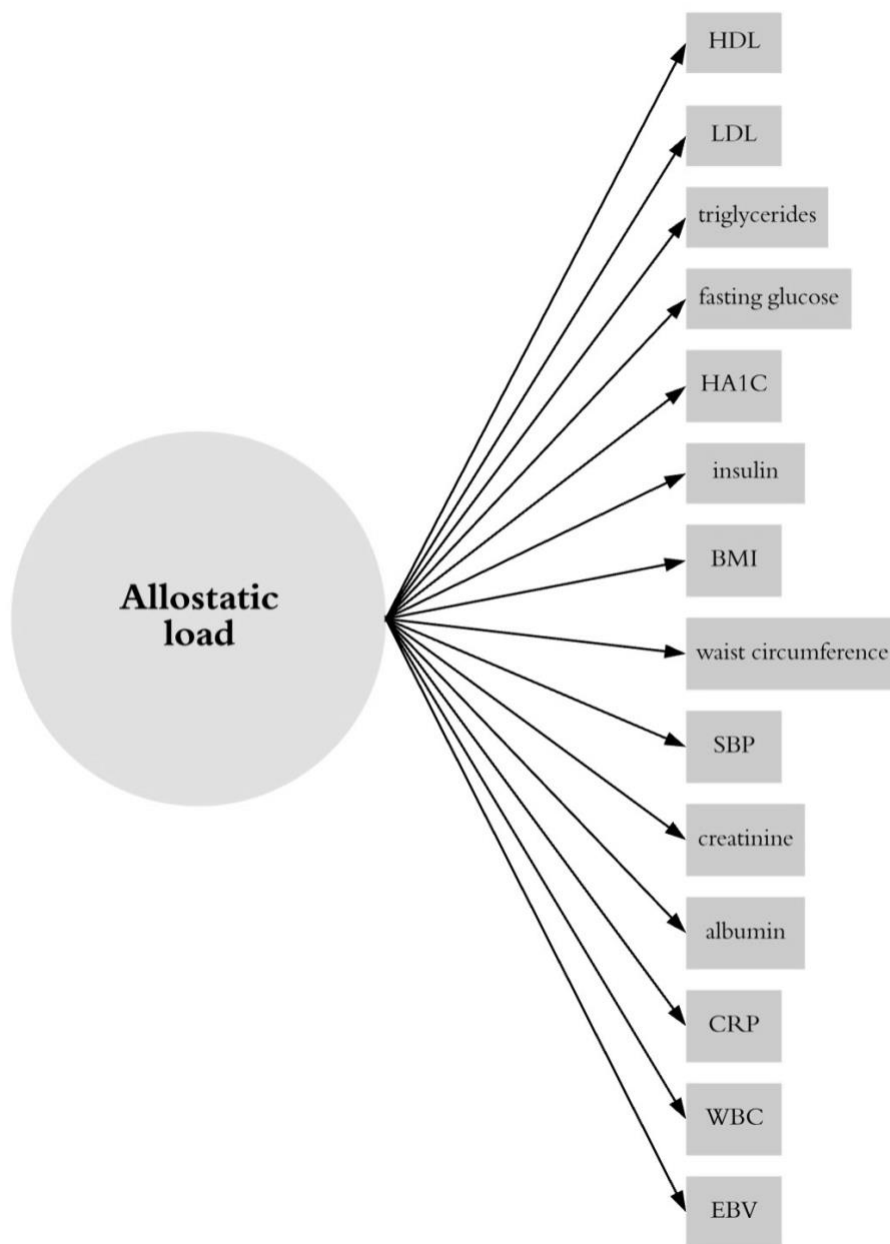


Figure 3. Allostatic Load Latent Indicators

HDL and LDL cholesterol. Cholesterol is transported through the bloodstream by carrier molecules comprised of fat (lipids) and proteins, which are known as lipoproteins (American Heart Association, 2017). There are two kinds of lipoproteins in the body (HDL and LDL) and the amount of each type of cholesterol in the blood can be quantified with a laboratory blood test. HDL cholesterol is known as the “good” form of cholesterol that is protective against heart disease and stroke (AHA, 2017). LDL cholesterol is referred to as “bad” cholesterol due to its contribution of fatty buildup in the arteries, thus predisposing individuals to heart disease, myocardial infarction, stroke, and peripheral artery disease (AHA, 2017). HDL cholesterol was a continuous variable (measured in mg/dL) with a range from 11 to 179, with higher values indicating more optimal HDL cholesterol levels (NCHS, 2016). LDL cholesterol was also a continuous variable (measured in mg/dL) with a range from 23 to 344, with higher values indicating less optimal LDL cholesterol levels (NCHS, 2016).

Triglycerides. Triglycerides are the most common type of fat found in the human body and they are responsible for storing excess energy from our dietary intake (AHA, 2017). These fats, when associated with high LDL cholesterol levels and low HDL cholesterol levels, are associated with fatty buildups in artery walls, which contributes to a higher risk of heart disease, myocardial infarction, and stroke (AHA, 2017). Triglycerides was a continuous variable (measured in mg/dL) with a range from 12 to 2549, with higher values indicating less optimal triglycerides levels (NCHS, 2016).

Insulin and fasting glucose. Insulin is a hormone that is synthesized in the pancreas and is released into the blood in order to manage blood glucose levels. When blood glucose levels increase following a meal, the pancreas releases insulin into the bloodstream, which allows both insulin and glucose to enter cells throughout the body in order to carry out vital metabolic processes (National Institute of Diabetes and Digestive and Kidney Diseases, 2017). Insulin allows muscle, fat, and liver cells to absorb glucose from the blood, while also stimulating liver and muscle tissues to store excess glucose as glycogen, thus ultimately lowering blood glucose levels (NIDDK, 2017). In a healthy individual, these functions allow insulin and blood glucose levels to remain within a normal, healthy range. In contrast, insulin resistance can develop over time when blood glucose levels are chronically elevated, ultimately increasing risk for prediabetes and type 2 diabetes, as well as other chronic conditions, such as heart disease, stroke, blindness, and kidney failure (NIDDK, 2017). The insulin and fasting blood glucose variables were collected first thing in the morning following a 9 hour fast in NHANES, both measured as continuous variables. Insulin was measured in uU/mL, ranging from 1 to 231.67, with higher values indicating higher amounts of insulin present in the blood (NCHS, 2016). Fasting blood glucose was measured in mg/dL, ranging from 38 to 584, with higher values indicating higher levels of glucose present in the blood at the time of laboratory assessment (NCHS, 2016).

Glycated hemoglobin. Another important metric for diagnosing prediabetes or diabetes is glycated hemoglobin, which is also commonly known as hemoglobin A1C (HA1C). This is a blood test that provides information about a person's average

blood glucose levels over the last three months. The HA1C test is based on the attachment of the glucose molecule to the hemoglobin in red blood cells, which typically have a lifespan of about three months (NIDDK, 2014a). This test has the advantages of being able to be drawn at any time without the need for prior fasting and also provides a better representation of the individual's average blood glucose levels over time. The HA1C is reported as a percentage, with a level below 5.7% being considered "normal" (NIDDK, 2014a). In NHANES, the HA1C variable was collected during the laboratory examination portion of the study, extracted from the blood and analyzed into a percentage, as previously discussed. This was a continuous variable ranging from 3.8 to 15.6, with higher values indicating a higher average blood glucose level over the preceding three months (NCHS, 2016).

Body mass index. Body mass index (BMI) is a very useful measure of being overweight or obese and is based on an individual's height and weight. BMI is used to estimate your body fat in order to determine risk for diseases that are associated with obesity (National Heart Lung and Blood Institute, 2017). Obesity during childhood and adolescence carries numerous immediate health risks, including hypertension, dyslipidemia, insulin resistance and diabetes, psychological disorders, and low self-esteem, as well as risk of heart disease, cancer, and stroke in adulthood (CDC, 2015). In NHANES, BMI was obtained from the physical examination portion of the study where the adolescents' height and weight were measured by the healthcare provider and a BMI variable was constructed using the standard BMI formula (kg/m^2). BMI was a continuous variable with a range from 12.5 to 73.3, with higher values indicating a higher BMI (NCHS, 2016).

Waist circumference. Waist circumference is another useful measure to screen for possible health risks that have been linked with being overweight or obese. Research has shown that if the majority of your fat stores are around your waist, as opposed to your hips, then you are at higher risk for heart disease and type 2 diabetes (NHLBI, 2017). Waist circumference was obtained in NHANES during the physical examination where a healthcare provider used a measuring tape around the waist of the adolescent, just above their hipbones, following an exhalation (NCHS, 2016). Waist circumference, measured in cm, was a continuous variable with a range from 37.8 to 178.2, with higher values indicating a larger waist circumference.

Systolic blood pressure. Accurate measurement of blood pressure is essential for hypertension screening, as well as for disease management for patients. Hypertension has consistently been found to be a powerful and independent risk factor for both cardiovascular and renal disease (NCHS, 2016). In NHANES, the blood pressure variables were ascertained in the MECs by a trained examiner who underwent specific blood pressure measurement training prior to collecting participant blood pressure data. The participants came to the MEC and after resting quietly in a seated position for five minutes, the examiner typically took three (sometimes four) blood pressure measurements (both systolic and diastolic) (NCHS, 2016). The American Heart Association (AHA) recommends that a minimum of two blood pressure measurements should be taken when assessing blood pressure, with the average of those readings being used to represent the patient's blood pressure (Handler, Zhao, & Egan, 2012). The systolic blood pressure (SBP)

was focused on for the purposes of this study, with an average SBP variable created using the mean of the second and third blood pressures measured in NHANES, per recommendations from the NHANES analytic and reporting guidelines (NCHS, 2016). SBP was a continuous variable (measured in mmHg), with higher values indicating a higher SBP.

Creatinine. Creatinine is a waste product that is produced by the metabolism of protein and is filtered along with other waste products by healthy kidneys into the urine. However, high blood pressure, hyperglycemia, and sustained toxic stress can damage the blood vessels in the kidneys, which adversely affects their ability to remove wastes and extra fluids from the body (NIDDK, 2014b), thus it is both a metric of cardiovascular and kidney health. This process over time can lead to a buildup of creatinine in the blood as the creatinine clearance decreases in the kidneys. In NHANES, serum creatinine was measured during the laboratory examination as a part of the Standard Biochemistry Profile (NCHS, 2016). Creatinine was measured as a continuous variable (measured in mg/dL) with a range from 0.14 to 15.66, with higher values indicating a higher level of creatinine in the blood (NCHS, 2016).

Albumin. Albumin is the primary protein synthesized by the liver and has several important functions in the body: it maintains normal plasma colloid oncotic pressure, is the primary binding protein in the blood, and is responsible for the transport of various substances in circulation (Ishida, Hashimoto, Seike, Abe, & Nakaya, 2014). Hypoalbuminemia is defined as a low serum albumin level in the blood, typically referring to a level less than 3.4 to 3.5 g/dL (NCHS, 2016).

Hypoalbuminemia is strongly associated with poor clinical outcomes (Louis-Vincent, Dubois, Navickis, & Wilkes, 2003) and can result from a variety of health conditions, including malnutrition, heart failure, hepatic cirrhosis, and kidney failure, however many cases of hypoalbuminemia are caused by acute and chronic inflammatory responses (Kaysen, 2009). When inflammation occurs in the body, the liver switches gears from producing albumin to producing other important proteins that are needed to fight the source of inflammation, thus leading to a precipitous drop in circulation albumin levels in the blood. In NHANES, serum albumin levels were measured during the laboratory examination portion of the survey as a part of the Standard Biochemistry Profile (NCHS, 2016). This is a continuous variable (measured in g/dL) ranging from 1.2 to 5.5, with higher values indicating a higher level of albumin present in the blood (NCHS, 2016).

C-reactive protein. C-reactive protein (CRP) is considered one of the best measures of the acute phase response to an infection or other cause of inflammation and can also be used to measure the body's response to more chronic inflammatory processes (Li & Fang, 2004; NCHS, 2016). Previous research has found that serum albumin levels tend to correlate negatively with CRP levels in patients with widespread inflammation, thus indicating that the liver downregulates albumin and upregulates CRP production in order to respond to inflammatory processes in the body (Ishida et al., 2014). CRP, measured in NHANES during the laboratory examination, was measured as a continuous variable (in mg/dL) with a range from 0.01 to 20, with higher values indicating a higher amount of CRP present in the blood (NCHS, 2016).

White blood cell count. White blood cell (WBC) count, similar to CRP, is commonly used as a clinical marker of systemic inflammation or infection, and it is also associated with increased risk for coronary heart disease, stroke, cancer, and mortality (Willems, Trompet, Blauw, Westendorp, & de Craen, 2010). Leukocytosis is typically defined as an elevated WBC count greater than 11,000 per mm³ (11.0 X 10⁹ per L) in adults, with higher counts present in young children, though these gradually decline throughout childhood to reach adulthood normal ranges (American Academy of Family Physicians, 2015). The WBC variable in NHANES was collected during the laboratory examination as part of the Complete Blood Cell Count with Differential. WBC was a continuous variable (measured as 1000 cells/uL) with a range from 1.5 to 83.2, with higher values indicating a higher level of WBCs present in the blood at the time of the examination (NCHS, 2016).

Epstein-Barr virus antibody. Epstein-Barr virus (EBV) is a common latent herpes virus infection in children and adolescents, which can undergo reactivation as a result of toxic stress (Christian, Deichert, Gouin, Graham, & Kiecolt-Glaser, 2009; Dhabhar, 2011; Ford & Stowe, 2013). Previous studies have utilized EBV antibodies in order to measure this viral reactivation, which is an indirect measure of impairment of the immune system in response to chronic, sustained stress (Glaser et al., 1991; Stowe et al., 2010). EBV was measured in NHANES with enzyme immunoassay (EIA) kits, both qualitatively and quantitatively, by means of an EIA index (NCHS, 2016). The EIA quantitative index value was used in this study as the EBV antibody variable, which was a continuous variable with a range from 0.01 to 7.17, with higher values indicating a higher EBV viral load (NCHS, 2016).

Race/ethnicity. The sole moderating variable that was examined in this study was the race/ethnicity of the adolescent, which reflected the racial/ethnic background that the individual identified with. This variable was self-reported by the study participants (if 16 years or older) or by the head of the household (typically a parent) for younger individuals during in-person interviews in NHANES. This was a categorical nominal variable, with the following categories in NHANES: non-Hispanic White, non-Hispanic Black, Mexican American, Other Hispanic, and Other Race (including Multi-Racial) (NCHS, 2016). Given that we excluded all missing data for this variable, as well as participants who responded “Other”, the remaining race/ethnicity groups included non-Hispanic White, non-Hispanic Black, and the two Hispanic groups (Mexican American and Other Hispanic), which were pooled into a larger Hispanic group in order to have relatively equal participants in each group for analysis. As such, the three race/ethnicity variable was recoded into the following three categories for this study: African Americans, Whites, and Hispanics.

Smoking. The first mediating variable that was included in this study was smoking, which was measured with a serum cotinine biomarker obtained during the laboratory examination portion of NHANES (NCHS, 2016). Cotinine is a major metabolite of nicotine that can be used as a marker for both active and passive (NCHS, 2016). Per NHANES, cotinine is typically preferable over nicotine for such assessments given the significantly longer half-life for cotinine (15-20 hours)(NCHS, 2016). Cotinine was a continuous variable (measured in ng/mL) with a range from

0.015 to 1156, with higher values indicating a higher exposure to tobacco smoke (NCHS, 2016).

Lead. The second mediating variable in this study was lead exposure, which was assessed with the serum lead biomarker during the laboratory examination portion of the NHANES survey. Lead levels are useful to quantify the amount of exposure that children and adolescents have had to this environmental toxin, which has been shown to adversely affect numerous physiological systems (NCHS, 2016). Lead was a continuous variable (measured in $\mu\text{g/L}$) in NHANES with a range from 0.25 to 55.2, with higher levels indicating a higher amount of lead present in the blood at the time of examination (NCHS, 2016).

Nutrition. The third mediating variable in this study was nutrition, a created variable based on 12 different dietary components obtained through a 24-hour recall survey in NHANES, which allowed us to assess the quality of the child's diet (Gu & Tucker, 2017; NCHS, 2016). These individual dietary components were combined and scored to create a Healthy Eating Index (HEI) variable for the purposes of this study, which has been extensively utilized and validated in previous research in order to determine the quality of an individual's diet, based on recommendations from the US Dietary Guidelines for Americans (Yu et al., 2015).

The 12 dietary components in the HEI-2010 are based on nine adequacy components and three moderation components. The nine adequacy components include: (1) total fruit, (2) whole fruit, (3) total vegetables, (4) greens and beans, (5) whole grains, (6) dairy, (7) total protein foods, (8) seafood and plant proteins, and (9) fatty acids, for which higher scores reflect higher intakes of those foods (Gu &

Tucker, 2017). The 3 moderation components include: (1) refined grains, (2) sodium, and (3) empty calories, for which higher scores reflect lower intakes of those foods (Gu & Tucker, 2017). In the HEI-2010, six components including total fruit, whole fruit, total vegetables, greens and beans, total protein foods, and seafood and plant proteins were scored from 0 to 5; five components including whole grains, dairy, fatty acids, refined grains, and sodium were scored from 0 to 10; and empty calories were scored from 0 to 20. A software package in R was utilized to create the HEI variable using data from NHANES and the MyPyramid Equivalent Database (MPED). The HEI nutrition variable was continuous, with a range from 0 to 100, with higher values indicating a healthier diet for the adolescent.

Physical activity. The final mediating variable that was included in this study was physical activity, which reflected the amount of time that the adolescent spent being active on a typical day. While there were several questions that asked how much physical activity the adolescent engaged in each day, there was quite a bit of variation in how the questions were asked across NHANES waves and to which age groups, which limited choices for which question to use for this study. Ultimately, the question within the Physical Activity questionnaire that was the best choice to assess physical activity for this population was “How many minutes per day do you spend walking or riding a bicycle?” (NCHS, 2016). The physical activity variable was a continuous variable, with a range from 1 to 600, with higher values indicating more time spent being physically active walking or biking (NCHS, 2016).

Covariates. There were two variables that were considered as covariates in this study, both of which were found in the Demographics survey in NHANES. Age

of the child can be considered a confounding variable given that according to the AL framework, the likelihood of developing higher AL increases through cumulative exposure to stress over time (Beckie, 2012). Thus, individuals that were older would theoretically be more likely to have higher AL, just based on the fact that they have had the chance for more stressful social and environmental exposures that could lead to systemic physiological dysregulation. Age of the child was a continuous variable (measured in years), which ranged from 12 to 18, given the inclusion criterion for this study (NCHS, 2016).

Additionally, the gender of the child can also be considered a confounder, given that some AL research has found a difference in AL prevalence between genders (Kusano et al., 2016; Widom et al., 2015), though specific mechanisms are unclear. Gender of the child was a categorical dichotomous variable in NHANES, with the following two options: male or female (NCHS, 2016).

Methodological Rigor

Allostatic load. There has been strong construct and predictive validity demonstrated for AL over the last few decades, initially established in McArthur Healthy Aging Study in the adult population with a range of physiological markers assessing the antecedents and longitudinal consequences of AL (Beckie, 2012). Recently, numerous studies have provided further support for AL construct validity (Barboza Solis et al., 2015; Friedman et al., 2015; Horan & Widom, 2015; Widom et al., 2015), including a limited number with pediatric study populations (Chen et al., 2015; Rainisch & Upchurch, 2013; Santacroce & Crandell, 2014).

Despite the widespread validity of the allostatic load construct in research, reliability continues to be its weakest link (Beckie, 2012). There is significant heterogeneity of AL measurement across studies, such as decisions about included biomarkers, methods of combining and weighting them, and optimal statistical analysis methods. Although the original AL construct was measured with an index of ten biomarkers, this was merely an initial attempt to operationalize the construct and not intended to be the “gold standard” (Seeman, T.; Karlamangla, A.; Sidney, S.; Liu, K.; McEwen, B.; et al., 2010). While consensus on this issue would be ideal for building reliability and further validity data for the AL construct, it might be somewhat unrealistic to expect that a single set of biomarkers of multisystem dysregulation could be equally predictive of all chronic disease outcomes, given the variability of pathophysiological mechanisms involved (Beckie, 2012).

Current study. A strong source for methodological rigor in the current study was the use of NHANES data. NHANES is a long-standing, well-respected and validated population health program that combines in-home interviews with trained personnel with physical examination and laboratory testing with healthcare providers (CDC, 2016a). The NHANES study design has broad oversight from consultation with stakeholders, collaborating agencies, and other members of the research community in order to ensure each wave of the survey can obtain data that is of vital importance for public health. Prior to any changes between data collection periods, NHANES conducts pilot testing of any new or revised material in order to ensure methodological rigor for their data collection methodology (CDC, 2013b).

Also, any laboratory methods utilized in NHANES were tested prior to data collection to ensure the reliability and validity of their protocols (CDC, 2013b).

There is a potential threat to the internal reliability in this current study, given the cross-sectional and correlational design, thus causal inferences between variables of interest cannot be definitively determined (Polit & Beck, 2017).

However, the external validity of the results is enhanced by the use of secondary data from the nationally representative sample in NHANES, thus making results from this study highly generalizable to other study populations (NCHS, 2016; Polit & Beck, 2017).

Data Management

The data from this study were managed, analyzed, and stored on a password- and firewall-protected computer in order to preserve the integrity of the data. However, given that the entirety of the data available from the NHANES study is de-identified and publicly available, there was no risk for breach of confidentiality for participants. Following completion of this study, the data was stored on a password-protected personal computer for potential use in future research projects.

Statistical Approach

Structural equation modeling. A structural equation modeling (SEM) statistical approach was used in this study, which combined confirmatory factor analysis (CFA) and structural regression modeling in order to analyze relationships between measured variables and unobservable latent constructs (Kline, 2016).

Latent variables were those that are not directly observable or measured, but were

indirectly measured from a set of observed variables. Based on theory, as well as empirical research, the goal of the researcher using SEM is to test whether a set of observed variables defines the latent constructs that are hypothesized to be related to each other in a certain way (Hoyle, 2012). Ultimately, the goal of SEM is to test whether the proposed theoretical model is supported by the sample data. If the data does support the model, then the hypothesized relationships between the latent constructs and measured variables exist, and if not then an alternative model needs to be developed and tested.

Confirmatory factor analysis. CFA was used to test a hypothesized theoretical measurement model by determining if it yielded a variance-covariance matrix that was similar to the sample variance-covariance matrix (Kline, 2016). The first step in CFA was model specification, which was based on theory and prior empiric research. Often one of the more challenging parts of SEM, CFA will not tell you how to specify the model, but instead estimates the parameters of the model once it has been specified by the researcher. Model identification was the second step in CFA, where we assessed whether or not the model is over- or under-identified by looking at the number of free parameters to be estimated (Hoyle, 2012). The next step was to estimate the factor loadings for the proposed model, which is traditionally done in CFA by decomposing the variance-covariance matrix, with a goal to have a hypothesized model that reproduces most of the original sample variance-covariance matrix (Kline, 2016). Factor loadings can be estimated with a variety of different estimation procedures, such as maximum likelihood (ML), generalized least squares (GLS), and unweighted least squares (ULS), which will

result in factor loading values for the indicator variables and a chi-square model-fit value (Hoyle, 2012; Kline, 2016). If the chi-square model-fit value is significant, then the sample variance-covariance matrix is not a good fit to the proposed CFA measurement model. In this study, CFA was used to construct the two latent variables that serve as the predictor variable (CSD) and the outcome variable (AL) using several measured indicators that theory and previous research suggested are indicative of those constructs.

Reliability of the CSD and AL latent constructs was evaluated with maximal reliability (MR) coefficient, which estimates reliability by assuming that the indicators making up those constructs have different weights, meaning some indicators are better than others at estimating the construct. MR is the maximal possible reliability for a linear combination of the construct indicators and involves the estimation of the optimal linear combination (OLC), which are the weights for each indicator. Note that MR measures reliability of a construct, which differs from Cronbach alpha that estimates inter-item correlation (Li, 1997; Raykov, 2012).

All indicators for the AL latent construct were continuous variables, which were transformed into a standard normal variable with mean = 0 and standard deviation = 1. These AL indicators were standardized in order to standardize the metric across these variables for analytic purposes. Indicators for the latent CSD construct were a mix of continuous and categorical measures, therefore they were not standardized. The mediator variables were directly measured variables, which were also standardized (mean = 0, and standard deviation = 1). All SEM models were estimated with maximum likelihood (ML) and model fit was evaluated with

multiple approximate fit indices (Fan & Sivo, 2007; Kline, 2016; West, Taylor, & Wu, 2012).

Missing data. Missing data was handled with full information maximum likelihood (FIML), a modern method to properly handle missing data, which improves parameter recoverability, reduces bias, and increases power (Baraldi & Enders, 2010; Enders, 2010). The missing data recoverability was evaluated with the fraction of missing information (FMI), which quantifies the missing data's influence on the sampling variance of a parameter estimate as the proportion of the total sampling variance that is due to the missing data (Enders, 2010).

Structural regression modeling. Once the CSD and AL latent constructs had been constructed and validated with CFA, structural regression modeling was utilized in order to determine the total, direct, and indirect effects of CSD on AL through the mediation pathways of interest, while also testing the moderating effect of race/ethnicity (see Figure 4 for study mediation model). For all analyses, significance was defined as p value $< .01$ in order to reduce the likelihood of committing a Type I error, given the large number of regression analyses performed and large sample size. All data compilation and cleaning was performed in SPSS, followed by all SEM analyses being performed in R.

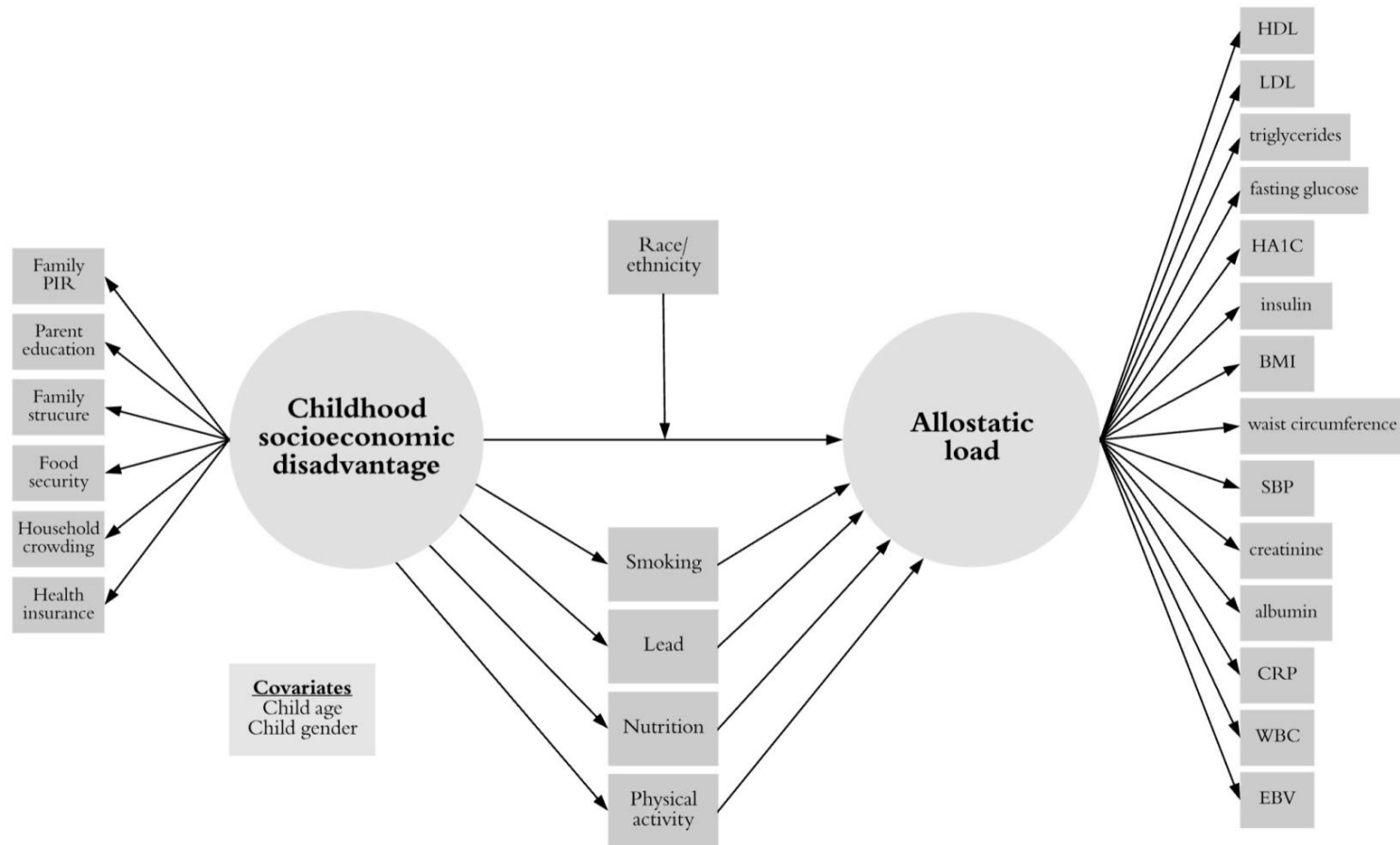


Figure 4. Study Mediation Model

Once the AL and CSD factor structures were fit-tested and seemed congruent with theory, these factors were tested for measurement invariance across the three race/ethnicity groups (African American, White, and Hispanic). This was done to ensure that there was no measurement bias inherent in those constructs that might confound the relationships found in the multi-group mediation model.

Measurement invariance testing included assessing for configural invariance (comparing factor structure between groups), weak factorial invariance (comparing factor loadings between groups), and strong factorial invariance (comparing indicator intercepts between groups). These models were gradually compared in the change in fit due to the addition of constraints; if the change in CFI (ΔCFI) was < 0.01 , we accepted the model with the added constraints. Alternately, if the ΔCFI was > 0.01 , we continued testing for partial strong invariance. Partial strong invariance meant that not all of the indicator constraints were held between race/ethnicity groups, but there were still enough constraints held in order to retain the model (Cheung & Rensvold, 2002; van de Schoot, Lugtig, & Hox, 2012).

Once measurement invariance had been established, we could compare the latent parameters between the race/ethnicity groups, which assessed univariate means, variances, and correlations between groups. These parameters were compared with the nested model change in χ^2 ($\Delta\chi^2$) when they were equated between groups. Thus, if the $\Delta\chi^2$ p -value $< .01$, we concluded that the parameters could not be equated between the race/ethnicity groups (Kline, 2016; Little, 2013).

After latent parameters had been compared between groups, we then tested the multiple group mediation model of interest. We included gender and age of the adolescent as covariates, which were added to the model to control for their effects on every predictor, mediator, and outcome. After the covariates were added, they were pruned to only keep the covariate paths that showed a meaningful effect. The mediation model with pruned covariate effects was the one we used to test for total, direct, and indirect effects across race/ethnicity groups.

For the appropriate estimation of the indirect effects, the Monte-Carlo simulation method was used as a resampling method (MacKinnon, Fairchild, & Fritz, 2007; MacKinnon, Lockwood, & Williams, 2004; Preacher & Selig, 2012). The total, direct, and indirect effects and difference between groups were tested by creating an empirical distribution of them based on the Monte-Carlo resamples. These empirical distributions were then tested against the null hypothesis value of 0, with the inferences made in function of the 95% confidence intervals (CI). The model was estimated with 20,000 Monte-Carlo samples, and also with maximum likelihood (ML), with the CI presented as the bias-corrected CI.

The structural regression measurement model included one predictor (CSD), one outcome (AL), and four mediators (cotinine, lead, nutrition, and physical activity). All total, direct, and indirect effects were compared between groups. The indirect effects of CSD on AL were estimated for the three race/ethnicity groups, and the addition of the indirect effects and the direct effect of CSD on AL yields the total effect of CSD on AL for each group. The indirect effects ($a*b$) represented the effect of CSD on AL through each mediator variable, the direct effect (c') represented the

specific effect of CSD on AL, and the total effects represented the overall effect of CSD on AL. Thus, mediation analyses allowed us to decompose the effect of the predictor on the outcome, allowing us specific information about how it exerts its influence (i.e. through which mediating pathways).

Study Limitations

There were several limitations for this study. This study was cross-sectional, which limited our ability to make causal inferences due to temporal ambiguity in the variables of interest. However, given that there is theoretical and empirical support identifying CSD as an antecedent to AL, it is reasonable to assume that CSD experienced early in life would precede the physiological alterations and downstream environmental and behavioral factors in this study model. Other study limitations are related to a lack of inclusion of key variables related to development of AL as a result of using secondary data. In NHANES, there was no measurement of the neuroendocrine hormones, which would have been ideal to include in the AL latent construct variable to enhance robustness of the measure. There are also several extraneous variables that could affect the relationship between CSD and AL that either weren't included in NHANES' study design or they were not specifically measured in adolescent participants, thus they could not be included in our measurement model.

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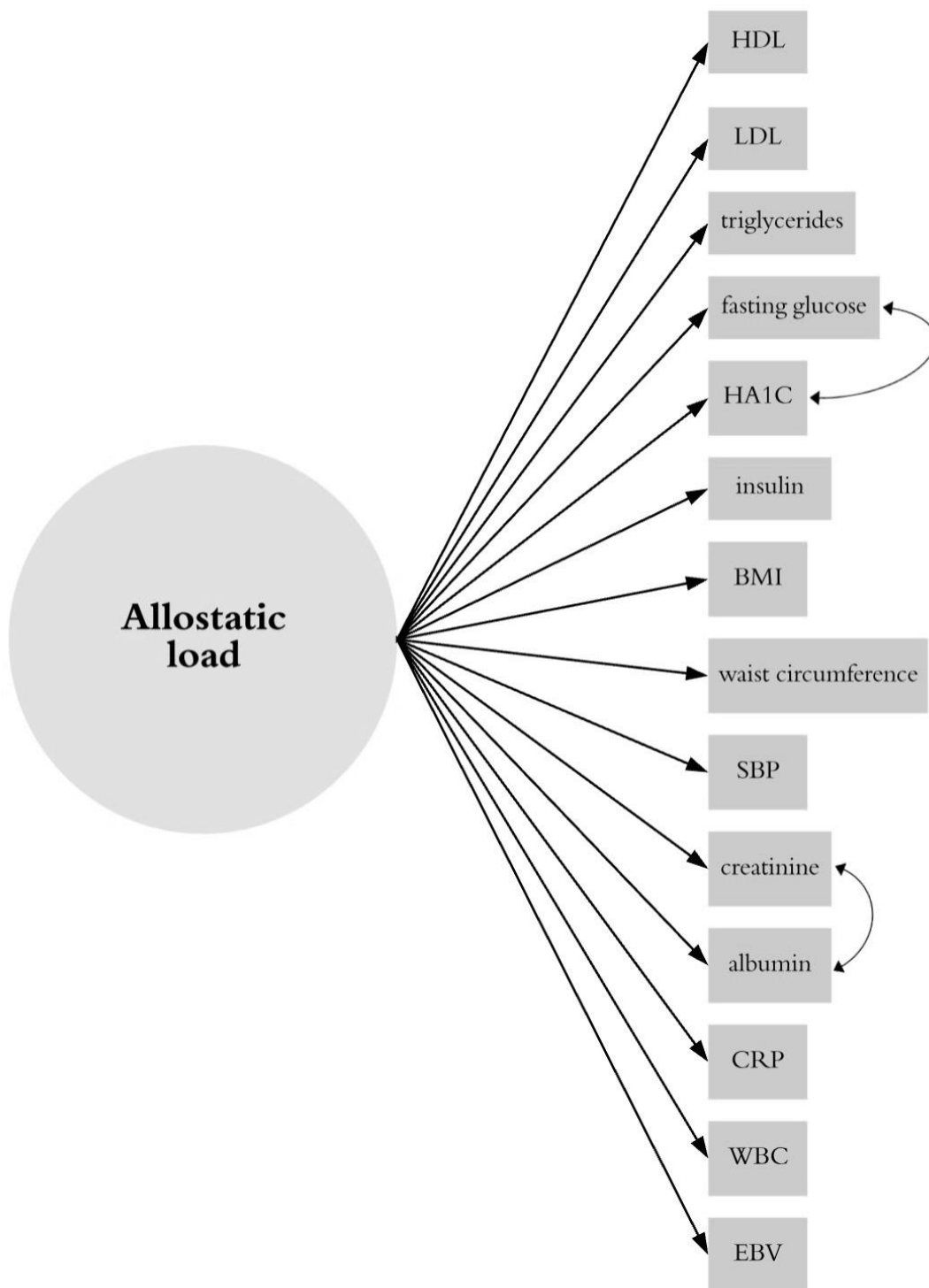
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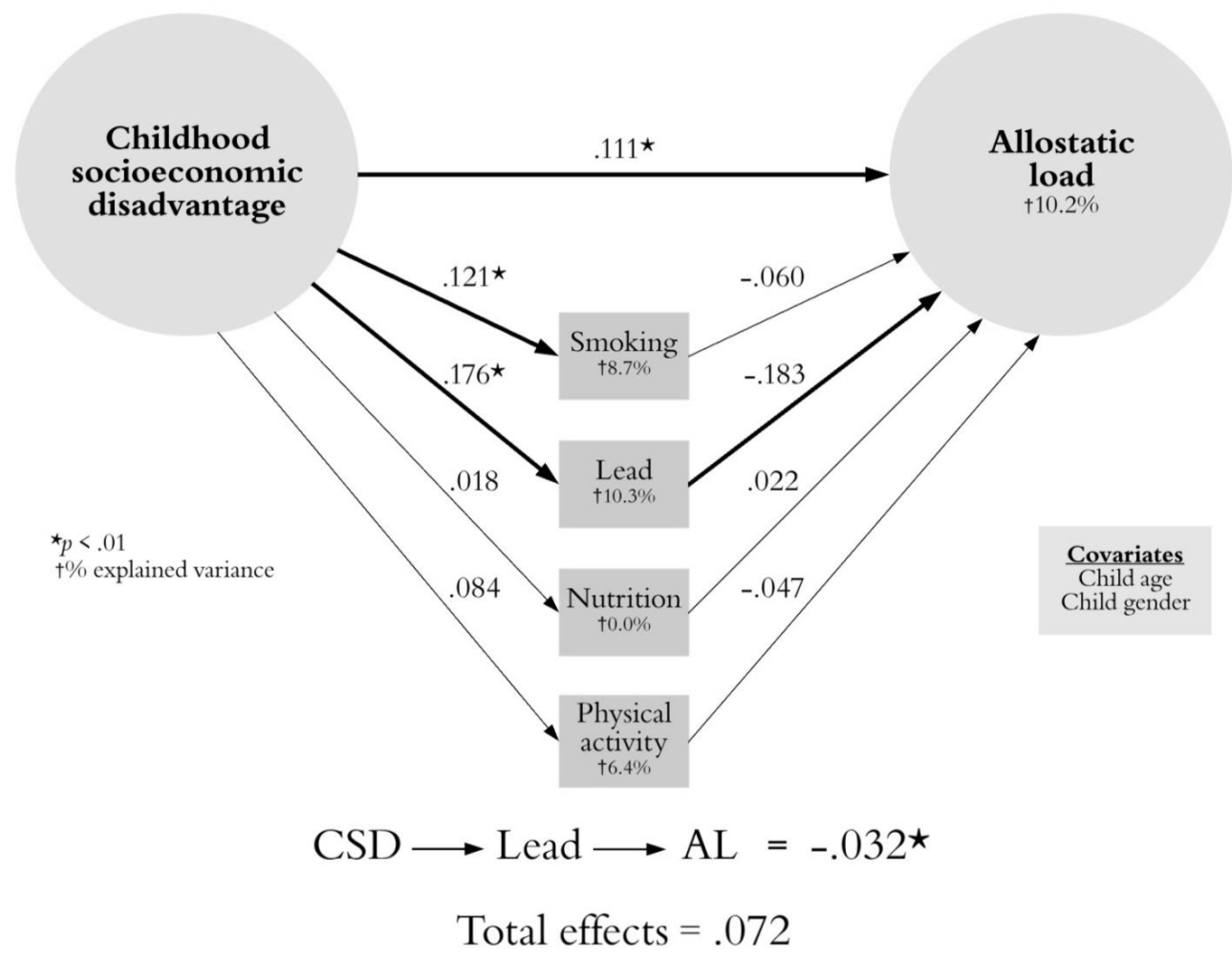
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Appendix A*Unidimensional Allostatic Load Factor Structure*

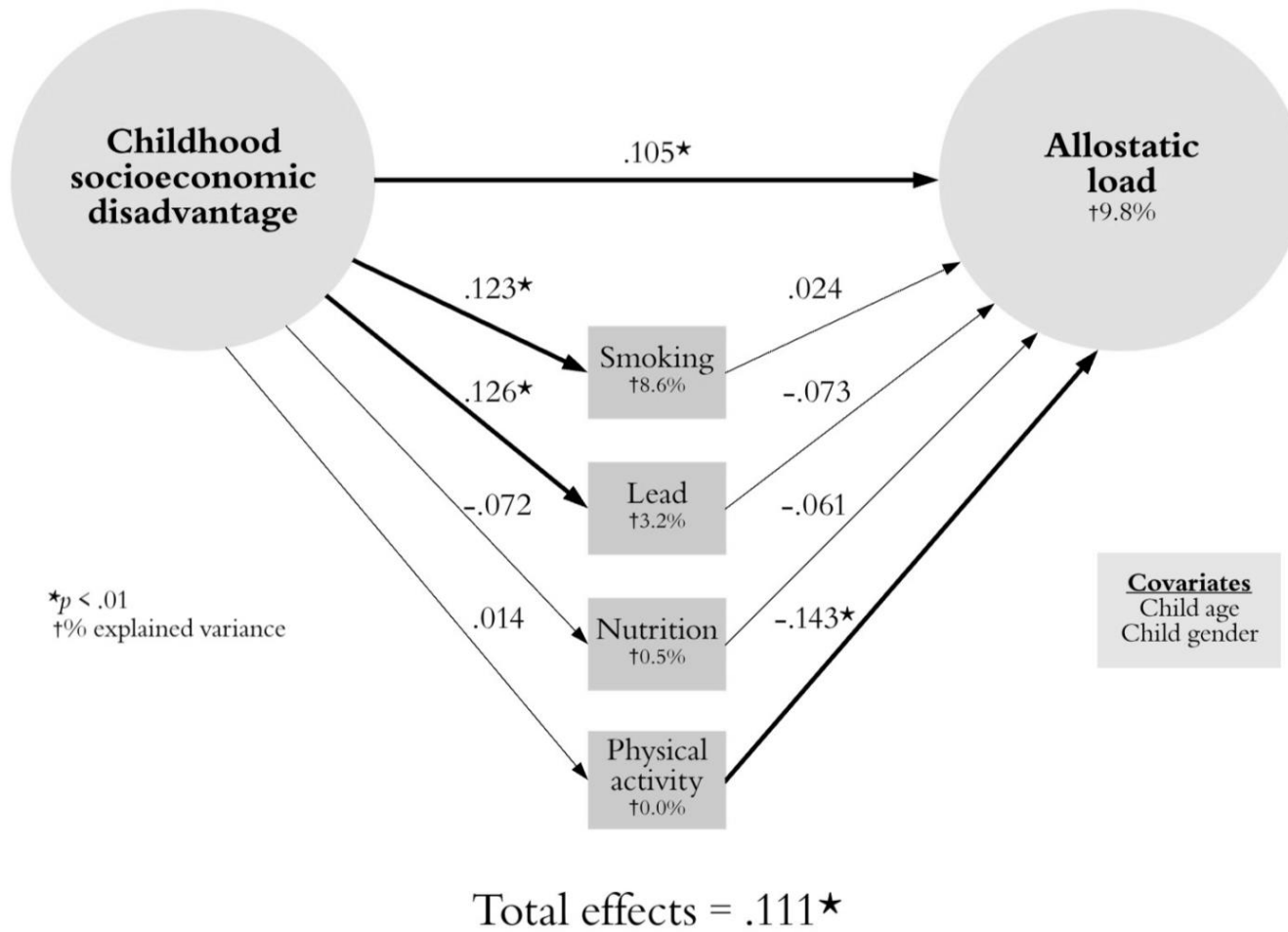
Appendix B

African American Total, Direct, and Indirect Pathways Model



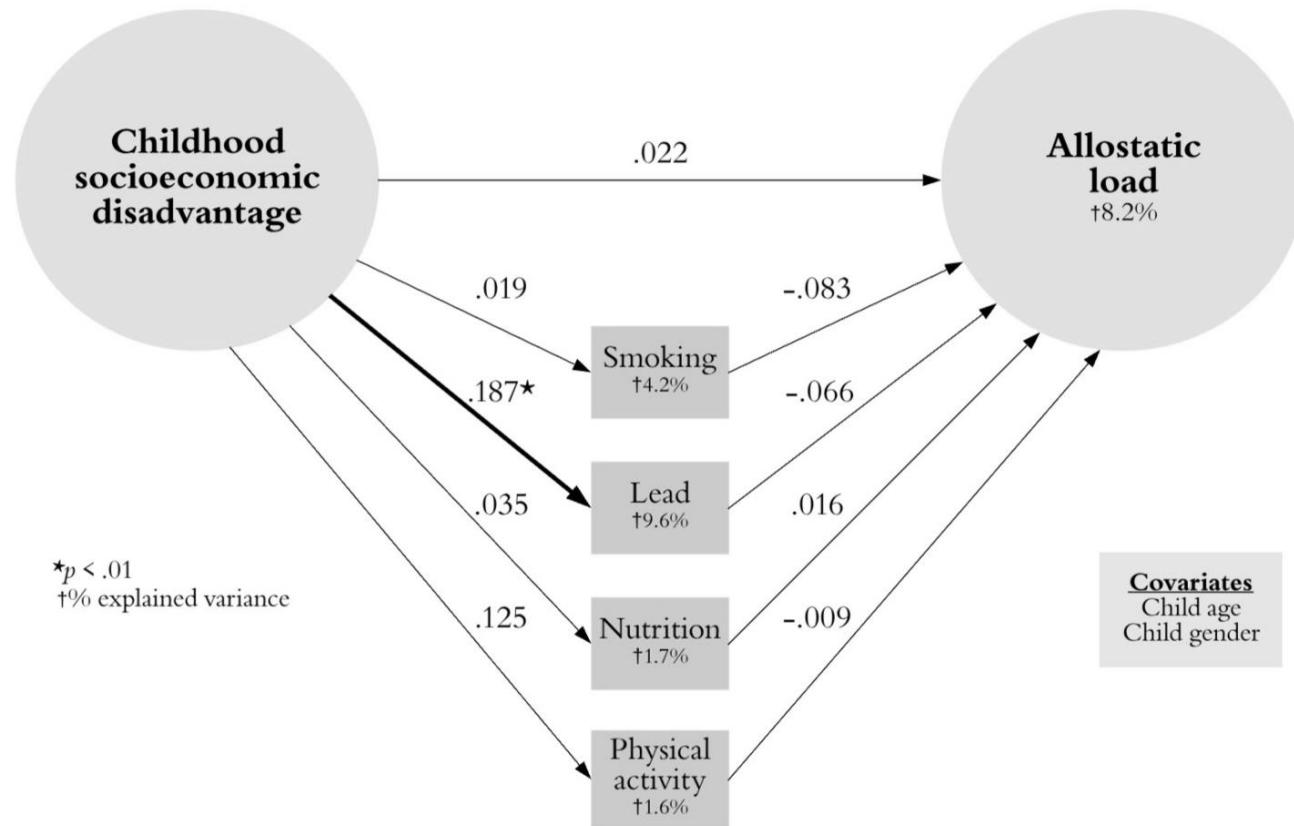
Appendix C

White Total, Direct, and Indirect Pathways Model



Appendix D

Hispanic Total, Direct, and Indirect Pathways Model



Total effects = .008

Testing Allostatic Load Factor Structures Among Adolescents: A Structural Equation

Modeling Approach

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Abstract

Objective: Allostatic load (AL) represents cumulative biological “wear and tear” that results from chronic stress exposure over time, ultimately increasing risk for chronic disease. A consensus is lacking regarding the best operationalization of AL, particularly for younger, less-studied populations. The purpose of this study was to test multiple hypothesized factor structures for AL to determine the best measurement approach for adolescents.

Methods: We analyzed biologic data for 1900 adolescents aged 12-18 from four waves (2003-2010) of the National Health and Nutrition Examination Survey (NHANES). AL indicator variables included cardiovascular (systolic BP, creatinine), metabolic (HDL, LDL, triglycerides, insulin, fasting glucose, HA1C, BMI, waist circumference), and immune (albumin, CRP, WBC, EBV) biomarkers. Structural equation modeling (SEM) was used to test the fit of five hypothesized AL factor structures.

Results: The data best supported a unidimensional factor structure, where the AL construct directly influenced each of the indicator variables. All but two of the indicators (HDL and albumin) had positive factor loadings, thus as AL increases, the values for those indicators also increase. The best indicators for AL were those measuring metabolic dysregulation, with BMI and waist circumference having the highest factor loadings (0.95 and 0.982, respectively).

Conclusion: BMI and waist circumference may be some of the earliest clinical signs of elevated AL that manifest among adolescents. Future research should aim to include neuroendocrine biomarkers in their AL measures in order to have a more robust estimation of AL in younger populations.

Keywords: allostatic load, adolescence, structural equation modeling, confirmatory factor analysis

Testing Allostatic Load Factor Structures Among Adolescents: A Structural Equation
Modeling Approach

According to the World Health Organization (2018), the global burden of chronic diseases (i.e. cardiovascular disease, cancer, obesity, diabetes) is rising, with projections that they will contribute to approximately 57% of global deaths by the year 2020. These diseases are common, costly, and often preventable health problems, affecting more than half of all individuals in the United States (US) (Centers for Disease Control and Prevention, 2017; Ward, Schiller, & Goodman, 2014), with an estimated \$1.3 trillion annual impact on our economy (Healthy People 2020, 2016; Hunter & Reddy, 2013). Although chronic diseases tend to be thought of as conditions of adulthood, roughly 25% of children and adolescents in the US are also affected (Miller, Coffield, Leroy, & Wallin, 2016), which has both immediate and lifelong effects on their optimal development and health. Health care professionals are interested in preventing the onset of chronic disease by better understanding and measuring key risk factors earlier in life in order to promote better health trajectories across all populations.

Allostatic load (AL) is a marker of cumulative biological “wear and tear” that captures the biological pathways through which social, behavioral and environmental factors contribute to development of chronic disease over time (Barboza Solís et al., 2015; Friedman et al., 2015). AL expands on the concept of allostasis, proposing that the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems protect the body by mounting adaptive responses to stressors in order to maintain homeostasis (McEwen (1998). Thus, AL is the biological result of chronic overactivity of these stress response pathways (Hux & Roberts,

2015), which over time leads to systemic dysregulation of biological systems and increased risk for chronic disease. Indeed, a vast body of literature has linked elevated AL to a myriad of chronic diseases in adulthood, including a variety of psychological disorders (Beckie et al., 2016; Kuhn et al., 2016), cardiovascular disease (Havranek et al., 2015; Steptoe & Kivimaki, 2013), diabetes (Steptoe et al., 2014), and adverse pregnancy outcomes (Hux & Roberts, 2015; Hux et al., 2014), as well as others. However, there is a lack of consistency across the literature in how AL is operationalized and scored, which makes the comparison and validity of findings across studies challenging (Beckie, 2012). Moreover, few studies have evaluated whether AL is a valid construct of biological “wear and tear” in younger individuals, warranting further investigation into which biological indicators may be the most salient biomarkers of AL for younger populations.

Selection of AL Indicators

AL is conceptualized as a latent construct that is best represented using a number of measured, biological indicator variables that represent stress-mediated systemic physiological dysregulation (Howard & Sparks, 2016). In past research, a key determinant for selection of indicators included in AL measures has been the availability of and logistical access to various biomarkers that are thought to represent the key body systems involved in development of AL. Many population-based studies have therefore utilized available cardiovascular, metabolic, and inflammatory indicators when creating their AL constructs (Kobrosly et al., 2013; Masterson & Sabbah, 2015; Theall et al., 2012), while excluding biomarkers of neuroendocrine function (i.e. cortisol, dehydroepiandrosterone [DHEA]), which are comparatively more challenging to ascertain at the population level. In contrast, studies using clinical sample populations have been more likely to include

assessment of neuroendocrine function within their AL indices, given they are better able to collect reliable and valid data on such measures (Chen et al., 2015; Howard & Sparks, 2016). Despite decades of AL research, there remains a lack of consensus regarding which indicators of AL are necessary to include in the construct in order to remain consistent with its biological premise and predictive utility in health outcomes across different populations.

Previous Estimation Approaches

In addition to AL indicator heterogeneity, estimation methods for AL also vary widely across the literature. Historically, the most common approach to measurement of AL taken has been a summative count method, with scores for each AL biomarker divided into risk quartiles based on AL psychometrics established in the foundational MacArthur Studies of Successful Aging (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997), which first tested the AL construct in an older adult population. Using this approach requires dichotomization of each AL indicator (into normal versus abnormal values) in order to create a summed total AL score, which leads to a loss of precision and explanatory power for each individual variable included. Additionally, high-risk quartiles validated in adult populations may be less clinically meaningful for younger individuals whose distribution of values for AL biomarkers is likely to be different than those observed in adults. Other more complex scoring methods have been proposed, including summative measures based on clinical cutoffs, recursive partitioning, canonical correlation, and factor analysis with latent modeling (Gruenewald et al., 2006; Karlamangla et al., 2002; McCaffery et al., 2012; Seplaki et al., 2006), but there is a lack of consensus on which statistical approach aligns best with the theoretical underpinnings of AL.

Use of Structural Equation Modeling

There are several potential advantages to employing a structural equation modeling (SEM) approach for AL measurement, and specifically the use of latent variable modeling with factor analysis. First, indicator variables can be treated as continuous variables, rather than the common practice of dichotomizing values at a high-risk cut-off level, leading to potential loss of information for the indicators (Beckie, 2012; Rosemberg et al., 2017). Additionally, factor analysis allows researchers to test proposed factor structures for the AL construct through evaluation of local and global model fit statistics, modification indices, and parameter estimates (Booth, Starr, & Deary, 2013). This type of complex modeling can also reduce the measurement error of the AL construct by reflecting only the common variance shared amongst the indicator variables, ultimately yielding a more reliable and valid measure.

To our knowledge, there are only a few studies that have utilized factor analysis to model the AL construct, which used a variety of approaches and had varying results. There are two studies that performed principle components analyses (PCA) (although methods were reported as exploratory factor analyses [EFA]) in which the authors aimed to determine the dimensionality (how many distinct attributes the construct has) of the AL construct in an adult population using the original 10 indicators for AL (Howard & Sparks, 2016; Johnston, 2004). PCA is a data reduction analysis that aims to understand underlying dimensions that are implied by correlations among indicator variables, ultimately interpreting the dimensions found as constructs (Jain & Shandliya, 2013). In contrast, EFA explains interrelationships amongst the indicator variables in order to determine which variables are more or less related to the larger latent construct through

local and global fit testing, ultimately yielding indicator factor loadings and a latent factor structure (Jain & Shandliya, 2013).

Keeping this in mind, the results from these two PCA studies reported different dimensionality of the AL construct, despite similar approaches and study populations (Howard & Sparks, 2016; Johnston, 2004). Howard and Sparks (2016) found evidence for a unidimensional AL construct that explained correlations between the indicators. In contrast, Johnston (2004) proposed that AL has three related subdimensions (cardiovascular, metabolic, and inflammation), with correlations between indicator variables relating directly to those three biological systems. While these studies did not produce true factor structures for AL or factor loadings for indicator variables (given they utilized PCA and not EFA), they offered some preliminary insight into how a latent AL construct can be modeled.

Confirmatory factor analysis (CFA) is similar to EFA in that it produces true factor structures and factor loadings for indicators, but is an approach that is driven by theory and empirical research, while EFA is purely data driven (Suhr, 2006). There have been five confirmatory factor analyses (CFA) that have tested a variety of AL factor structures to determine the best measurement approach for this construct (Booth, Starr, & Deary, 2013; Gross, 2008; McCaffery et al., 2012; T. Seeman et al., 2010; Wiley, 2015). Booth et al. (2013) found support for a second order three subfactor AL structure, similar to that proposed by Johnston (2004), in an older adult population. The remaining four CFA studies tested a variety of AL factor structures, ultimately finding support for several different structures, including a second order five subfactor AL structure (Seeman et al., 2010) as well as several residualized AL structures (Gross, 2008; McCaffery et al., 2012;

Wiley, 2015). In the study by Seeman et al. (2010), the retained AL factor structure had five subfactors, including heart rate variability, blood pressure, inflammation, metabolic, and cortisol, with the individual indicators loading onto the subfactors and the subfactors loading onto an overall AL factor. In contrast, other studies found support for residualized AL structures where all indicators loaded onto a unidimensional AL construct, with those same indicators also sharing variance with other physiological systems (Gross, 2008; McCaffery et al., 2012; Wiley, 2015). Given these differences in how AL has been operationalized in previous studies using SEM approaches and the lack of studies employing such methods to generate AL constructs among younger populations, there is a clear need for further research on the ideal measurement approach, particularly in a less studied adolescent population.

Study Purpose

Given the heterogeneity in measurement of the AL construct across studies and the relative paucity of research parameterizing AL in younger populations, the purpose of this study is to test five hypothesized factorial structures of AL using SEM among a U.S. population-based sample of adolescents in order to determine the best measurement model for this construct in an adolescent population.

Methods

Study Design and Sample

Data for the present study were derived from four waves (2003 through 2010) of the National Health and Nutrition Examination Survey (NHANES), which is designed to assess the health and nutritional status of children, adolescents, and adults in the United States each year (National Center for Health Statistics, 2016). Data were collected via in-

home surveys conducted by trained interviewers and via a physical exam and laboratory testing completed by healthcare professionals in mobile examination centers (MECs) (NCHS, 2016). The data are free, de-identified, and publicly available on the NHANES website.

Inclusion and Exclusion Criteria

The sole inclusion criterion for the current study was being 12 to 18 years of age, given adolescence was the time period of interest for measuring the AL indicator variables. There were no specific exclusion criteria, therefore, any participant who met the inclusion criterion were retained. The final study sample that met inclusion and exclusion criteria was 1900 adolescents.

Study Measures

Allostatic load. A total of 14 variables measuring dysregulation across several physiological systems were included as indicators of AL. Physical measurements included systolic blood pressure (SBP), body mass index (BMI), and waist circumference, which were collected by a trained health care professional in the MECs. Laboratory-assessed biomarkers included creatinine, insulin, fasting glucose, glycated hemoglobin (HA1C), high-density and low-density lipoprotein (HDL and LDL), triglycerides, albumin, C-reactive protein (CRP) level, white blood cell count (WBC), and Epstein-Barr viral index (EBV). All laboratory methods utilized to collect and analyze these biomarkers from NHANES were rigorously tested prior to data collection in order to ensure the reliability and validity of their protocols (Centers for Disease Control and Prevention, 2013).

Protection of Human Subjects

The parent NHANES study was approved by the National Center for Health Statistics Research Ethics Review Board (NCHS, 2016). The current study was reviewed by the Marquette University Institutional Review Board and declared exempt, given the study constituted secondary data analysis utilizing de-identified information.

Data Analysis

The analysis for this study was performed in R (R Core Team, 2018). We utilized structural equation modeling (SEM) with the R package lavaan (Rosseel, 2012). As described by Raykov (2012), the SEM framework allows researchers to develop and test factors, such as evaluation of multidimensional structures, correlations between constructs, evaluation of multiple reliability measures, and reducing measurement error of the underlying measured indicators in order to estimate a more precise measure of the latent AL construct (Kline, 2016; Little, 2013). CFA was used within the SEM framework in order to test multiple factor structures for the AL indicators, which were compared based on their fit indices, proper estimation solution, and theoretical meaning of the parameter estimates.

Five AL factor structures were tested in this study to model the AL construct (see Figure 1). First, we tested a unidimensional factor structure (Model A), in which all of the indicators were explained by a single AL factor. We then tested three second order factor structures (Models B, C, and D), in which indicators loaded directly onto physiological systems or specific biological processes (subfactors), and then these subfactors loaded onto an overall AL factor. These factor structures included: (1) a second order two subfactor structure, whereby the indicators loaded onto cardiometabolic and inflammation first

order factors, (2) a second order three subfactor structure, in which the indicators loaded onto cardiovascular, metabolic, and inflammation first order factors, and (3) a second order five subfactor structure, whereby the indicators loaded onto cardiovascular, insulin resistance, lipids, weight, and inflammation first order factors. Finally, we tested a five correlated factors structure (Model E) representing key physiological systems and processes that are associated with AL (using the same five subfactors as in Model D), all of which were intercorrelated. These five AL factor structures were chosen based on the allostatic load theoretical framework and previous empirical research that have utilized SEM to model this construct.

The reliability of the selected AL latent factor structure was then evaluated with the maximal reliability (MR) coefficient, which estimates the reliability of a factor or scale assuming the underlying indicators have different weights. Thus, MR is the maximal possible reliability for a linear combination of the indicator items and involves the estimation of the optimal linear combination (OLC) (i.e. the weights for each item). MR was estimated with the R package *semTools* (*semTools Contributors, 2018*).

All indicators for the AL latent construct were continuous measures. These indicators were transformed into a standard normal variable with mean = 0 and standard deviation = 1, which was performed so that the indicators would all be in the same metric. SEM models were estimated with maximum likelihood (ML) and model fit was evaluated with multiple approximate fit indices (Fan & Sivo, 2007; Kline, 2016; West et al., 2012). Missing data was addressed with full information maximum likelihood (FIML), which is a modern method that properly handles missing data by improving parameter recoverability, reducing bias, and increasing power (Baraldi & Enders, 2010; Enders,

2010). The missing data recoverability was evaluated with the fraction of missing information (FMI), which quantifies the missing data's influence on the sampling variance of a parameter estimate as the proportion of the total sampling variance that is due to the missing data (Enders, 2010).

Results

Descriptive Statistics

The mean age of the study participants was 15.036 years ($SD = 2$, range = 12-18) and there was an approximately equal distribution of females and males (48.3% female, 51.7% male) and racial/ethnic groups (27.6% White, 37.7% African American, 34.7% Hispanic) in the study population. Table 1 provides additional descriptive statistics for each of the 14 biological indicator variables used to model the AL construct.

Tested Factor Structures

Table 2 reports the fit indices for the five tested factor structures. Models D and E presented the best fit indices, but the models both had unstable parameters. For Model D, the standardized second order factor loadings were at the boundary (1.00) for two of the first order factors (WEI and INFL), which indicated that this factor solution did not provide interpretable parameters. Model E presented negative residual variances (out of bounds) as well as low factor loadings for the INF second order factor with a $p > .3$. Fit indices between models A, B, and C were equivalent, but models B and C also presented out of bounds parameters, meaning those parameters were uninterpretable. Specifically, factor correlations for these two models were estimated to be higher than 1, indicating that some of the proposed first order factors were not distinguishable, thus suggesting a unidimensional factor structure for AL. Model A was the only tested factor structure that

had proper fit indices with no parameters out of bounds. Therefore, given the AL theoretical framework, fit indices, and parameter estimates for the five models, we selected model A as the preferred factor structure for the AL construct for this adolescent study population (see Figure 2).

Based on modification indices, two residual correlations between indicators were included (as shown in Figure 2): between fasting glucose and HA1C ($r = 0.628, p < .001$), and between albumin and creatinine ($r = 0.243, p < .001$). These residual correlations were kept because of shared variance between that is attributable to other physiological processes than AL. Fasting glucose and HA1C share variance related to glucose metabolism, while albumin and creatinine share variance for conditions related to kidney function, both of which can be unrelated to stress and AL.

Table 3 presents the factor loadings and R^2 for model A. The null hypothesis is rejected for every factor loading with all p values $< .01$. AL is defined by positive factor loadings for every indicator except two (albumin and HDL), which means that individuals with higher AL will have higher values for positive loading indicators and lower values for negative loading indicators. The indicators that best represented AL were BMI and waist circumference, which had the highest absolute value of the factor loadings, while the indicators that least represented AL were EBV and HA1C, which had the lowest factor loadings. Even though the R^2 for some indicators were low in this study population, we decided to retain them given their theoretical and biological relevance to the AL construct.

When diagnosing the effect of missing data in the model, we found that the FMI was high (above 0.5) for the factor loadings of LDL, triglycerides, and insulin due to the large amount of missing data for these indicators (over 1,000). The parameter estimates for

those indicators are still reliable, but there is a penalty of larger standard errors for those indicators due to this missing data influence. Additionally, the MR coefficient for the AL construct was 0.988, which demonstrated a high internal reliability.

Discussion

The purpose of this study was to compare several factor structures for the AL construct in an adolescent population in order to determine the best measurement approach for this construct among younger individuals. Our findings provide support for a unidimensional AL structure such that the individual indicators that represent dysregulation of various body systems load onto a single AL factor. A unidimensional model implies that each AL biomarker is directly influenced by the AL construct, rather than indirectly influenced through a related physiological system. To our knowledge, this is the first SEM study in a pediatric population that supports a unidimensional AL factor structure.

While our findings are consistent with that of the PCA study in an older adult population carried out by Howard and Sparks (2016), much of the adult AL literature that has utilized SEM supports either second order factor structures (Booth et al., 2013; Johnston, 2004; Seeman et al., 2010) or a residualized AL factor structure (Gross, 2008; McCaffery et al., 2012; Wiley, 2015). This likely reflects differences in the age of the study population (adults or older adults versus adolescents) and the corresponding differences in how stress manifests physiologically over time. Given that AL is thought to represent the body's "wear and tear" over time (Booth et al., 2013), it is logical that in an adolescent population we may not see the widespread dysregulation of AL biomarkers across multiple body systems that have been observed in studies utilizing adult populations. As a result,

there was likely less variability in many of the AL indicators for this younger population, which likely contributed to fit indices supporting a unidimensional factor structure.

Overall, local and global fit indices for the selected unidimensional AL factor structure (Model A) provided an adequate fit to the data (CFI 0.89, RMSEA 0.069, SRMR 0.067), which suggests that there is indeed a core of common shared variance amongst these biological markers of systemic dysregulation. This factor structure suggests that as AL increases in adolescents, the indicators with positive factor loadings also increase, while those with negative factor loadings decrease. A possible explanation for the lack of better model fit could be our inability to include all of the theorized biomarkers involved in the pathways between chronic stress and development of AL in adolescents. Specifically, this study was unable to include biomarkers from the neuroendocrine system (i.e. cortisol, DHEA) given they were not available in NHANES, inclusion of which could have potentially improved fit indices and provided a more robust AL measure. However, in research carried out among adult populations in which such neuroendocrine biomarkers have been included in AL measures (Seeman et al., 2010), those indicators had the lowest factor loadings compared to those from other physiological systems. The low factor loadings of the neuroendocrine indicators suggest that while it is ideal to include these biomarkers in AL measurement for theoretical purposes, models that do not include them are likely still valid and clinically meaningful for predicting chronic disease risk.

Consistent with previous AL literature using SEM, the biomarkers that were the best indicators of AL were those associated with dysregulation of the metabolic system (Booth et al., 2013; Seeman et al., 2010). Particular for this study, BMI and waist circumference had the highest factor loadings (0.965 and 0.982, respectively), with 93.2% and 94.9% of

the variance in those indicators explained by AL. These two indicators suggest that an individual with higher AL is likely to have elevated BMI and waist circumference, both of which are associated with obesity (National Heart Lung and Blood Institute, 2017). The high factor loadings in these AL indicators suggests that they are perhaps the earliest clinical signs of elevated AL that manifest in adolescent populations. Given that obesity amongst children and adolescents has become a serious health concern in the 21st century (Gungor, 2014; Kelly et al., 2013), this is an important finding that could aid health care providers in identifying individuals with elevated AL in its early phases where intervention might be more effective at reducing risk of developing chronic disease.

The factor loadings for the remaining AL biomarkers in this adolescent population were relatively low (ranging from 0.06 to 0.338), with the lowest primarily found amongst those associated with dysregulation of the cardiovascular and immune systems, similar to previous research using NHANES data (Gross, 2008). The studies that did observe higher factor loadings for the cardiovascular and inflammatory indicators (Booth et al., 2013; Seeman et al., 2010) were carried out among adult and older adult study populations, therefore these individuals would have had more time to develop elevated AL across multiple systems, whereas adolescents have not. As such, drastic systemic alterations in the stress regulatory systems observed in adult populations may be unlikely to be present in a younger, relatively healthy study sample.

Moving forward with AL research in pediatric populations, an argument could be made to modify the biomarkers included in measures of AL to include biological indicators that are more likely to become dysregulated earlier in life in order have a more robust estimation of AL. While measuring the neuroendocrine mediators can be logistically

challenging, these are theoretically antecedent to biomarkers reflecting systemic dysregulation in the cardiovascular, metabolic, and immune systems (such as those focused on in this study). Thus, dysregulation of neuroendocrine stress hormones, such as cortisol, may be more likely to emerge in childhood and adolescence than biomarkers linked to other downstream physiological systems and processes. While these neuroendocrine AL biomarkers have not had high factor loadings for adult populations, they might be more relevant indicators of elevated AL in pediatric populations. A suggestion for future pediatric AL research utilizing an SEM approach would therefore be to incorporate a measure of hair cortisol as an indicator of more long-term HPA axis dysregulation, which overcomes the measurement challenges of salivary or serum cortisol use and provides a more stable measurement of chronic stress (Fischer et al., 2017). Additionally, if we are to better understand why some children develop elevated AL while others don't under similar stressful conditions, DHEA has been proposed to be a potentially important marker for stress resilience (Juster, McEwen, & Lupien, 2010) and is involved in turning off the HPA axis, thus warrants consideration for inclusion in future AL constructs in younger populations.

The findings of this study provide preliminary evidence for how best to model the AL construct within an adolescent study population. Moving forward in future research, given the low factor loadings for many of the AL indicators that are often used in adult AL research, this unidimensional AL factor structure should be validated in other pediatric populations. Additionally, researchers might want to consider paring down the number of AL biomarkers that are included the AL construct in order to facilitate transition of this concept over into clinical practice. Future research could help determine the ideal

combination of weighted biomarkers through use of SEM and factor analyses in order to promote consensus on the best two or three indicators from each of the key AL systems that are relevant for pediatric populations. Limiting of indicators included could help contain research costs and make it more feasible to follow children long-term in longitudinal biobehavioral studies, which are better able to capture development of elevated AL over time.

Study Limitations

These findings should be interpreted in the context of limitations that existed for this study. The data are cross-sectional, which did not allow assessment of whether the currently observed levels of the AL indicators truly reflected a cumulative process of dysregulation developing over time. Additionally, there was no measurement of neuroendocrine hormones, which serve as mediators in the development of AL through their effects on the HPA axis. While there are significant logistical challenges for measuring such biomarkers at the population level, hormones that reflect dysregulation of HPA axis activity would have been ideal to include in the AL latent construct for this adolescent population.

Conclusion

This is the first known AL study using SEM for an adolescent population that supports a unidimensional AL factor structure reflecting common shared variance amongst several biological indicators representing this construct. Further research in adolescent and pediatric populations may be warranted in order to better delineate which biologic pathways contributing to elevated AL emerge first in life, why this is the case, and how we could best intervene earlier in life in order to mitigate chronic disease risk over the life

course. AL is a promising theoretical framework that allows better understanding for how social and environmental stressors can become biologically embedded and negatively impact the health of children and adolescents, which could program for ill health in adulthood. Ultimately, health care providers may be able to utilize the AL theoretical framework in order to identify adolescents at greatest risk for developing chronic disease and thereby focus preventative efforts on these individuals in order to best mitigate disease risk.

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Conflicts of Interest

The authors have no conflicts of interest to declare in conducting this research or preparing this manuscript for publication.

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Table 1. Allostatic Load Indicator Descriptive Statistics

AL Indicators	Total Sample (N = 1900)		White (N = 525)		African American (N = 716)		Hispanic (N = 659)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Systolic BP (mmHg)	108.995	10.171	108.422	10.463	109.966	9.847	108.435	10.211
Creatinine (mg/dL)	0.746	0.162	0.753	0.158	0.785	0.162	0.7	0.154
HDL (mg/dL)	53.205	12.701	51.884	12.744	55.648	13.356	51.612	11.515
LDL (mg/dL)	89.106	26.606	89.521	28.201	88.901	27.815	89.035	23.855
Triglycerides (mg/dL)	85.797	50.815	96.288	60.613	71.26	34.176	95.004	55
HA1C (%)	5.217	0.442	5.163	0.385	5.275	0.5	5.197	0.409
Fasting glucose (mg/dL)	90.294	14.292	93.222	22.361	88.342	10.201	90.372	9.398
Insulin (uU/mL)	12.957	13.67	12.283	14.693	13.734	15.182	12.556	10.709
BMI (kg/m ²)	23.709	5.995	23.254	5.579	24.388	6.799	23.34	5.289
Waist circumference (cm)	81.152	15.009	81.569	14.413	80.388	16.454	81.642	13.779
Albumin (g/dL)	4.376	0.337	4.44	0.33	4.246	0.325	4.464	0.312
EBV	3.539	1.75	2.768	1.961	3.888	1.616	3.756	1.523
CRP (mg/dL)	0.256	0.623	0.21	0.369	0.369	0.665	0.259	0.715
WBC (1000 cells/uL)	6.873	2.125	7.35	2.17	5.887	1.877	7.565	1.934

† Abbreviations: AL; allostatic load, systolic BP; systolic blood pressure, HDL; high-density lipoprotein, LDL; low-density lipoprotein, HA1C; hemoglobin A1C (i.e. glycated hemoglobin), BMI; body-mass-index, EBV; Epstein-Barr viral index, CRP; C-reactive protein, WBC; white blood cell count, SD; standard deviation

Table 2. Fit Indices for Tested Factor Structures

	χ^2 (df)	CFI	Gamma-hat	Adj gamma-hat	RMSEA	SRMR
Model A	747.55 (75)	0.890	0.952	0.933	0.069 (.064,.073)	0.067
Model B	732.09 (74)	0.890	0.952	0.932	0.069 (.065,.077)	0.069
Model C	701.42 (85)	0.900	0.958	0.941	0.062 (.058,.066)	0.065
Model D	596.12 (84)	0.921	0.966	0.953	0.055 (.051,.059)	0.049
Model E	846.95 (81)	0.932	0.972	0.957	0.053 (.048,.057)	0.056

† Abbreviations: χ^2 ; chi-square exact-fit, df; degrees of freedom, CFI; comparative fit index, RMSEA; root mean square error of approximation, SRMR; standardized root mean square residual

Table 3. Factor Loadings and R^2 for Allostatic Load Indicators

Indicator	Factor loadings (SE)	p -value	R^2
CREAT	0.111 (0.025)	< .001	0.012
ALBUM	-0.255 (0.025)	< .001	0.065
CRP	0.164 (0.027)	< .001	0.027
HDL	-0.342 (0.024)	< .001	0.116
LDL	0.212 (0.035)	< .001	0.045
TRIGLY	0.317 (0.034)	< .001	0.101
EBV	0.083 (0.025)	.001	0.007
HA1C	0.079 (0.025)	.002	0.006
GLUC	0.121 (0.033)	< .001	0.013
INSUL	0.578 (0.030)	< .001	0.338
WBC	0.204 (0.025)	< .001	0.042
SBP	0.334 (0.026)	< .001	0.110
BMI	0.965 (0.018)	< .001	0.932
WAIST	0.982 (0.018)	< .001	0.949

† Abbreviations: CREAT; creatinine, ALBUM; albumin, CRP; C-reactive protein, HDL; high-density lipoprotein, LDL; low-density lipoprotein, TRIGLY; triglycerides, EBV; Epstein-Barr viral index, HA1C; glycated hemoglobin, GLUC; fasting glucose, INSUL; insulin, WBC; white blood cell count, SBP; systolic BP, BMI; body mass index, WAIST; waist circumference

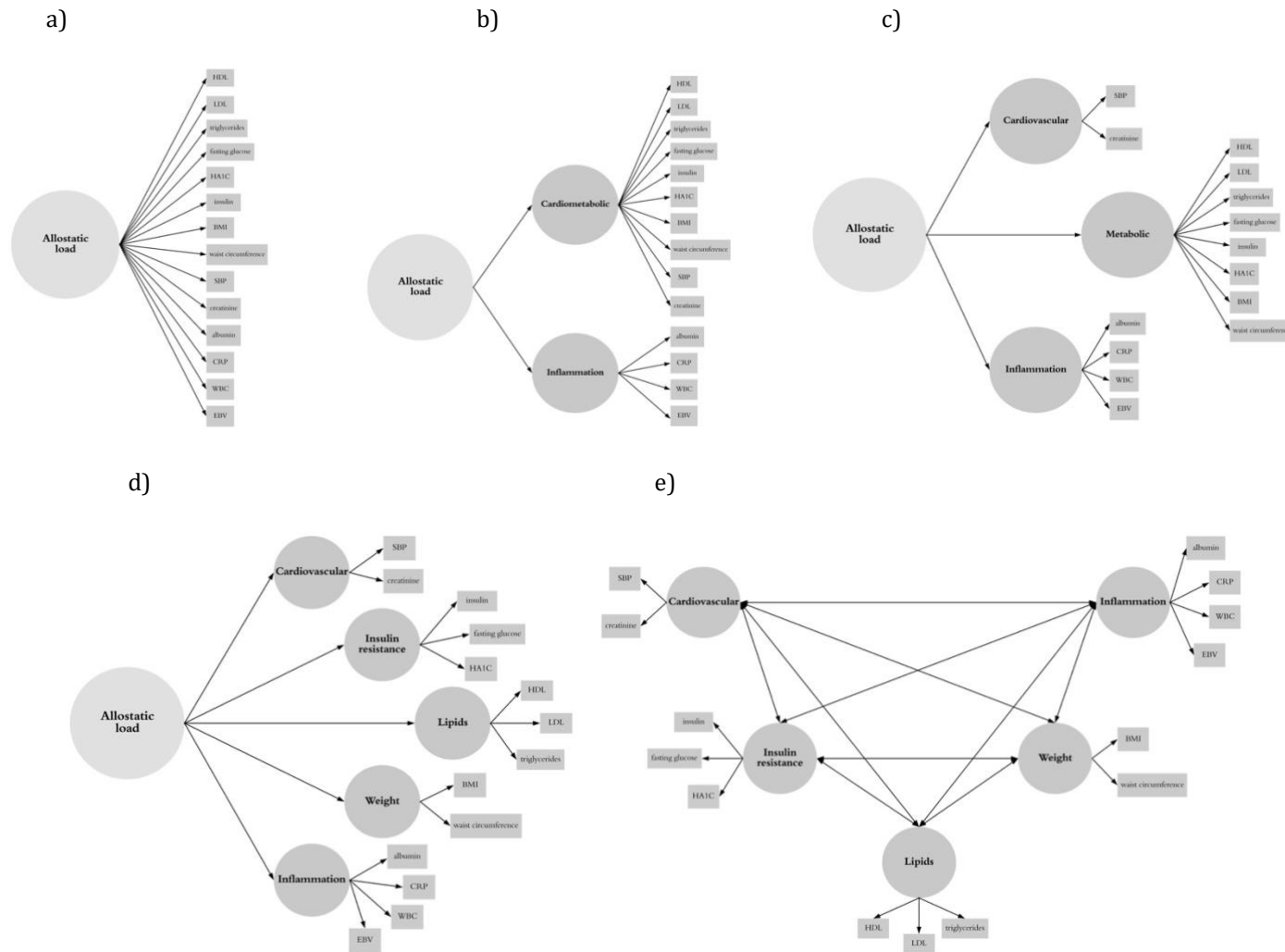


Figure 5. Proposed Allostatic Load Factor Structures. a) Model A, unidimensional factor structure; b) Model B, second order 2-subfactor structure; c) Model C, second order 3-subfactor structure; d) Model D, second order 5-subfactor structure; e) Model E, 5 correlated factors structure

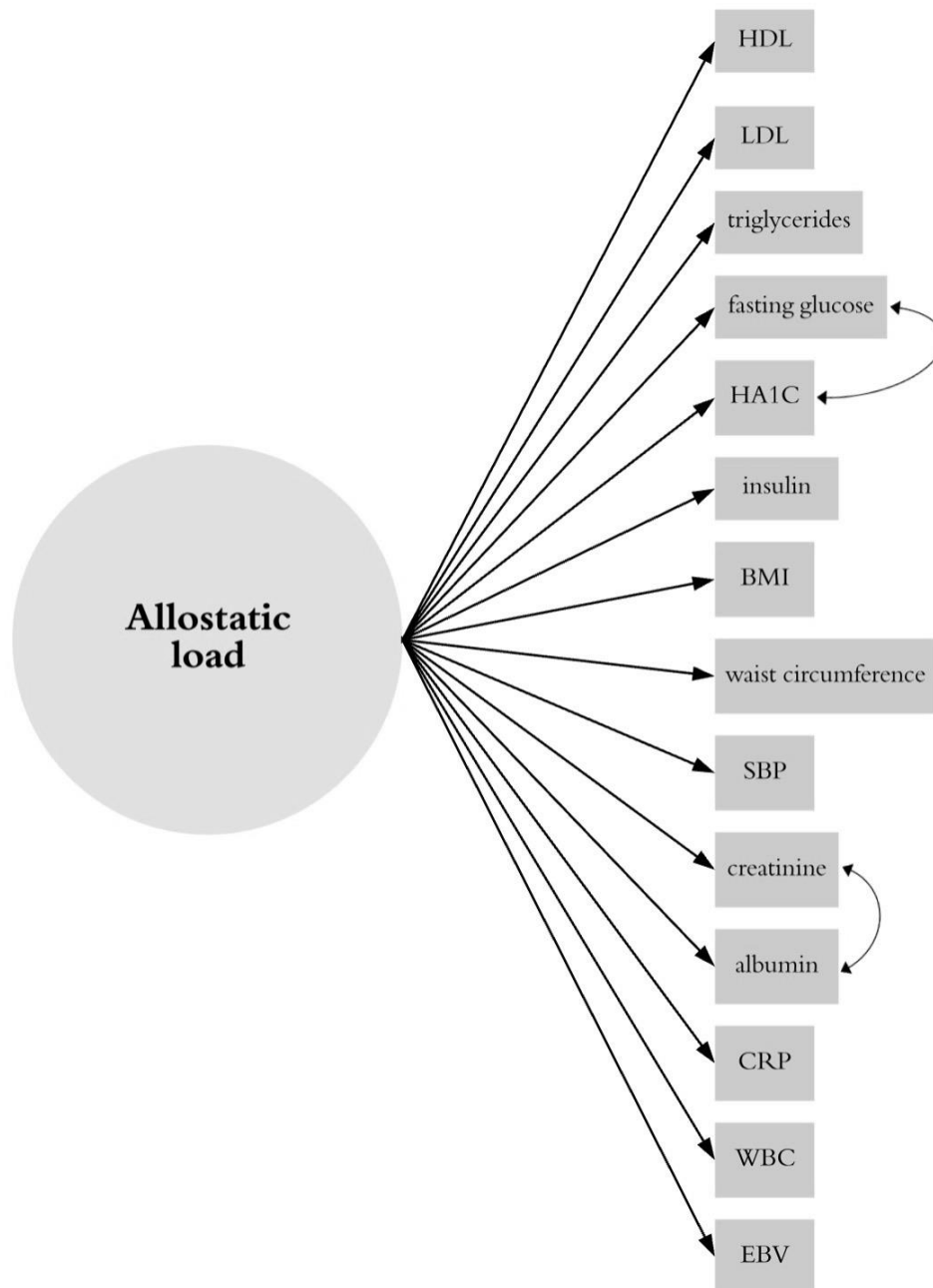


Figure 6. Unidimensional Allostatic Load Factor Structure. The 14 biomarkers that represent cardiovascular, metabolic, and immune system function load directly onto a single AL factor. The majority of the AL biomarkers had positive factor loadings, with HDL and albumin as the only negative factor loadings. Two residual correlations were retained to improve model fit, which indicates these biomarkers share variance that is not related to AL. Fit indices for this unidimensional AL factor structure were as follows: χ^2 (df) = 747.55 (75), CFI = 0.890, adj gamma-hat = 0.933, RMSEA = 0.069 (0.064, 0.073), SRMR = 0.067.

Childhood socioeconomic disadvantage and allostatic load in adolescence: Exploring the
role of environmental and behavioral mediators

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Abstract

While chronic diseases tend to be thought of as adult conditions, these diseases have become more common among children and adolescents¹, with lifelong effects on their optimal health and development². Such conditions are thought to result in part from elevations in allostatic load (AL), which reflects the cumulative biological risk for chronic disease resulting from biological, social, and environmental stressors. Childhood socioeconomic disadvantage (CSD) has been shown to predict AL in adulthood, though adolescence remains an understudied life course period. Additionally, research suggests differential exposure and vulnerability to stressors among certain minority populations, which may increase their risk for AL and poor health outcomes upon exposure to CSD. The purpose of this study was to examine the relationship between CSD and AL in adolescence, the contribution of smoking, lead, nutrition, and physical activity as mediators of this association, and the extent to which these effects vary across race/ethnicity. We utilized self-reported and biological data on 1900 adolescents aged 12-18 from four waves (2003-2010) of the National Health and Nutrition Examination Survey (NHANES). Structural equation modeling (SEM) was used to examine relationships between latent construct variables (CSD and AL) and measured mediating variables (smoking, lead, nutrition, and physical activity) across race/ethnicity groups. White adolescents had the sole significant total effects pathway, indicating that CSD had the greatest total contribution to AL in this group. There was a small, positive direct effect of CSD on AL that was significant for both African American and White adolescents, with a smaller nonsignificant direct effect for Hispanics, suggesting different pathways were more relevant for certain groups. A sole significant indirect pathway (CSD to AL mediated by lead) was found for African American

adolescents only, though the reversed directionality suggests a need for a different measurement approach for cumulative lead exposure.

Keywords: childhood socioeconomic disadvantage, allostatic load, adolescence, structural equation modeling

Childhood socioeconomic disadvantage and allostatic load in adolescence: Exploring the role of environmental and behavioral mediators

1. Introduction

Chronic diseases have become the greatest epidemic of the 21st century³, with cardiovascular disease, cancer, diabetes, and chronic respiratory disease collectively responsible for over 80% of all chronic disease deaths worldwide⁴. In an attempt to combat this global epidemic, the World Health Assembly endorsed a new global health goal in 2013, which was to reduce unavoidable global mortality from chronic diseases by 25% by the year 2025⁵. As a primary driver of illness and health care utilization in the United States (US)³, the economic cost of chronic diseases approaches \$1.3 trillion per year^{6,7}. Although these diseases used to be exclusive to adulthood, they are becoming more common among children and adolescents¹, which has both immediate and lifelong effects on their optimal development and health².

2. Background

2.1. Toxic Stress

The stress response is a generalized adaptive response of the body to any demand for a change in homeostasis⁸. Stress responses can differ in their adaptive value for the individual based on timing, duration, and the environmental context in which they occur⁹. Positive and tolerable stress responses tend to be associated with acute, short-lived stressors with a successful return to homeostasis, while a toxic stress response results from prolonged or frequent exposure to stressors, ultimately resulting in systemic dysregulation affecting multiple body systems¹⁰. Importantly, when toxic stress occurs during sensitive periods of development, such as childhood and adolescence, these adverse

biological effects can become programmed into long-term pathophysiological processes, thus increasing vulnerability to adverse outcomes ¹¹.

2.2. Childhood Socioeconomic Disadvantage

There is a wide body of literature demonstrating that early life exposure to socioeconomic disadvantage can lifelong adverse health outcomes through biological embedding (i.e. altered biological functioning as a result of an adverse exposure)^{12,13}, which likely plays an important role in shaping risk for onset of chronic disease early in life. Childhood socioeconomic disadvantage (CSD) can be defined as the comparative deprivation that a child experiences related to their access to financial and social resources within a hierarchical social structure ¹⁴, based on parental, household, and neighborhood socioeconomic factors ^{15,16}. Previous research suggests that the toxic stress experienced by children from a disadvantaged environment can have permanent effects on the brain structures that are involved with stress adaptation, which can have lifelong implications for their health ¹⁷⁻¹⁹. Additionally, CSD has been linked with a variety of adulthood chronic diseases, including cardiovascular disease^{12,20}, obesity^{15,21}, diabetes^{22,23}, cancer^{24,25}, and several psychological disorders^{26,27}. The specific mechanisms through which CSD affects chronic disease risk are debated, but toxic stress provides a potential explanatory mechanism for how an adverse social exposure, such as CSD, can directly affect biological processes and increase risk for disease.

2.3. Allostatic Load

Over time, the adverse biological consequences of CSD can accumulate and lead to development of elevated allostatic load (AL), which reflects the increased “wear and tear” that the body experiences due to repeated attempts at adaptation to stressors ²⁸⁻³⁰. AL was

initially conceptualized by Bruce McEwen, who hypothesized that the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems work together to protect the body by mounting adaptive responses to stressors³¹⁻³³. AL has been widely found to be associated with early life stressful exposures (i.e. adverse childhood experiences, poverty, trauma, abuse)³⁴⁻³⁶ and later life chronic diseases, such as various psychological disorders³⁷⁻⁴⁰, cardiovascular disease⁴¹, diabetes^{42,43}, obesity⁴⁴, and adverse perinatal outcomes^{45,46}. The majority of the AL research has measured this construct in adult populations, though there some pediatric studies that have linked AL with socioeconomic disadvantage⁴⁷⁻⁴⁹ and increased asthma prevalence⁵⁰ in adolescents. As the evidence for the importance of early life stressful exposures and development of AL continues to grow, there is an ongoing need to not only study AL in younger populations, but also to use more complex modeling strategies to best measure this complex biological construct.

2.4. Environmental and Behavioral Factors

In addition to the toxic stress biological pathway, there are several environmental and behavioral risk or protective factors have been identified as important pathways between CSD, AL, and chronic disease. Active and passive cigarette smoke exposure has been causally linked to a variety of chronic conditions across all age groups^{51,52}, with nicotine shown to be a potent activator of the HPA axis⁵³, which could contribute to chronic neuroendocrine dysregulation and AL development^{54,55}. Lead is an environmental toxin that has been shown to adversely affect numerous body systems, including the nervous, cardiovascular, hematopoietic, endocrine, renal, and reproductive systems⁵⁶. Infants and young children are often exposed to the highest levels of lead⁵⁷, which can have

significant long-term health consequences, given the rapid brain development during this time⁵⁸. There is also preliminary evidence that lead can directly impact HPA axis functioning, with the potential to predispose individuals for higher vulnerability to stress^{59,60}, though the exact biological mechanisms linking lead exposure and AL are unclear. Nutrition and physical activity are important health behaviors for adolescents that can be protective or confer risk for disease. A higher quality diet has been associated with lower levels of obesity and inflammation^{61,62}, and lower risk for developing diabetes, cardiovascular disease, and several types of cancer⁶³. Physical inactivity has been associated with a wide number of chronic diseases, including cardiovascular disease, diabetes mellitus, obesity, hypertension, cancer, and all-cause mortality^{64,65}. While attention to adulthood physical activity levels has been prevalent in disease prevention literature, there is increasing attention being paid to this behavior during childhood and adolescence in order to cultivate this protective factor earlier in life.

2.5. Difference in Effects Across Race/Ethnicity

There are two potential mechanisms by which race/ethnicity might alter the effects that CSD has on AL development for adolescents. First, there are some stressors that are unique to minority populations, such as perceived racism or discrimination, which could contribute to increased toxic stress, and potentially increased vulnerability to stress as well^{42,66}. As AL accumulates through frequent dealings with discrimination, this can predispose minority individuals for higher stress reactivity to any future stressors they encounter. Therefore, two adolescents of different racial/ethnic backgrounds with the same exposure of CSD could have different health outcomes based on their exposure and vulnerability to stress. And second, certain mediating pathways linking CSD and AL may be

more relevant or important for different race/ethnic groups compared to others. Neighborhoods where there is a greater proportion of minorities tend to have poorer quality housing and environmental conditions that are more likely to contain higher levels of lead contamination^{58,67} and more aggressive smoking advertising⁶⁸. In addition, discrimination stress and neighborhood quality can also shape minority health behaviors, including dietary choices/ and amount of physical activity^{69,70}. Therefore, the mediating roles of smoking, lead, nutrition, and physical activity might have a more significant contribution to AL for certain minority groups compared to others.

3. Current Study

While a relationship between CSD and AL have been consistently demonstrated in adult populations, it is unclear whether elevated AL emerges earlier in life among those experiencing CSD, as this association has infrequently been measured in pediatric populations. Adolescence is thought to be a sensitive period of development^{10,71}, given that it is marked by rapid physiological changes with pubertal development, as well as dramatic social changes as the individuals gain more independence and prepare for adulthood^{19,72,73}. As such, the adverse effects that result from disadvantage during this period have a greater potential to adversely affect the long-term health of the adolescent. Additionally, there is a need to identify the extent to which environmental and behavioral factors may explain socioeconomic disparities in AL and whether these associations vary across race/ethnic groups, which could help identify targeted interventions that are more likely to promote health equity.

The purpose of this study is to examine the total, direct, and indirect effects of CSD on AL in adolescence through environmental and behavioral mediators, and also assess

whether race/ethnicity serves a moderating role. By doing so, this study hopes to enhance understanding of how stressful early life exposures can become biologically embedded and adversely affect health, while identifying potential intervenable pathways between CSD and AL.

4. Methods

4.1. Study Design

This study utilized a cross-sectional, correlational design using secondary data from four waves (2003-2010) of the National Health and Nutrition Examination Survey (NHANES). NHANES assesses the health and nutritional status of children, adolescents, and adults in the United States annually through in-home surveys conducted by trained interviewers, as well as physical examinations and laboratory testing completed by healthcare professionals⁵⁶. The public-use data are free, de-identified, and publicly available on the NHANES website.

4.2. Sample Population

Inclusion criteria for the current study was being 12 to 18 years of age and having complete data for the race/ethnicity variable, which was needed for the multi-group comparisons in the mediation model. There were no exclusion criteria, thus all who met inclusion criteria were retained in the final study sample ($N = 1900$ adolescents).

4.3. Measures

4.3.1. Childhood Socioeconomic Disadvantage

The CSD predictor variable was a latent construct created using six measured variables found in NHANES that reflected material and social deprivation experienced by the adolescent, including the following: family poverty-income ratio (PIR), parent

education level, family structure, food security, household crowding, and health insurance status. Family PIR was a continuous variable based on the Department of Health and Human Services' (HHS) poverty guidelines, with higher values indicating a higher family income. Parent education level was a categorical variable measuring the highest degree of education that the parent completed, with the following categories: less than college education or college graduate or above. Family structure was a categorical variable and measured whether the adolescent resided in a one- or two-parent household, with the following categories: married or living with partner (two-parent) or unmarried (one-parent). Household food security was a continuous variable (range 0 to 18) in NHANES measuring the degree to which the quality and quantity of the household members' diets in the previous year were affected by food availability, with higher scores indicating higher food insecurity⁵⁶. Household crowding was a continuous variable created by dividing the total number of people in the household by the total number of rooms, with higher values indicating higher crowding. Health insurance status was a categorical nominal variable measuring if the adolescent was insured, with the following two options: yes or no⁵⁶.

4.3.2. Allostatic Load

The AL outcome variable was a latent construct created using 14 measured biomarkers found in NHANES that were representative of systemic dysregulation across key physiological systems related to AL, including the following: systolic blood pressure (SBP), body mass index (BMI), waist circumference, creatinine, insulin, fasting glucose, glycated hemoglobin (HA1C), high-density and low-density lipoproteins (HDL and LDL), triglycerides, albumin, C-reactive protein (CRP) level, white blood cell count (WBC), and Epstein-Barr viral index (EBV). All indicators for AL were continuous variables and were

transformed into a standard normal variable (with mean = 0 and standard deviation = 1) in order to standardize the metric across the indicators.

4.3.3. Environmental and Behavioral Mediators

Smoke exposure was measured via serum cotinine, a major metabolite of nicotine that can be used as a marker for this exposure⁵⁶. Cotinine was a continuous variable (measured in ng/mL) with higher values indicating a higher smoke exposure⁵⁶. Lead exposure was measured via a serum lead biomarker, which was a continuous variable (measured in µg/L), with higher levels indicating a higher amount of lead present in the blood⁵⁶. Dietary quality was measured with the Healthy Eating Index (HEI), which assessed how closely the adolescents' diet adhered to the key recommendations of the Dietary Guidelines for Americans⁷⁴. HEI was a continuous variable (range 0 to 100), which was calculated using self-reported dietary recall data from NHANES and data from the MyPyramid Food Equivalents database^{56,69,75}, with higher scores indicating a healthier diet. The physical activity variable reflected amount of time per day that the adolescent spent being active (either walking or riding a bicycle). This was a self-reported continuous variable, with higher values indicating more minutes per day of physical activity. The four continuous mediator variables were all standardized prior to analysis (mean = 0, and standard deviation = 1).

4.3.4. Race/Ethnicity

The race/ethnicity variable refers to that of the adolescent participant, which was self-reported by the adolescent (if 16 years or older) or reported by the caregiver. Race/ethnicity was a categorical nominal variable, including non-Hispanic White, non-Hispanic Black, Mexican American, and Other Hispanic groups in NHANES. For the

purposes of this study, the two Hispanic groups were pooled into a larger Hispanic group in order to allow comparison across race/ethnicity groups in statistical analysis. In this study, the three race/ethnicity groups that were used in analyses were African American, White, and Hispanic.

4.3.5. Covariates

Age of the adolescent was considered a potential confounding variable given that the likelihood of developing higher AL increases over time through cumulative exposure to stressors⁷⁶. Age was measured continuously in years, ranging from 12 to 18 years.

Additionally, the gender of the child was also considered a potential confounder, given that some AL research has found gender differences in how stress manifests physiologically as well as AL prevalence^{35,77}. Gender was a categorical dichotomous variable, with the following two options: male or female⁵⁶.

4.4. Protection of Human Subjects

The parent NHANES study was approved by the National Center for Health Statistics Research Ethics Review Board⁵⁶. The current study was reviewed by the Marquette University Institutional Review Board and declared exempt, given this was a secondary data analysis utilizing completely de-identified information.

4.5. Data Analysis

Data analysis for this study was performed in the R software environment⁷⁸ using the lavaan⁷⁹ and semTools⁸⁰ packages. The mediation analysis was performed utilizing the structural equation modeling (SEM) framework^{81,82}, which allowed us to estimate the total, direct, and indirect effects between CSD and AL simultaneously in a comprehensive model. All SEM models were estimated with maximum likelihood (ML) and model fit was

evaluated with multiple local and global fit indices^{81,83,84}. Missing data was handled with full information maximum likelihood (FIML), a modern method to properly handle missing data, which improves parameter recoverability, reduces bias, and increases power^{85,86}. The missing data recoverability was evaluated with the fraction of missing information (FMI), which quantifies the missing data's influence on the sampling variance of a parameter estimate as the proportion of the total sampling variance that is due to the missing data⁸⁵.

4.5.1. Latent Factor and Measurement Invariance Testing

Confirmatory factor analysis (CFA) was used to test the factor structures for the AL and CSD latent constructs through local and global fit-testing. Following fit-testing, measurement invariance for the AL and CSD latent factors were tested across the three race/ethnicity groups. In SEM, measurement invariance testing is a key step that is necessary prior to comparing relationships between latent variables across any kind of group (in this case, across race/ethnicity). By doing so, we are testing how the two latent constructs perform from a measurement standpoint across groups so that the relationships we find in later analyses represent reality and not measurement bias. Measurement invariance testing included configural invariance (factor structure), weak invariance (factor loadings), and strong invariance (indicator means), where the models were gradually compared in the change in fit (ΔCFI) due to the addition of constraints. Once measurement invariance was established, latent parameters between race/ethnicity groups were also compared, which assessed the equality of latent factor means, variances, and correlations between groups using nested model change in χ^2 ($\Delta\chi^2$) values^{81,82}.

4.5.2. Multiple Group Mediation Model Testing

The mediation measurement model included one predictor (CSD), one outcome (AL), and four mediators (cotinine, lead, HEI, and physical activity). All direct, indirect, and total effects were compared between groups. The indirect effects represented the effect of CSD on AL through each mediator, the direct effects represented the specific effect of CSD on AL, and the total effects represented the overall effect of CSD on AL. Model covariates were added to control for their effects on every predictor, mediator, and outcome. These covariate effects were pruned to only keep the covariate paths that showed a meaningful effect. The indirect, total, and difference between effects were tested using the Monte-Carlo resampling method (20,000 samples)⁸⁷⁻⁸⁹, which created empirical distributions that were tested against the null hypothesis value of 0, with the inferences made in function of the 95% confidence intervals (CI).

5. Results

5.1. Descriptive Statistics

The mean age for the study participants was 15.036 years ($SD = 2$, range = 12-18). There was an approximately equal distribution across gender (48.3% female, 51.7% male) and race/ethnicity groups (27.6% White, 37.7% Black, 34.7% Hispanic). See Table 1 for additional descriptive statistics for the AL and CSD indicator variables, as well as for the mediators.

5.2. Model Construction and Measurement Invariance Testing

5.2.1. Construction of Latent Factors

Both AL and CSD were modeled as unidimensional structures that were defined by their respective indicator variables. The factor structure for AL was previously tested by comparing multiple alternative theoretical structures, finding best fit with a

unidimensional AL structure for this adolescent population². The latent factor reliability was high for both AL (MR = 0.988) and CSD (MR = 1.02), indicating a precise estimation of the two constructs. The CSD factor presented a Heywood case^{90,91}, where the CSD latent construct explained 100% of variance in the family PIR indicator for African Americans. According to recommendations by Kolenikov and Bollen⁹⁰ and Savalei and Kolenikov⁹¹, because the 95% CI for this negative variance crossed zero (95% CI = -0.34, 0.25) this finding was likely a result of sampling variability and did not require any correction prior to inclusion in the CSD latent construct.

5.2.2. Establishing Measurement Invariance

The model fit indices and model comparison for the test of factor measurement invariance are presented in Table 2. The configural invariance and weak invariance models both presented good fit across race/ethnicity groups, indicating that the factor structures and factor loadings for the AL and CSD latent constructs measured equivalently. The constraints added for the full strong invariance model presented a change in CFI of 0.043, suggesting that certain indicators for AL and CSD were measuring differently across groups. As a result, we then tested for partial strong invariance, resulting in an acceptable change in CFI of 0.007 with good model fit. Given that the majority of the indicators for CSD and AL demonstrated partial strong measurement invariance, these constructs were determined to be invariant across race/ethnicity and our modeling strategy for further analyses was not affected.

5.2.3. Univariate Means and Variances

Table 3 shows the predictor, outcome, and mediator variable means and variances for each race/ethnicity group. Mean CSD and lead were lower for White adolescents,

cotinine differed across all groups (Hispanics had the lowest and Whites had the highest), and HEI was higher for Hispanics. There were no mean differences for AL or physical activity across groups. African American adolescents had a wider variance in AL, which indicated a greater variability in AL levels for this group. Additionally, CSD had a narrower variance for Hispanics, cotinine variance differed across all groups (Whites had the widest and Hispanics the narrowest), lead had a wider variance for Whites, and physical activity had a wider variance in African Americans. There were no variance differences for HEI across groups.

5.3 Structural Regression Mediation Model

Once measurement invariance had been established and factor parameters had been compared across race/ethnicity, we then proceeded to test the structural regression mediation model of interest to address our three study aims.

5.3.1. Covariate Effects

Age and gender of the child were the two covariates included in our mediation model, which initially were modeled to have an effect on the predictor, outcome, and mediator variables. These effects were then pruned to only retain those that were statistically meaningful in the final model (if they had a $p < .01$ and if the overall model comparison ($\Delta\chi^2$) presented equivalent fit with the covariate effects constrained to 0). Gender had a significant effect on lead for all groups (African American = 0.361 [0.078 SE], White = 0.254 [0.091 SE], Hispanic = 0.520 [0.083 SE]), as well as on smoking (0.253 [0.080 SE]) and HEI (-0.255 [0.081 SE]) for Hispanics. Age had a significant effect on AL (African American = 0.122 [0.021 SE], White = 0.120 [0.023 SE], Hispanic = 0.147 [0.021 SE]) and smoking (African American = 0.141 [0.020 SE], White = 0.136 [0.023 SE], Hispanic = 0.084

[0.020 SE]) for all groups, as well as on lead for African Americans (-0.110 [0.020 SE]).

There were no other retained covariate effects in the final measurement model.

5.3.2. Total, Direct, and Indirect Effects of CSD on AL

The total, direct, and indirect effects of CSD on AL are presented in Figures 2 through 4 for African American, White, and Hispanic adolescents. The total effects of CSD on AL that rejected the null hypothesis was for White adolescents only ($\beta = 0.105$ [0.016, 0.204]), with total effects that were smaller in magnitude and nonsignificant for both African American ($\beta = 0.068$ [-0.003, 0.149]) and Hispanic ($\beta = 0.008$ [-0.080, 0.096]) adolescents. Therefore, higher levels of CSD predicted higher levels of AL for all three race/ethnicity groups, with the measurement model capturing the largest amount of total variability in AL for the White adolescents.

In models adjusting for our mediators of interest, CSD had a small, positive direct effect on AL for both African American ($\beta = 0.111$, SE = 0.039 [0.041, 0.195] and White ($\beta = 0.105$, SE = 0.048 [0.017, 0.205]) adolescents, which was smaller in magnitude and not statistically significant among Hispanic adolescents. CSD also had a small, positive direct effect on lead for African Americans ($\beta = 0.176$, SE = 0.04 [0.108, 0.264]), Whites ($\beta = 0.126$, SE = 0.048 [0.034, 0.222]), and Hispanics ($\beta = 0.187$, SE = 0.046 [0.105, 0.287]), indicating higher CSD predicted higher lead levels for all groups. CSD also had a small, positive direct effect on cotinine for African Americans ($\beta = 0.121$, SE = 0.04 [0.047, 0.206]) and Whites ($\beta = 0.123$, SE = 0.049 [0.033, 0.224]), with a smaller, nonsignificant direct effect found for Hispanics. This finding indicated that higher CSD predicted higher levels of smoke exposure for these two groups. Lead was found to have a small, negative direct effect on AL for African Americans adolescents only ($\beta = -0.183$, SE = 0.041 [-0.263, -0.102]), indicating

that higher lead levels predicted lower AL for this group. Lastly, physical activity had a small, positive direct effect on AL for White adolescents only ($\beta = -0.143$, $SE = 0.073$ [0.009, 0.293]), indicating higher levels of physical activity predicted lower AL for this group. All other direct effects in the model did not reject the null hypothesis.

Based on the Monte-Carlo 95% CI resampling method, there was a single indirect effects pathway between CSD and AL that rejected the null hypothesis, which was the mediating pathway through lead for African American adolescents ($\beta = -0.032$ [-0.056, -0.015]). This finding indicated that when CSD increased, lead levels also increased, which resulted in decreased AL for this group of adolescents. There were no other significant indirect pathways in the tested mediation models.

5.3.3. Model Explained Variance

In Figures 2 through 4, the explained variance for each pathway in the mediation model is presented for each race/ethnicity group. For African Americans, cotinine and lead had the highest explained variance of the mediator variables (8.7% for cotinine and 10.3% for lead), indicating that these were the mediators best predicted by CSD in the model. For Whites, cotinine had a similar explained variance with the African Americans (8.6%), though the explained variance for lead was far smaller in magnitude for this group (3.2%). Hispanic adolescents had a smaller explained variance in cotinine (4.2%) from the other two groups, but a larger explained variance in lead (9.6%). The explained variance for AL was similar across groups, ranging from 8.2% (Hispanics) to 10.2% (African Americans). In total, these findings indicated that the proposed mediation model had low overall predictive ability, as it accounted for a small proportion of explained variance in AL for all groups.

6. Discussion

The sole total effects pathway between CSD and AL that was statistically significant was for the White adolescents, which suggested that the mediation model best accounted for the relationship between CSD and AL in this population. We had hypothesized that minority adolescents might demonstrate a stronger association between CSD and AL, given the potential for greater exposure and vulnerability to discriminatory stress⁹²⁻⁹⁴, which could contribute to adverse health behaviors to a greater extent as coping mechanisms^{42,69,70}. However, we found that the White adolescents had the largest and only significant total effects pathway between CSD and AL, rather than the minority groups, which could be related to several factors. First, it is possible that there are other mediating variables that are more relevant for African American and Hispanic adolescents in contributing to AL that were not included in this study's mediation model. For example, past research has shown that early life social support can be protective for development of AL when the child or adolescent has a supportive caregiver that can buffer the stress from disadvantage^{14,64}. It is possible that the African American and Hispanic adolescents in this study population had a greater social support network in place, which could have shielded them from the negative effects of CSD^{95,96}.

Additionally, resilience to stress, which develops over time based on past success with stress coping, has been thought to affect the degree to which CSD can influence AL development^{97,98}. As such, if minority individuals are able to successfully cope with the increased toxic stress that is unique to those populations, they could have higher stress resilience than their White counterparts, which could in turn lead to a small total effect of CSD On AL. Incorporating measures of both social support and resilience in future

pediatric AL research will aid in clarifying differences in experiences of CSD across racial/ethnic groups, as well as understanding how those differences translate into risk for disease across the life course.

In the model adjusting for the mediating pathways, there was a small, positive direct effect of CSD on AL for both African American and White adolescents, with the largest direct effect found for African Americans. In contrast, the direct effect of CSD on AL for Hispanic adolescents was much smaller in magnitude than the other two groups and was nonsignificant. These findings suggest that there might be differences in the most relevant pathways linking CSD and AL between African American and Hispanic adolescents. A larger direct effect for the African Americans suggests that the included mediators contribute less to the overall variance in AL, while for Hispanics those mediators explained the relationship between CSD and AL to a greater extent. It is possible that there are other more important mediating pathways for African American adolescents that were not accounted for in the model, or that the Hispanic adolescents had protective factors which buffered the effects of CSD on AL. Despite experiencing high levels of socioeconomic disadvantage and associated stressful exposures, Hispanics may experience relatively low levels of stress, which could contribute to their paradoxical health advantage, known as the “Hispanic paradox”⁹⁹. This lends support to our findings that African American and Hispanic adolescents might experience CSD, and the resultant toxic stress, in different ways, with different risk and protective factors determining their development of AL.

Another key finding from our analysis was the identification of lead as a potentially important mediator of the relationship between CSD and AL, which was only significant for the African American adolescents. While we found a positive association between CSD and

lead exposure among all three race/ethnic groups, the magnitude of effect was larger for African American and Hispanic adolescents, compared to their White peers. Due to historical residential segregation into low-quality neighborhoods, minority adolescents are more likely to be exposed to higher levels of lead through soil, water, and air contamination^{58,100}. Lead is particularly caustic for health given that it stored in long-term repositories in our bones and soft tissues, so even if the most significant lead exposure was years prior during infancy or early childhood, it is possible for lead to leach back into the bloodstream long after the exposure has ceased¹⁰¹. This environmental risk factor has the potential for great explanatory power for some of the health disparities that we see in this country that tend to be more highly distributed amongst minority populations. Health care providers need to continue their awareness of the potential for ongoing lead exposure when assessing children and adolescents from more disadvantaged neighborhoods, even in older individuals who have more distant lead contamination histories.

The directionality of the relationship between lead and AL within the CSD-AL mediating pathway was not in the anticipated direction across all three racial/ethnic groups. The damaging effects of lead on physical and psychological health has been well-documented⁵⁷, especially for young children who are more vulnerable to its adverse effects⁵⁸. However, evidence linking environmental lead exposure directly to development of AL is more limited⁵⁹, with no known research to date examining this relationship among adolescent populations. The few human studies that have examined the effects of lead on the HPA axis have conflicting findings thus far, with reports of both blunted and heightened cortisol awakening responses in children¹⁰² and adults^{59,60}. If lead disrupts HPA axis functioning, it is logical to expect that this effect over time will contribute to higher AL with

increasing lead exposure, which is not consistent with our findings. However, given that lead only transiently remains in the bloodstream following acute exposure and is retained in an individual's bones and soft tissues over time¹⁰¹, it is likely that for adolescents, their highest exposure to lead was when they were younger (< 6 years old) due to high incidence of hand-mouth behaviors during early development⁵⁷. While adolescents may experience ongoing lead contamination through water, air, and soil (especially in low-quality, segregated neighborhoods), the quantity of lead exposure tends decrease as we get older, which was found in in this study. Thus, the reversed directionality between lead and AL in our study findings suggests that measurement of cumulative lead exposure over one's life might be best estimated with measures that can more precisely estimate cumulative exposure over time.

The overall predictive ability of the structural mediation model specified in our study was low, as evidenced by small effect sizes and low explained variance in AL across all groups. The low explanatory power found in this study is likely due a combination of factors. First, it is plausible that the adverse effects of CSD on AL observed in previous studies only becomes evident across multiple body systems in adulthood. Thus, in this younger adolescent population, the magnitude of the effect between CSD and AL is likely much smaller, and as a result harder to detect. Additionally, AL is a complex variable that is affected by a wide variety of risk factors and exposures that contribute to a dysregulated stress response, subclinical disease across multiple body systems, and eventual chronic disease^{17,103}. Thus, there are several extraneous variables previously linked to AL that we could not include in the measurement model (due to unavailability in the dataset). Such variables include previous life experiences (particularly important are adverse childhood

experiences)^{10,104}, social support¹⁰⁵, genetic and epigenetic factors^{9,106}, and perceived discrimination⁹⁴. Adverse childhood experiences (ACEs), social support, and epigenetic DNA methylation would likely would serve as mediators between CSD and AL, as these factors either confer risk or protection from the adverse effects of CSD. Genetic predisposition to stress and racial discrimination likely serve moderating roles, as they make some individuals more susceptible to the adverse effects of CSD, but don't fall on the causal pathway between CSD and AL. Lastly, for the Hispanic group in particular who had the poorest overall model performance, this could in part be attributed to the heterogeneity of this group that resulted from combining two smaller Hispanic populations in NHANES. As such, this heterogeneity could have confounded some of the relationships between variables and resulted in lower overall effect sizes for this group.

7. Study Limitations

These findings should be interpreted in the context of several study limitations. The study design was cross-sectional, limiting our ability to make casual inference due to temporal ambiguity in the variables of interest. However, given that there is theoretical and empirical support identifying CSD as antecedent to AL, it is reasonable to assume that CSD experienced in early life will precede physiologic alterations and environmental and behavioral mediators of interest. Additionally, we were also unable to measure change in the predictor, mediating, and outcome variables over time, all of which have the potential to be dynamic, which could impact findings. It would have been informative to measure how long the adolescents had experienced CSD, as well as tracking changes in the AL biomarkers for those individuals over time to illustrate the development of AL as a dynamic process. Additionally, in NHANES there was no measurement of the

neuroendocrine hormones, which would have been ideal to include in the AL latent construct variable to provide input from the neuroendocrine system, as this is a key component of the AL process. Despite these limitations, this study contributes to the existing literature base by using a robust SEM approach to model complex relationships between CSD, environmental and behavioral risk factors, and AL across race/ethnic groups in an understudied adolescent population.

8. Conclusion

To our knowledge, this is the first study to utilize latent modeling to test relationships between CSD and AL in an adolescent population that assesses the total, direct, and indirect effects of CSD on AL operating through environmental and behavioral factors, while also examining variation in these effects across race/ethnicity. Findings from this study highlight the importance of exposure to CSD as a predictor for development of AL for adolescents, while also elucidating different mechanisms at play across different racial/ethnic populations. Allostatic load provides a powerful and integrative framework for understanding how adverse social exposures, such as CSD, can affect health and disease risk through biological stress pathways as well as downstream effects on health behaviors. Taking this kind of approach, we will be better equipped to identify which pathways between CSD and AL are more important for which populations, which is more likely to promote health equity for all. Future AL research in pediatric populations should aim to incorporate not only psychobiological, social, and environmental mechanisms related to AL development, but also molecular mechanisms (i.e. DNA methylation of key stress regulation genes), which will enhance our understanding of how genes and the environment interact to shape the health of children.

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10. Conflicts of Interest

The authors have no conflicts of interest to declare in conducting this research or preparing this manuscript for publication.

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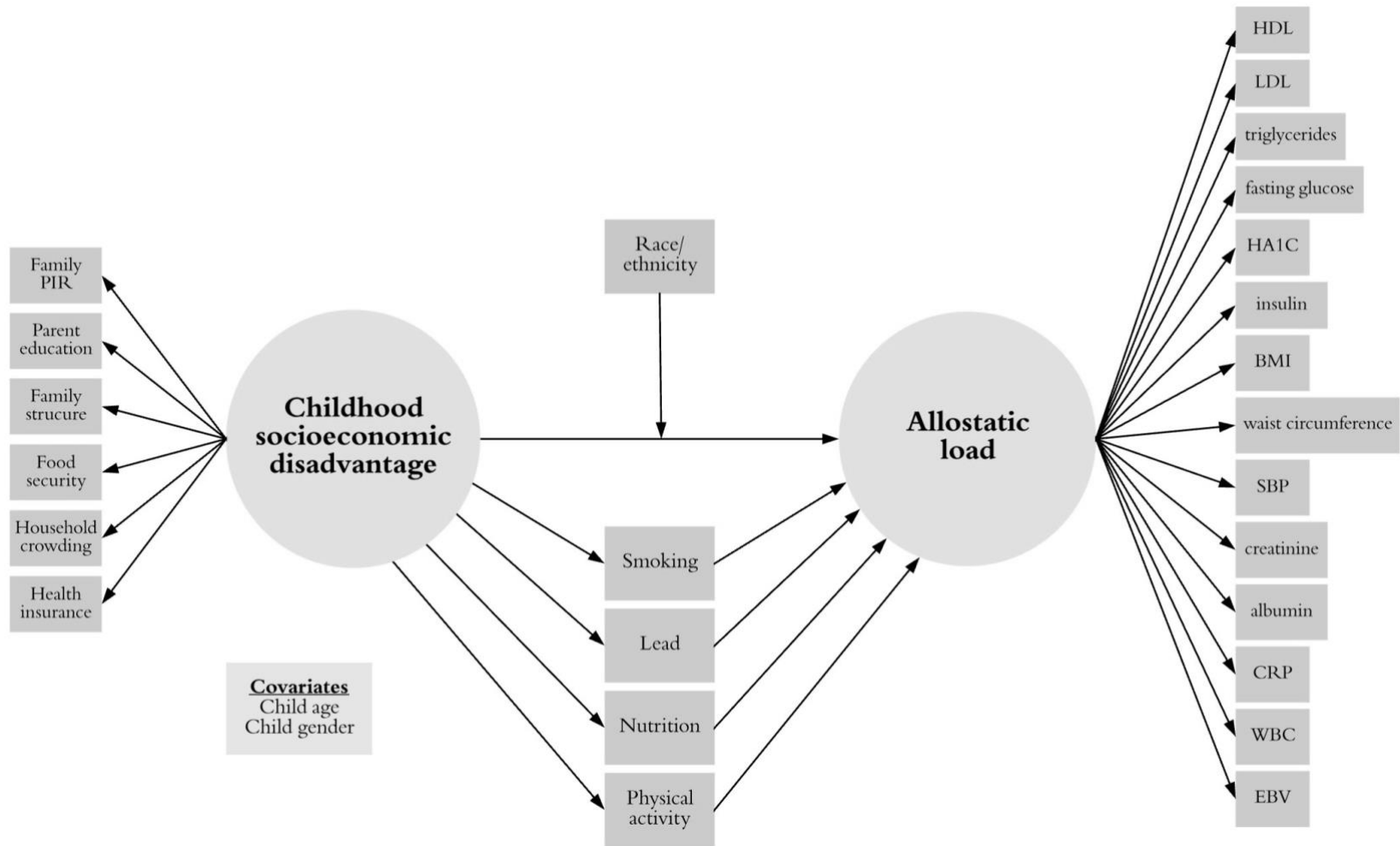


Figure 1. Study Mediation Model

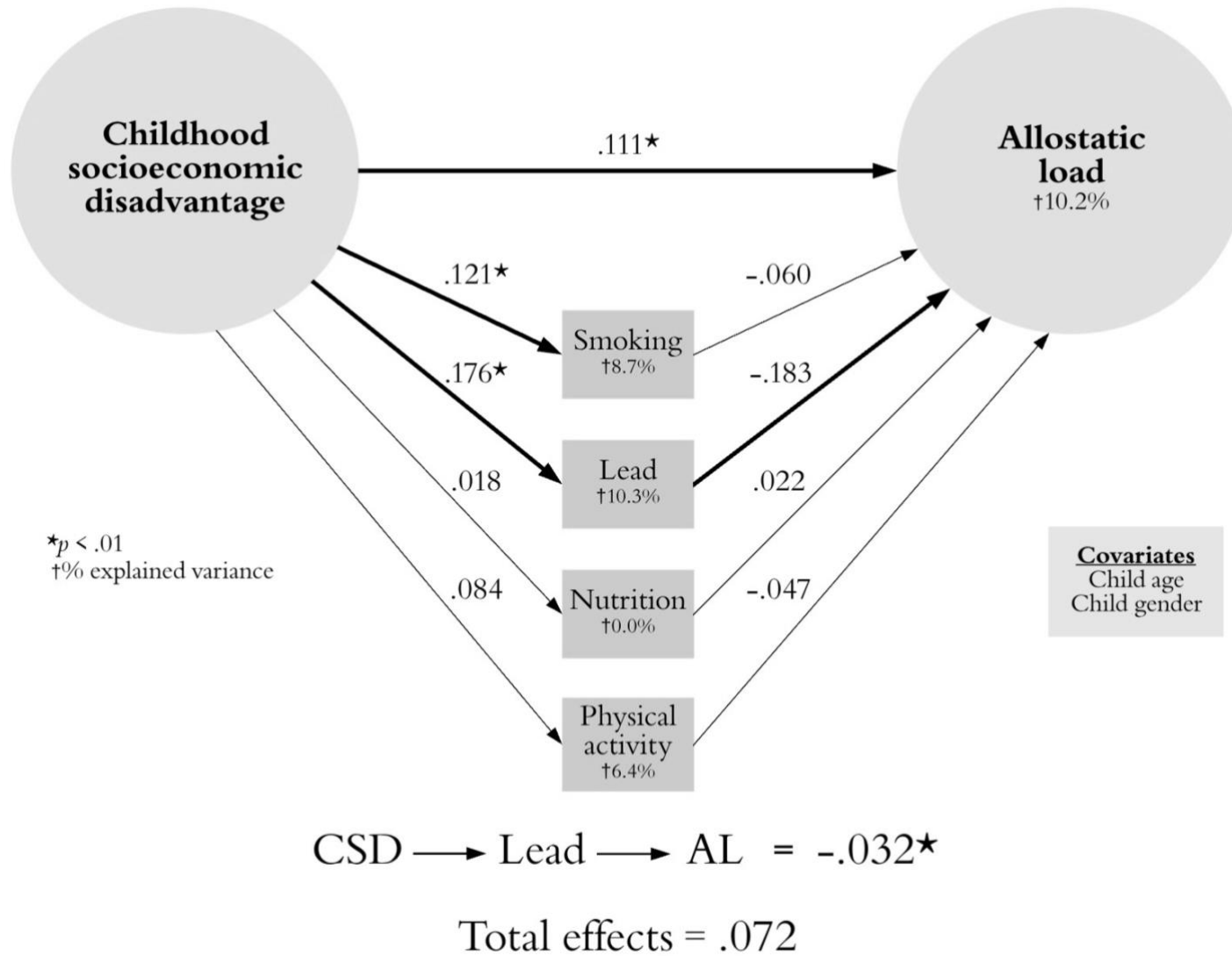


Figure 2. African American Total, Direct, and Indirect Effects

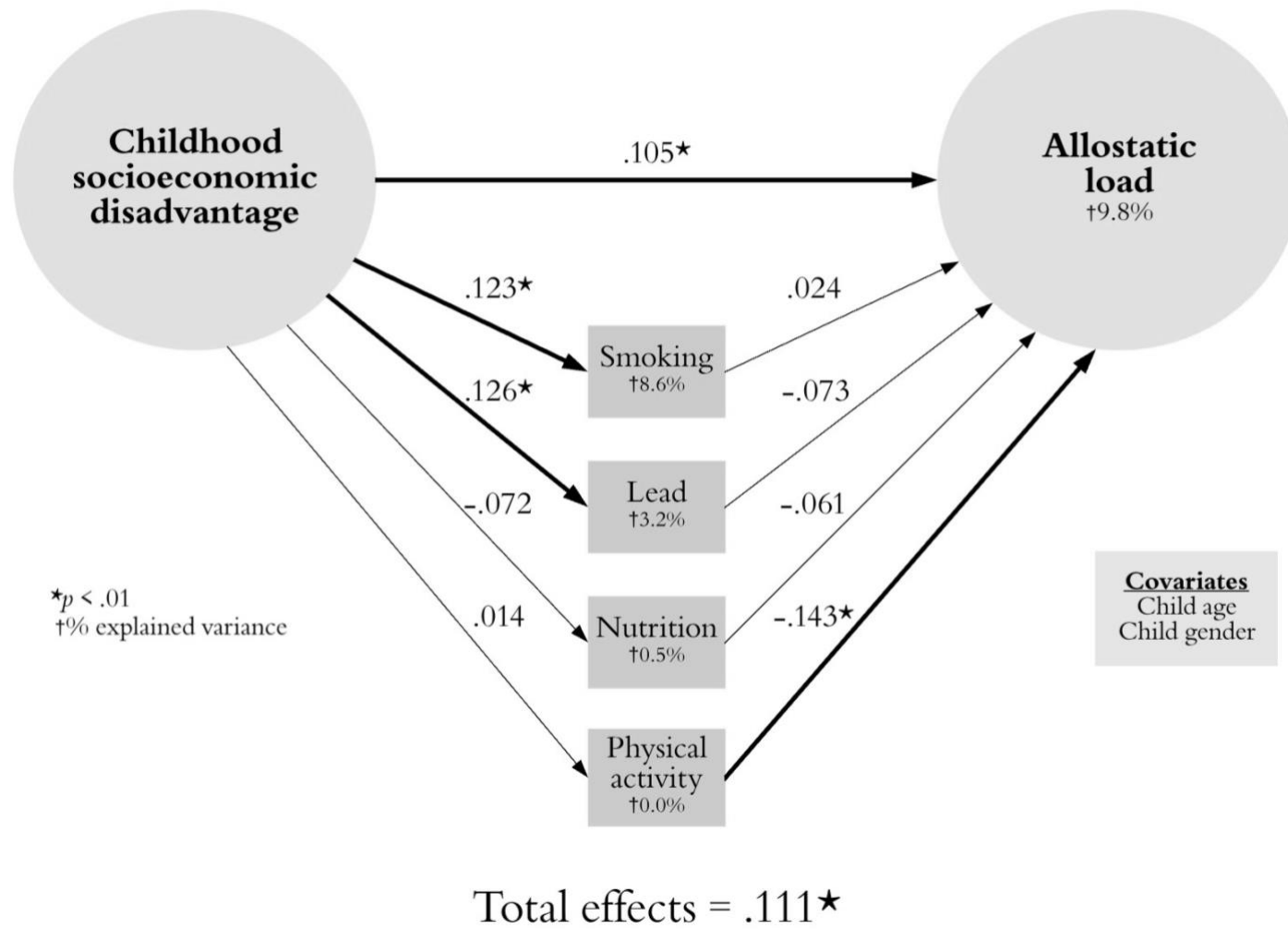


Figure 3. White Total, Direct, and Indirect Effects

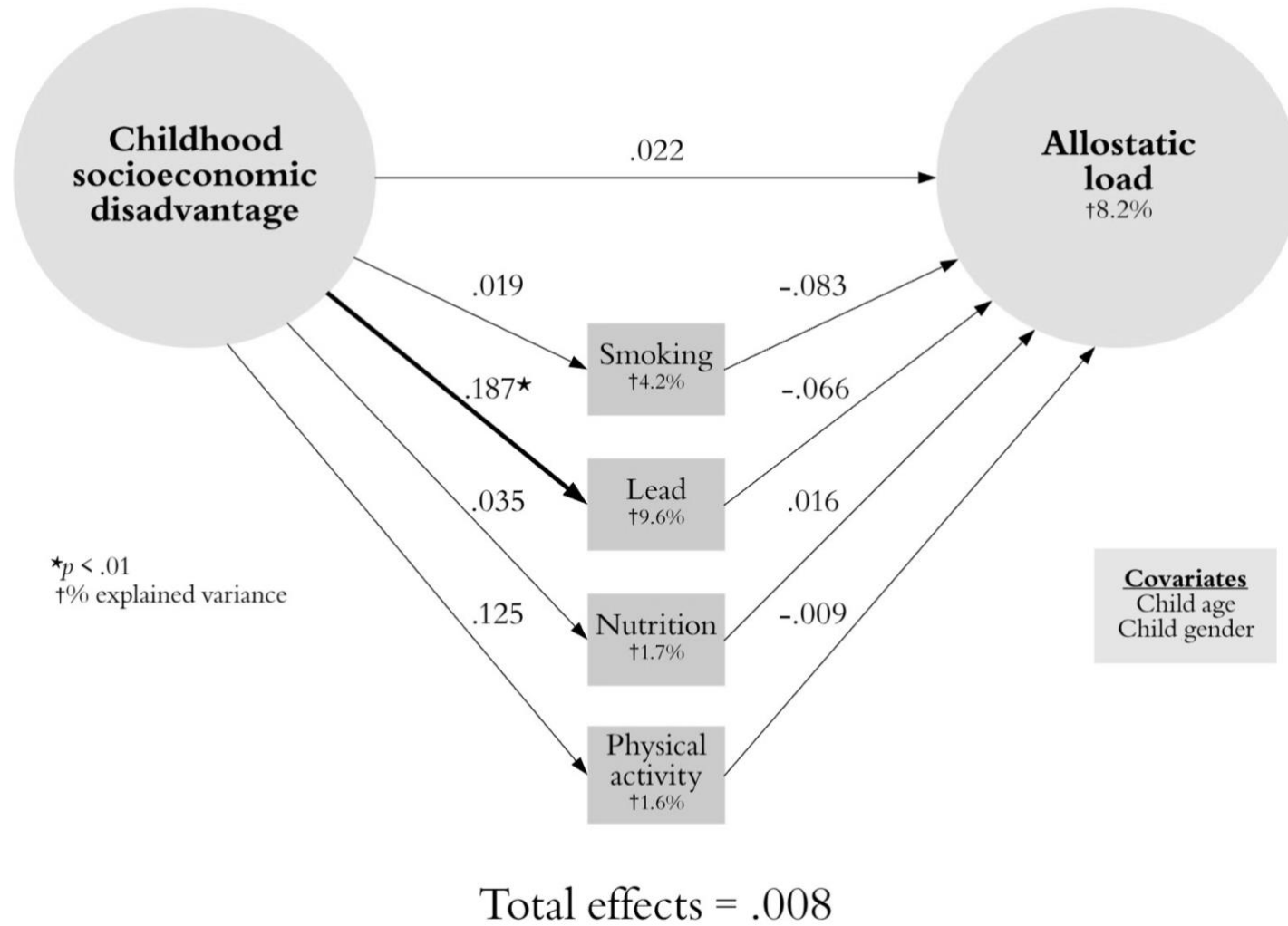


Figure 4. Hispanic Total, Direct, and Indirect Effects

Table 1. Descriptive Statistics for Study Variables

Variable	Total Sample (N = 1900)		White (N = 525)		African American (N = 716)		Hispanic (N = 659)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Allostatic load</i>								
SBP	108.995	10.171	108.422	10.463	109.966	9.847	108.435	10.211
Creatinine	0.746	0.162	0.753	0.158	0.785	0.162	0.7	0.154
HDL	53.205	12.701	51.884	12.744	55.648	13.356	51.612	11.515
LDL	89.106	26.606	89.521	28.201	88.901	27.815	89.035	23.855
Triglycerides	85.797	50.815	96.288	60.613	71.26	34.176	95.004	55
HA1C	5.217	0.442	5.163	0.385	5.275	0.5	5.197	0.409
Fasting glucose	90.294	14.292	93.222	22.361	88.342	10.201	90.372	9.398
Insulin	12.957	13.67	12.283	14.693	13.734	15.182	12.556	10.709
BMI	23.709	5.995	23.254	5.579	24.388	6.799	23.34	5.289
Waist circ	81.152	15.009	81.569	14.413	80.388	16.454	81.642	13.779
Albumin	4.376	0.337	4.44	0.33	4.246	0.325	4.464	0.312
EBV	3.539	1.75	2.768	1.961	3.888	1.616	3.756	1.523
CRP	0.256	0.623	0.21	0.369	0.369	0.665	0.259	0.715
WBC	6.873	2.125	7.35	2.17	5.887	1.877	7.565	1.934
<i>Childhood socioeconomic disadvantage</i>								
Family PIR	2.052	1.545	2.858	1.634	1.186	1.463	1.652	1.298
Family structure	0.605		0.767		0.396		0.692	
Parent education level	0.115		0.194		0.11		0.057	
Food security	1.877	3.472	0.964	2.707	2.321	3.875	2.123	3.419
Crowding	0.866	0.552	0.682	0.409	0.85	0.424	1.031	0.705
Insurance	0.831		0.938		0.868		0.705	
<i>Mediators</i>								
Cotinine	15.467	56.496	27.408	75.866	15.039	55.759	6.828	33.978

Lead	1.303	1.232	1.043	1.662	1.466	1.04	1.326	0.979
Nutrition	42.642	12.174	41.671	12.407	41.812	11.596	44.338	12.437
Physical activity	36.557	46.804	33.455	35.706	38.805	57.393	35.876	38.464

† *Abbreviations:* SBP; systolic blood pressure, HDL; high-density lipoprotein, LDL; low-density lipoprotein, HA1C; glycated hemoglobin, BMI; body-mass-index, waist circ; waist circumference, EBV; Epstein-Barr viral index, CRP; C-reactive protein, WBC; white blood cell count, PIR; poverty-to-income ratio, SD; standard deviation

Table 2. Measurement Invariance Model Comparison

Model	χ^2 (df)	CFI	Gamma Hat	RMSEA	$\Delta\chi^2$ (Δdf)	ΔCFI	Keep?
Configural	1650.1 (717)	.881	.961	.045 (.042,.048)	–	–	–
Weak	1767.1 (753)	.871	.957	.046 (.043,.048)	116.9 (36)	.010	Yes
Strong	2128.2 (779)	.828	.944	.052 (.049,.055)	361.2 (26)	.04	No
Strong partial	1844.2 (774)	.863	.955	.047 (.044,.049)	77.1 (21)	.007	Yes

† *Abbreviations:* χ^2 ; chi-square exact-fit, df; degrees of freedom, CFI; comparative fit index, $\Delta\chi^2$; change in chi-square exact-fit, Δ df; change in degrees of freedom, Δ CFI; change in comparative fit index

Table 3: Univariate Means and Variances

	African American	White	Hispanic
<i>Means (SE)</i>			
AL	0	0.071 (0.054)	0.077 (0.050)
CSD	0	-0.710 (0.070)	0.118 (0.052)
COTIN	-0.005 (0.039)	0.204 (0.062)	-0.152 (0.024)
LEAD	0.131 (0.033)	-0.218 (0.062)	0.017 (0.032)
HEI	-0.068 (0.036)	-0.081 (0.045)	0.139 (0.041)
PHYS	0.039 (0.062)	-0.064 (0.052)	-0.027 (0.044)
<i>Variances (SE)</i>			
AL	1	0.732 (0.061)	0.644 (0.051)
CSD	1	1.126 (0.125)	0.637 (0.079)
COTIN	0.974 (0.054)	1.798 (0.118)	0.361 (0.021)
LEAD	0.713 (0.039)	1.815 (0.118)	0.631 (0.036)
HEI	0.906 (0.049)	1.036 (0.065)	1.042 (0.059)
PHYS	1.496 (0.106)	0.580 (0.056)	0.661 (0.050)

† Abbreviations: SE; standard error, AL; allostatic load, CSD; childhood socioeconomic disadvantage, COTIN; cotinine, HEI; Healthy Eating Index, PHYS; physical activity