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The Effects of Poverty and Allostatic Load on the Development of Chronic Disease

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The Effects of Poverty and Allostatic Load on the Development of Chronic Disease

by

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ABBREVIATIONS

BRHS	Biopsychosocial Religion and Health Study
AHS-2	Adventist Health Study – 2
SDA	Seventh-day Adventist
SES	Socioeconomic Status
AL	Allostatic Load
CCI	Charlson Comorbidity Index

ABSTRACT OF THE THESIS

The Effects of Poverty and Allostatic Load on the Development of Chronic Disease

by

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Dr. Kelly Morton, Chairperson

Research suggests that there is a significant impact of poverty on poor health outcomes. Poverty is associated with limited access to education and healthcare, increased exposure to violence, and chronic stress that contribute to the development of chronic diseases. The poverty and chronic disease relationship is potentially associated with chronically elevated stress biomarkers. The present study investigated the relationship between demographics, poverty (during childhood, young adulthood, and mid/late adulthood), allostatic load—a cumulative measure of system dysregulation—and the Charlson Comorbidity Index, a measure of chronic disease and mortality, using data from the Biopsychosocial and Religion and Health Study (BRHS; Lee et al., 2009) a subset of participants in the Adventist Health Study-2 cohort of Seventh-day Adventists. Of this subset 387 were examined on demographics, poverty, allostatic load (preclinical elevations in 13 biomarkers), chronic diseases and likelihood of mortality. Poverty experienced during childhood—but not during young adulthood or older adulthood—predicted chronic disease severity in late life. Ethnicity moderates the child poverty and AL relationship such that Black individuals have higher risk of elevated stress markers than their White counterparts. Allostatic load has a stronger impact on comorbidity in younger individuals, suggesting a premature aging effect.

CHAPTER ONE

INTRODUCTION

Physiological Conceptualization of Stress

Severe or chronic stress causes "wear and tear" on the physiological systems that accumulates over time; demands by the environment can create an imbalance in physiological systems (Wenzel, Glanz, & Lerman, 2002). This disruption may affect physical and/or psychological systems, requiring adaptational stress responses to reestablish balance. Typically, organisms cope with the demands through cognitive, affective and/or behavioral means and homeostasis is maintained. However, when demands outpace coping abilities, homeostasis is not maintained, functioning is impaired, and stress continues to disrupt systems. When stress is experienced at chronic or extreme levels, functioning becomes impaired across multiple organ systems resulting in increased morbidity and mortality risk (Schneiderman, Ironson, & Siegel, 2005). Chronic stress is particularly taxing because it requires cognitive, affective and/or behavioral systems to continuously work to compensate for such demands. Fatigue in these systems eventually leads to erosion in biological systems. When biological stress regulation fails, chronic health conditions such as high blood pressure, heart disease, diabetes, asthma, arthritis, and depression may follow (Medline Plus, 2011). With age, the risk of developing chronic disease or precursors to chronic disease increases. Chronic stress may cause premature aging and potentiate the risk of disease development.

Prevalence of comorbid, chronic conditions in older adults escalates with advancing age. Up to 45% of the general population and 88% of those over age 65 have at least one chronic health condition (Wolff, Starfield, & Anderson, 2002). About 57

million Americans currently have multiple, chronic conditions and it is estimated that this number will increase to 81 million by 2020 as the population ages, particularly with the "baby boomer" generation reaching late life. Ongoing research on the relationship between stress and effects on chronic disease prevalence and progression, and how to predict these conditions in preclinical biomarker elevations may further our understanding of the mechanisms linking chronic stressors to chronic disease and premature aging.

The body's automatic response to perceived stress involves the release of glucocorticoids and epinephrine (Tsigos & Chrousos, 2002). When acute stress is perceived, both the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are activated. First, increased SNS activity triggers the secretion of epinephrine from the adrenal medulla. Next, HPA activation triggers the secretion and transport of corticotropin-releasing hormone (CRH) to the anterior pituitary which then stimulates the secretion of the adrenocorticotropic hormone (ACTH) which enters circulating blood. ACTH, in turn, activates the adrenal cortex to release glucocorticoids into systemic circulation. Cortisol—the primary glucocorticoid stress hormone in humans—and sympathetic activation are involved in regulating and storing energy in organ systems to meet environmental demands. Removal of the acute stressor abates SNS activation. Additionally, when an acute stressor is no longer present, cortisol controls negative feedback effects to inhibit further activation of the hypothalamus and pituitary gland. The SNS is considered the "fight or flight" system triggered during times of acute arousal, vigilance, or perceived threat causing the sensation of an "adrenaline rush" commonly felt during high stress moments.

Chronic or repeated demands for the activation of these stress hormones may jeopardize healthy responses, causing organs to habituate to over- or under-respond to stressors (McEwen & Stellar, 1993). Neuroendocrine profiles that deviate from normal, healthy responses include: repeatedly activated, non-habituating, prolonged, and inadequate responses (McEwen, 2006). Over time, the chemical fluctuations cause system dysregulation in metabolic, inflammatory, and cardiovascular (CVS) biomarkers because of excessive activation. Short-term activation of the HPA axis is crucial for the acute stress response, however, chronic HPA activation results in unhealthy elevations of glucocorticoids, serum glucose, and lipid levels, immunosuppression, and increased cardiovascular tone, which are associated with biological aging and chronic diseases (Seeman et al., 1997). For example, excessive physiological activation may lead to tertiary health problems, such as cardiovascular diseases (i.e., strokes and heart attacks), metabolic syndromes (i.e., diabetes), and premature mortality (McEwen & Stellar, 1993).

Allostatic Load

McEwen's (1998) Allostatic Load (AL) theory explains this link between chronic stress and poor health effects. He posits that the excessive strain of repeated acute and/or chronic stressors has long-lasting effects on the stress-sensitive neuroendocrine, cardiovascular, immune, and neural systems. AL as such is a measure of preclinical elevations in biomarkers across these sensitive organ systems caused by over exposure to stressors, leading to chronic wear and tear and eventually disease (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). AL is a cumulative, multisystem measure of physiological dysregulation that may determine preclinical pathology and assess latent risk for

comorbidities before a disorder is overtly present (Karlamangla et al., 2002). Theories often explain biological systems as linear and rigid models of homeostasis that aim primarily to reduce fluctuations in the system to avoid negative health outcomes (Canon, 1932). General systems theories look at each system individually instead of cumulatively and simultaneously. Over time, these general systems theories have shifted into more dynamic, nonlinear approaches, examining physiological systems as interactive with more fluctuations and less rigidity (Carlson & Chamberlain, 2005). The concept of allostasis and allostatic load emphasize this dynamic and nonlinear approach by measuring dysregulation in multiple adaptive systems as a collective. As such, allostatic load provides a life course, multi-system perspective of maladaptive physiological responses to stressors that may predict pathology before symptoms of disease overtly arise (Karlamangla et al., 2002).

Measuring Allostatic Load

AL provides a comprehensive summary of multiple biological system dysregulations that may result from excessive stress exposures and lead to premature aging. Seeman, McEwen, Rowe, and Singer (2001) developed a measure of AL that includes 10 parameters of biological functioning. Specifically, gathered blood and urine samples are used to determine functioning of the HPA axis, SNS (e.g., primary mediators), cardiovascular system, and metabolic processes (e.g., secondary mediators). The biological parameters include (a) systolic and (b) diastolic blood pressure, (c) waist-to-hip ratio, (d) total cholesterol/high-density lipoprotein (HDL) ratio, (e) blood plasma levels of glycosylated hemoglobin (HbA1c), (f) urinary cortisol, (g)

urinary norepinephrine, (h) urinary epinephrine, (i) HDL cholesterol, and (j) dehydroepiandrosterone sulfate (DHEA-S). Individuals are flagged as "high-risk" if they fall above or below the calculated threshold of either the upper or lower quartile (depending on the specific measure) of the sample on a standard distribution of collected biomarker data (Geronimus, 2006). Individuals are allocated one point for each of the ten parameters in which they score at "high-risk." Additionally, individuals taking medication for diabetes, hypertension, or high cholesterol are assigned one point for HbA1c, blood pressure, or total cholesterol, respectively, even if their current biomarker levels are not at the designated high-risk quartile, because an exisiting chronic disease diagnosis signals deterioration to the system has occurred though medications may control the biomarker levels.Higher scores indicate greater AL and risk for morbidity and mortality (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002). The HPA activation and elevated cortisol levels associated with AL predict a wide range of risk factors including obesity, hypertension, diabetes, hyperlipidemia, and accelerated brain aging with impaired cognitive and psychological functioning (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). How AL is related to different stressors, such as poverty at different times of life is of potential interest. Early stress exposure, for example, may damage the regulation systems and lead to cumulative damage. Chronic long-term stressors may be equally as damaging.

Conceptualization of Poverty

According to the National Center for Children in Poverty (2010), 19% of American children (14 million) live in financially impoverished families. From 2000 to

2008, child poverty increased by 21% and continues to rise. Wood (2003) defines poverty as an economic state that does not allow for adequate provision of basic family and child needs, such as sufficient food, clothing, and housing. The culture and debilitating conditions of poverty have a significant effect on child development and health (Evans, 2004). Children born into poverty are at risk for developmental delay, learning disability, grade retention, expulsion or suspension, high school dropout, and young adult unemployment. Children living in poverty show significant deficits in several indices of cognitive and socioemotional development, including verbal memory, vocabulary, math and reading achievement, and a variety of behavioral problems (Korenman, Miller, & Sjaastad, 1995). Neurocognitive development is also compromised, particularly affecting brain regions (e.g., left perisylvian, medial temporal region, prefrontal cortex, anterior cingulate) that regulate working memory, cognitive control, language, and memory (Farah et al., 2006). In terms of physical health, compared to their peers, impoverished children are more likely to have poor to fair rather than excellent self-reported health. Impoverished children have higher rates of hospital admission, disability, and early mortality likely due to poor access to preventative, curative, and emergency medical care, while also having worse nutrition, parenting and housing, as well as higher exposure to harmful toxins like pollution (Evans, 2004). As such, poverty often presents as a milieu of factors aside from insufficient basic needs being met (e.g., food, clothing, and housing). The negative effects of child poverty are often mediated by an accumulation of multiple environmental risks. These risks permeate relations within the home, including an increased exposure to family turmoil, violence, and separation in unstable and chaotic households (Evans, 2004). Children living in impoverished conditions have less social

support, less responsive parents, and experience more authoritarian parenting. They are also read to less often, watch more TV, and have less access to books and computers. Environmental risks also pervade their living conditions, including increased exposure to air and water pollution, and crowded, noisy, lower quality home conditions, as well as dangerous neighborhoods that offer fewer community and educational resources. Each psychosocial and physical risk factor of poverty has adverse developmental effects on children; exposure to such cumulative risks over time leads to physical, socioemotional, and cognitive morbidities in such children. Charmandari, Tsigos, and Chrousos (2005) suggest that childhood is a critical period and that children and adolescents, compared to adults, are more vulnerable to the physiological effects of stressors.
These effects may be pervasive and likely have lasting effects into adulthood (Evans & Wachs, 2010).

In a study on life course poverty, Rank and Hirschl (2001) found that a significant percentage of individuals will encounter poverty at some point in adulthood, particularly during early (ages 20-40) and later adulthood (ages 60-80). The prevalence of poverty in adulthood is related to race, education, and, to a lesser extent, gender. African Americans, individuals with less than 12 years of education, and women are more likely to experience poverty at some point in adulthood. Research on the effects of poverty in older adults suggests a significant social gradient in health, where socioeconomic status is linked to self-reported health status, physiological health, and psychological well-being (Marmot & Fuhrer, 2004). One theory is that poverty-related stress, influences an individual's ability to cope and regulate physiological imbalances, leading to poorer physical health (Wadsworth, Raviv, Reinhard, Wolff, Santiago, & Einhorn, 2008).

Individuals who undergo chronic poverty (difficulty meeting expenses for basic needs for an extended period) are more vulnerable to negative health outcomes due to elevated HPA axis activation, which has been linked to several comorbid chronic diseases and deterioration of immune functioning (Taylor, Repetti, & Seeman, 1997). Victims of chronic stress tend to repetitively cycle through the three-phase syndrome of alarm, resistance, and exhaustion, which over time leads to cumulative damage to biological systems (Taylor, Repetti, & Seeman, 1997). McEwen and Stellar (1993) posit that chronic stressors can impair the body's ability to meet these demands, creating allostatic load and cumulative damage. They argue that increases in stress leads to cumulative damage on the body that results in early morbidity and mortality. Chronic poverty or poverty at certain developmental stages may create this type of chronic stress and subsequent physiological damage.

Many studies have investigated the association between stress and health, (McEwen, 1993, 1998, 2007 & 2008, Schneiderman, Ironson, & Siegel, 2005, Glei, Goldman, Chuang, & Weinstein, 2007), but few have examined the mediating physiological pathways that link poverty to chronic disease. Additionally, researchers often examine the stress of poverty in association with individual biomarkers (i.e., perceived stress and cortisol levels, life challenges and epinephrine or norepinephrine levels, etc.). The current study examines the relationship between poverty in three different developmental periods, allostatic load that may become elevated earlier in life as a result of the chronic stress of poverty, and severity of chronic disease.

Hypotheses

The purpose of the present study is to examine the relationship between a specific stressor (poverty) and elevated stress biomarkers of cumulative physiological dysregulation (AL) to predict comorbid conditions leading to a mortality risk score (CCI) in older adults. The study examines poverty at three-time points: childhood (under age 18), young adulthood (age 18-35), and older adulthood (within the last year). The specific hypotheses to be tested are:

(1) After controlling for gender, ethnicity, age, and education
    a. Poverty during childhood will
        i. More strongly predict AL than poverty during young and middle/late adulthood.
        ii. more strongly predict chronic disease than poverty during young and middle/late adulthood.

(2) Allostatic load will
    a. fully mediate the child poverty and chronic disease relationship.
    b. partially mediate the adult or recent poverty and chronic disease relationship.

(3) Demographic factors such as gender and ethnicity will moderate the poverty and comorbidity relationship.

CHAPTER TWO

METHOD

Participants and Procedures

This study will use data from the Biopsychosocial and Religion and Health Study (BRHS; Lee et al., 2009). Participants for the study were recruited from the Adventist Health Study-2 (AHS-2), a cohort study of lifestyle and cancer in 97,000 Seventh-day Adventists (SDAs) across North America in 2003-2006 (Butler et al., 2008). Of these, a random sample of about 21,000 were mailed a 20-page BRHS stress, religion and health survey and 10,988 returned usable surveys in 2006-2007. Information on demographics, poverty, and physical comorbidities were gathered with the BRHS questionnaire. A subsample of 845 individuals who completed the survey and resided within a 60-mile radius of the campus was invited to also complete assessments on biometrics, biomarkers, and functional status in study clinics on campus or in a mobile clinic in Los Angeles. These assessments provided data for AL. Out of those invited, 622 were scheduled, 532 came into the clinic, and 511 provided complete, usable data. The Institutional Review Board gave approval for the study as minimal risk and a written informed consent was given to all participants.

Of these 511 a total of 124 were excluded from all analyses due to missing data or not meeting the study inclusion criteria of >50 years and Black or White ethnicity. Thus, 24 did not provide a blood sample, 16 did not provide a urine sample, 13 were missing poverty data, 5 were missing the Charlson Comorbidity Index data and 66 were under age 50 or not Black or White. This left 387 for the investigation. These included were compared to the 124 excluded on demographics. The participants included were similar

to those excluded on age, ethnicity, and education. however, those included were more likely to be male than those participants who were not included in the study.

The final sample consisted of 153 males (39.5%) and 234 females (60.5%) with a mean age of 68.96 years (*SD* = 11.304). The sample was primarily White (59.9%), had some college or higher (92.6%), with little to no financial difficulty in the past year (92.2%) (see Table 1).

Biological data was collected from participants who arrived at a scheduled morning appointment after fasting for 12 hours and completing both the AHS-2 and the BRHS questionnaires. An overnight urine sample was brought to the clinic where blood pressure, body measurements, and fasting blood samples were taken. All clinical procedures, including assays of blood work and urine samples were conducted in the clinic or laboratory setting and all data coded in an SPSS V.23 database.

Measures

Demographic variables

Participants provided information on age, race (Black or White), gender, and education (1-9 point scale; grade school to doctoral degree) using a self-report questionnaire. These variables were used as controls in the statistical analyses.

Table 1. Sample demographics and variables of interest (N=387).

	N	*%*	*Mean*	*SD*
Age	387		68.96	11.30
Sex				
Female	234	60.5		
Male	153	39.5		
Ethnicity				
White	232	59.9		
Black	155	40.1		
Childhood Poverty			2.65	
Not at all	103	26.6		
A little	91	23.5		
Somewhat	78	20.2		
Fairly	67	17.3		
Very	48	12.4		
Young Adulthood Poverty			1.99	
Not at all	159	41.1		
A little	125	32.3		
Somewhat	60	15.5		
Fairly	34	8.8		
Very	9	2.3		
Mid/Late Adulthood Poverty (last year)			1.35	
Not at all	317	81.9		
A little	40	10.3		
Somewhat	7	1.8		
Fairly	12	3.1		
Very	11	2.8		
Education (years completed)			6.86	1.676
Some High School	3	.8		
High School Diploma	12	3.1		
Trade School Diploma	10	2.6		
Some College	74	19.3		
Associate Degree	45	11.7		
Bachelor's Degree	83	21.6		
Master's Degree	81	21.1		
Doctoral Degree	76	19.8		
	Mean	*SD*	*Minimum*	*Maximum*
Allostatic Load	3.6	2.00	0	10
Charlson Comorbidity Index	3.11	1.67	1	11

Poverty

Insufficient financial resources may cultivate feelings of instability, hopelessness, and anxiety that affect psychological and physiological functions. Poverty was measured with a self-report rating of "*How difficult was it for you to meet expenses for basic needs (food, clothing, and housing) when you were <18 years, 18-35 years, and in the last year"* on a 5-point rating scale (1 =*Not at all* to 5 =*Very difficult;* Pudrovska, Schieman, Pearlin, & Nguyen, 2005). Previous studies suggest that economic hardship is correlated with depression, physical distress, and lower self-reported health (Ross & Huber, 1985; Ross & Wu, 1995), as well as, morbidity and mortality (Pearlin et al., 1981). This item was modified to assess a retrospective report of poverty at three points across the lifespan in the present study.

Allostatic Load (AL)

The AL score was composed of 13 parameters that provide information on levels of physiological activity across a range of major physiological regulatory systems. These included the hypothalamic-pituitary-adrenal (HPA), the sympathetic nervous, cardiovascular, and endocrine systems.

The 13 parameters included: (a) waist-hip ratio (WHR; central adipose tissue deposition, metabolic-linked assessment for obesity), (b) systolic blood pressure (SBP) and (c) diastolic blood pressure (DBP) for cardiovascular function; (d) norepinephrine (NE) and (e) epinephrine (EPI) for sympathetic function, (f) cortisol and (g) DHEA-S for HPA function, (h) interleukin-6 (IL-6) and (i) C-reactive protein (CRP) measuring inflammatory mediators, (j) total cholesterol (TC), (k) HDL, and (l) TC to HDL ratio

measuring metabolic process and risk for atherosclerosis, and (m) hemoglobin A1c (HbA1c; glycosylated hemoglobin identifies average glucose levels over the previous 3-months for metabolic process, control of blood glucose levels, and risk for diabetes). The specific methods used to assess these parameters are detailed below. Each of the 13 variables were divided into quartiles based on their individual distributions. Biomarkers that fell into the "highest risk" quartile (the top quartile for all parameters except for HDL cholesterol and DHEA-S for which ranking in the lowest quartile corresponds to the highest risk) were assigned one point. AL was calculated by summing the number of points accumulated across all 13 parameters. Therefore, the range for AL is 0 through 13. Individuals taking medication for diabetes or hypertension were allocated one point for HbA1c or blood pressure, respectively, to account for physiological damage to the metabolic or cardiovascular systems. The specific measures used for each of these 13 parameters are as follows:

1. *Waist-Hip Ratio* - WHR was calculated by waist circumference (mid-point between the lower ribs and upper margin of the iliac crest) divided by hip circumference (widest point around maximal buttocks) in inches. Waist and hip circumference was measured three separate times. An average was calculated from the three measurements for the final WHR used in analyses. WHR is a measure of abdominal fat accumulation; scores above 0.9 or 0.85 for men and women, respectively, indicate obesity and are predictive of CVD and greater mortality risk in older adults (Price, Uauy, Breeze, Bulpitt, & Fletcher, 2006).

2-3. *Blood Pressure* – Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed after a 10-minute resting period in a quiet room using an automated blood pressure monitor (an Omron blood pressure monitor) and different sized arm cuffs. SBP and DBP were measured three times and the data averaged, and expressed in mmHg.

4-6. *Twelve-hour Urine Samples*. - Urine collection kits, including simple instructions for collection, were mailed to participants prior to their clinic appointment. Participants were instructed, after an initial void, to collect the urine sample in a container containing [preservative] the evening before their clinic visit between 7 p.m. to 7 a.m., store the container in a cool place, and bring the sample to their clinic visit. Participants were also instructed to avoid certain foods (ie: coffee, cocoa, tea, citrus fruits, bananas, vanilla, and chocolate) for several days, as they can raise catecholamine levels in the urine. Participants returned the filled urinary container, the urine volume was recorded, and 4 ml of urine were aliquoted into 4 4-ml cryovials per study participant. Samples were transported on ice across campus, logged into a database, and stored at -80 °C until analyses. Urine samples were used to evaluate 12-hour urinary cortisol, norepinephrine and epinephrine levels. Data were normalized for volume by expressing the concentration of these variables by dividing the values by the concentration of urinary creatinine.

a. Creatinine. Urinary creatinine levels were assessed by commercial enzyme-linked immunoassay (ELISA) kits (Metra, San

Diego, CA) after samples were centrifuged at low speed (200 x g) for 3 minutes to remove debris, and then diluted 1:40 with distilled water. Plates containing samples run in duplicate were read on a plate reader at 490 nm, and values determined based on the standard curve of known concentrations of creatinine. Standards ranged from 0 to 40 mmol/L. Intra- and inter-assay variability was 1.7% and 4.3%, respectively.

b. Catecholamines. High physiologic blood levels of the catecholamines, norepinephrine (NE) and epinephrine (EPI), are associated with psychological or physical stressors. Serum catecholamine concentrations were measured by high-performance liquid chromatography with Coulechem detection. Values were determined from known concentrations of NE and EPI, and data expressed in ng/ml.

c. Cortisol. Cortisol was assessed in overnight 12-hour urine samples along with known standards with an ELISA kit (Enzo, Farmingdale, NY) run in duplicate, according manufacturer's instructions. Sample values were determined using a plate reader set at an optical density of 450 nm immediately after the stop solution was added to each well. Samples with concentrations outside the range of the standard curve (0-10 µg/ml) were diluted and re-run. Kit sensitivity was 0.005 µg/ml. Intra-assay and inter-assay variability with the kits were ~8.1 and 9.9%, respectively.

7-13. *Fasting Blood Samples* - Measures of DHEA-S, IL-6, CRP, TC, HDL, and HbA1c were obtained from serum samples collected before 10:00 a.m. For

all ELISA kits, the assays were run with duplicate samples and standards on each plate, according to manufacturer's instructions.

a. Serum DHEA-S levels were assessed with enzyme-linked immunosorbent assay (ELISA) kits (ALPCO, Salem, NH) in the Department of Pathology and Human Anatomy. Plates included standards, and samples and standards were run in duplicate using a plate reader. The intra- and inter-assay precision averaged 9.3% and 9.2%, respectively, and the sensitivity of the kit was 0.005 µg/ml.

b. Inflammatory Markers – IL-6 and CRP are major markers of inflammation that rise in blood during periods of chronic stress, which is linked to premature aging and accelerated risk of cardio-metabolic disease (Kiecolt-Glaser, 2003). Serum CRP and IL-6 levels were determined using high-sensitivity Quantikine ELISA kits were run according to manufacturer's instructions (Alpco, Salem, NH and R&D Systems, Minneapolis, MN, respectively). For CRP, the samples were diluted 1:500, and the plates were read immediately after applying the stop solution on a plate reader set at 450 and 620 nm to correct for optic distortion in the plate. The range of detections was 1.9 to 150 ng/ml with the limit of detection at 0.124 ng/ml. Intra- and inter-assay variability was 6% and 9.5%, respectively. For IL-6, samples were run neat. Standards ranged from 0 to 10 pg/ml. Plates were read on a plate set at 490 nm or 650 nm. Correction for optical imperfections in the plate was done by determining the difference in values between these wavelengths. Intra- and inter-assay

variability was 7.4% and 7.8%, respectively. The minimal detectable level was 0.039 pg/ml.

c. HDL and TC were assessed with the CLIA-waived Cholestech LDX Analyzer (San Diego, CA). Whole blood was applied to a Cholestech LDX cassette, and the cassette placed into the analyzer to simultaneously measure HDL and TC, triglycerides and glucose. LDL cholesterol was determined by subtracting the HDL levels from TC. Quality control testing with standards were performed before each clinic to verify results within established ranges, before patient samples were tested.

d. HbA1c was assessed with the Cholestech GDX Analyzer from frozen stored blood samples after thawing (Selvin, Coresh, Jordahl, Boland, & Steffes, 2005). A self-check with a standard was run before each sample. Next, sample was applied to the A1c test cartridge and the cartridge inserted into the analyzer for HbA1c assessment, according to manufacturer's instructions.

Charlson Comorbidity Index.

The Charlson Comorbidity Index (CCI) measures the risk of mortality in a clinical population by classifying comorbid conditions that influence 1-year mortality risk. It has been adapted to fit a variety of needs and populations, including self-report questionnaires (de Groot, Beckerman, Lankhorst, & Bouter, 2003). The full index includes 19 medical conditions with varying weights (1-6) and a total score between 0-37

(Charlson, Pompei, Ales, & MacKenezie, 1987). Age is also a predictor of mortality. Individuals above age 50 are assigned 1 point, with an additional point for each decade above age 50. CCI is the sum of the condition weights; a higher score indicates higher disease risk for mortality.

A modified version used in the study was composed of 14 self-reported diseases, weighted according to the strength of their association with mortality, as shown in Table 2. Conditions were assigned as: 1 point (myocardial infarction (MI), congestive heart failure (CHF), angina, arrhythmia, peripheral vascular disease, cerebrovascular disease, hypertension, connective tissue disease, ulcer disease, diabetes), 2 points (tumors, leukemia, lymphoma), or 6 points (metastatic solid tumors) based on disease prognosis and severity ratings. The index used is modified from its original version and does not include dementia, chronic pulmonary disease, liver disease, hemiplegia, renal disease, or acquired immunodeficiency syndrome (AIDs). Higher scores indicate a higher prognostic burden of comorbid disease, and a higher likelihood of earlier mortality. Information on self-reported diseases was gathered through the BRHS 2006-2007 questionnaire. Table 1 details the descriptive information of the variable.

Table 2. Charlson Comorbidity Conditions with Weights.

Assigned Weights For Disease	Condition
1	Myocardial Infarction
	Congestive Heart Failure
	Angina
	Arrhythmia
	Peripheral Vascular Disease
	Cerebrovascular Disease
	Hypertension
	Connective Tissue Disease
	Ulcer Disease
	Diabetes
2	Tumors
	Leukemia
	Lymphoma
6	Metastatic Solid Tumor

Note. Age would be added to the comorbidity score for participants creating age-comorbidity variable. A risk point of 1 is added to the Charlson Index score for each decade over 40 years of age. Therefore, an age of 50 adds one point whereas an age of 70 adds 3 points.

CHAPTER THREE

PUBLISHABLE PAPER

THE EFFECTS OF POVERTY AND ALLOSTATIC LOAD ON THE DEVELOPMENT OF CHRONIC DISEASE

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Abstract

Objective: Poverty is a stressful experience associated with negative health outcomes such as chronic disease and mortality risk. The poverty and chronic disease relationship may be affected by chronically elevated stress biomarkers assessed as allostatic load. The present study investigates the relationship among life-course poverty, allostatic load, and the Charlson Comorbidity Index, a measure that predicts the one-year mortality for a patient who may have a range of comorbid conditions.

Method: Biopsychosocial and Religion and Health Study (BRHS; Lee et al., 2009) participants from the Adventist Health Study-2 cohort of Seventh-day Adventists were assessed; 387 were examined on poverty, chronic diseases, and allostatic load (preclinical elevations in 13 biomarkers).

Results: The results suggest that age and ethnicity are associated with allostatic load, such that older age and being Black predict higher levels of allostatic load. Also, poverty experienced during childhood—but not during young adulthood or older adulthood—predicts chronic diseases. Age moderates the relationship between allostatic load and chronic disease; such that, participants who were in the lower age group were more affected by allostatic load compared to participants in the sample that were older in age.

Discussion: The results highlight the detrimental effects of childhood poverty and allostatic load on the severity of chronic disease. Both independently predicted health outcomes but no mediation was demonstrated. Demographic factors moderated these effects. Therefore, childhood poverty likely has a milieu of factors, aside from elevated stress biomarkers, that lead to poor health.

Introduction

In 2015, approximately 43.1 million people (13.5%) in the United States were living in poverty, 13.4 million were children under the age of 18. (U.S. Census Bureau, 2016). The ruthless course of poverty adversely affects the lives of many. Poverty is defined as an economic state that does not allow for adequate provision of basic family and child needs, such as sufficient food, clothing, and housing (Wood, 2003). However, poverty includes more than just a lack of economic resources; it encompasses a milieu of disadvantages that can be extremely stressful. These stressful risk factors include, but are not limited to, increased exposure to community violence, family turmoil, crowding, noise, and other hazardous interactions (Evans & English, 2002). Impoverished children have higher rates of hospital admission, disability, and early mortality due to limited access to preventative, curative, and emergency medical care, while also having worse nutrition, parenting and housing, and higher exposure to harmful toxins (Evans, 2004).

Individuals exposed to chronic stress experience deterioration in biological regulatory systems. While the body is designed to regulate and maintain homeostasis, chronic stress can disrupt optimal physiological functioning. Perceived stress triggers a series of neurochemical fluctuations that activate a variety of metabolic, inflammatory, and cardiovascular responses. Excessive activation of the biomarkers associated with these systems cause significant physiological "wear and tear" and lead to chronic health problems such as, asthma, cardiovascular diseases (i.e., strokes and myocardial infarctions), diabetes, gastrointestinal disorders, and cancer, viral infections, and autoimmunity (McEwen & Stellar, 1993). Individuals enduring chronic stressors are also at higher risk for age-related metabolic disorders, elevated inflammation levels and

cortisol secretion, and accelerated cognitive decline and cellular aging (Danese & McEwen, 2012).

McEwen's (1998) allostatic load (AL) theory describes the link between stress and the development of chronic disease. He posits that the excessive strain of repeated acute and/or chronic stressors has long-lasting effects on the neuroendocrine, cardiovascular, immune, and neural systems. As such, AL, is a measure of the preclinical elevations in biomarkers across these sensitive organ systems caused by over exposure to stressors, leading to chronic wear and tear and eventually disease (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). An AL index is a cumulative, multisystem measure of physiological dysregulation that may determine preclinical pathology and assess latent risk for comorbidities (Karlamangla et al., 2002). AL measures dysregulation in multiple adaptive systems collectively, instead of examining individual systems, and provides a life course perspective of maladaptive physiological responses to stressors that may predict pathology before symptoms of disease overtly arise (Karlamangla et al., 2002).

Though poverty is linked to chronic disease (Adler & Ostrove, 1999), we do not yet know whether poverty exposure at different points in the life course has differential effects on allostatic load or on chronic disease severity. It is possible that only childhood poverty creates actual change in the stress reactivity and regulation systems to lead to elevations in allostatic load (AL) and disease severity. As such, poverty exposures during young and late adulthood will be compared to poverty during childhood to examine health outcomes (allostatic load and chronic disease severity). AL will be examined as a potential mediator of the child poverty to chronic disease relationship.

Method

Biopsychosocial and Religion and Health Study (BRHS; Lee et al., 2009) data from the Adventist Health Study-2 (AHS-2) cohort of Seventh-day Adventists (Butler et al., 2008) included the 10,988 who responded to a mailed, 20-page survey that included assessments of demographics, poverty, and physical comorbidities. The primary study population of the AHS-2 cohort includes Blacks and Whites. Of the survey respondents, 845 who resided within a 60-mile radius of the campus were invited to complete assessments on biometrics and biomarkers in study clinics on campus or in a mobile clinic in Los Angeles. Of these, 511 provided usable data and 387 met study inclusion criteria of ≥50 years of age and either Black or White with no missing data on relevant variables. Those included and excluded were similar on age, ethnicity, and education; however, more males were included in the sample than excluded. Descriptive statistics for participants are presented in Table 1.

Measures

Control Variables

Participants provided information on age, race (Black or White), gender, and education level (1 = Grade school, 2 = Some High school, 3 = High school diploma, 4 = Trade school diploma, 5 = Some college, 6 = Associate degree, 7 = Bachelor's degree, 8 = Master's degree, 9 = Doctoral degree) on the BRHS questionnaire in 2006-7.

Poverty

Poverty at three age periods was rated on a 5-point scale (1=Not at all to 5=very difficult) on three items: "*How difficult was it for you to meet expenses for basic needs (food, clothing, and housing) when you were <18 years; 18-35 years; and in the last year"* (Pudrovska, Schieman, Pearlin, & Nguyen, 2005).

Allostatic Load

AL was created by first dividing each of 13 biomarkers into quartiles, then assigning a 1 to the "highest risk" quartile (top quartile on all but HDL cholesterol and DHEA-S which were the bottom quartile) and a 0 to the other quartiles and finally summing across these 13 dichotomized biomarkers (Table 3). This created an AL score that could range from 0 to 13. Individuals taking medication for diabetes or hypertension were allocated one point for HbA1c or blood pressure, respectively, to account for physiological damage to the metabolic or cardiovascular systems that may have been masked by the medications. The parameters used for AL calculation included waist-hip ratio (WHR; central adipose tissue deposition, metabolic-linked assessment for obesity), systolic and diastolic blood pressure (SBP and DBP, respectively assessed three times after a 15 minute rest period and averaged; cardiovascular function), catecholamine, norepinephrine (NE) and epinephrine from overnight urine samples (EPI; sympathetic function), cortisol and DHEA-S (HPA function), interleukin-6 and C-reactive protein (IL-6 and CRP, respectively from fasting blood samples; inflammatory mediators), total cholesterol (TC), HDL, and TC to HDL ratio from fasting blood samples (metabolic process; risk for atherosclerosis), and hemoglobin A1c (HbA1c, glycosylated

hemoglobin from fasting blood samples to assess average 3 month glucose levels; metabolic process). See Table 4 for description of equipment used to measure parameters.

Table 3. Allostatic Load Biomarker Quartile Parameter.

	Biomarker	*Cut-Off score*	*Normative Range*	*Sample Mean*
Highest	Systolic Blood Pressure	≥138.0 mmHg	90-120 mmHg	126.23 mmHg
	Diastolic Blood Pressure	≥79.67 mmHg	60-80 mmHg	72.94 mmHg
	Waist/Hip Ratio	≥0.96	< 0.80 (women); <.90 (men)	0.88
	Norepinephrine	≥61.20 mg/gm creatinine	0 to 600 pg/mL	52.18 mg/gm creatinine
	Epinephrine	≥7.78 mg/gm creatinine	0 to 900 pg/mL	7.38 mg/gm creatinine
	Cortisol	≥67.92 mg/gm creatinine	10 to 20 µg/dl (morning)	57.38 mg/gm creatinine
	Interleukin-6	≥5.64 pg/ml		6.00 pg/ml
	C-Reactive Protein	≥2336.76 mg/L	<30 mg/L	2239.6232 mg/L
	Total Cholesterol (TC)	≥208 mg/dL	<200 mg/dL	117.15 mg/dL
	TC/HDL ratio	≥4.8	--	3.90
	Glycosylated Hemoglobin	≥6.3%	4% to 5.6%	5.9%
Lowest	HDL	≤38 mg/dL	>60 mg/dL	46.92 mg/dL
	DHEA-S	≥0.82 µg/ml	0.13 to 1.3 µg/ml (female, age 60-69); 0.42 to 2.9 µg/ml (male, age 60-69)	0.69 µg/ml

Table 4. Allostatic Load Biomarker measurements.

Allostatic Load Biomarker	Method/Equipment Used
• Waist-Hip Ratio	Waist circumference divided by hip circumference in inches. Measured 3 times and averaged for final WHR.
• Systolic Blood Pressure, Diastolic Blood Pressure	Automated blood pressure monitor (*Omron*)
• Creatinine, Catecholamine (Norepinephrine & Epinephrine), Cortisol	ELISA kits used to measure urine samples
• DHEA-S, IL-6, CRP	ELISA kits used to measure fasting blood samples
• TC, HDL, and HbA1c	Cholestech LDX Analyzer

Charlson Comorbidity Index (CCI)

CCI was composed from 14 diseases assessed on the BRHS 2006-2007 questionnaire. Conditions were weighted according to the strength of their association with mortality risk, as shown in Table 2. Conditions were assigned as: 1 point (myocardial infarction (MI), congestive heart failure (CHF), angina, arrhythmia, peripheral vascular disease, cerebrovascular disease, hypertension, connective tissue disease, ulcer disease, diabetes), 2 points (tumors, leukemia, lymphoma), or 6 points (metastatic solid tumors) based on disease prognosis and severity ratings. The index used is modified from its original version and does not include dementia, chronic pulmonary disease, liver disease, hemiplegia, renal disease, or acquired immunodeficiency syndrome (AIDs) as these had not been included in the BRHS questionnaire. Higher scores indicate a higher prognostic burden of comorbid disease, and a higher likelihood of earlier mortality (Charlson, Pompei, Ales, & MacKenezie, 1987).

Results

Assumptions for normality, homoscedasticity, linearity, and multicollinearity were met. A hierarchical linear regression was performed to examine the effects of poverty on AL, after controls (Table 5). Variables were entered in the following blocks: (a) demographics (gender, education, ethnicity, age), gender and ethnicity were dummy coded, with females and Whites as the reference group, (b) childhood poverty, (c) young adulthood poverty, and (e) mid/late adulthood poverty, (f) ethnicity x child poverty, (g) age x child poverty. The regression model accounted for a small, but statistically significant proportion of the variance in AL, $R^2 = .084$, $F(9, 383) = 4.898$, $p < .001$ (Table 5). Ethnicity and age were positively associated with AL, such that as age increased by one year, AL increased by .048 points after controls $p < .0001$, CI [.029, .067]. Subjects who were Black, on average, had an increase of .859 points in AL, compared to White subjects, after controls $p < .0001$, CI [.416, 1.302]. None of the three poverty exposures independently predicted AL after controls.

Table 5. Regression of Lifetime Poverty on AL

	b	SE	β	t	*p*
Gender (-1 = female, 1 = male)	0.061	0.215	0.015	0.284	0.776
Ethnicity (-1 = white, 1 = black)	0.859	0.225	0.209	3.816	0.000**
Education	-0.111	0.068	-0.093	-1.648	0.100
Age	0.048	0.009	0.269	5.071	0.000**
Child Poverty	0.048	0.083	0.032	0.576	0.565
Young Adulthood Poverty	0.027	0.108	0.014	0.252	0.801
Mid/Late Adulthood Poverty	-0.051	0.123	-0.022	-0.409	0.683
Ethnicity x Child Poverty	0.005	0.079	0.003	0.062	0.951
Age x Child Poverty	0.003	0.007	0.020	0.385	0.700

Note. * $p < .05$, ** $p < .001$, two-tailed.

A hierarchical linear regression was performed to examine whether poverty and AL predicted CCI, after controls. Variables were entered in the following blocks: (a) demographics (gender, education, ethnicity, age), gender and ethnicity were dummy coded, with females and Whites as the reference group, (b) childhood poverty, (c) young adult poverty, and (d) mid/late adulthood poverty, and (e) AL, (f) gender x AL, (g) ethnicity x AL, (h) age x AL, (i) child poverty x AL. The regression model accounted for a significant proportion of the variance in CCI, $R^2 = .707$, $F(12, 383) = 74.576$, $p < .001$ (see Table 6). Age, child poverty, and AL significantly predicted CCI. The results also suggest a significant interaction between age and AL on CCI, $\beta = -.107$, $t = -3.519$, $p < .001$. We we examined this further, results showed that for those in the lower age group (one standard deviation below the mean), each additional AL point results in a .066 unit increase in CCI, b = .0657, t(df) = 5.3762(374), $p < .0001$, CI [.0416, .0897]. For those in the mean age group, each additional AL point results in a .034 unit increase in CCI, b = .0342, t(df) = 3.8961(374), $p < .001$, CI [.0169, .0515]. And, for those in the higher age group (one standard deviation above the mean age), each additional AL point results an insignificant .003 unit increase in CCI, $p > .05$. This interaction indicates that AL has very little impact on chronic disease severity in older individuals, but a significantly greater impact on chronic disease severity for individuals younger in age, which is suggestive of a premature aging effect (Figure 1).

Table 6. Regression of Lifetime Poverty and AL on CCI

	b	SE	β	t	*p*
Gender (-1 = female, 1 = male)	-0.003	0.018	-0.005	-0.167	0.868
Ethnicity (-1 = white, 1 = black)	0.019	0.02	0.032	0.983	0.326
Education	-0.015	0.012	-0.043	-1.322	0.187
Age	0.0420	0.002	0.790	25.143	0.000**
Child Poverty	0.040	0.014	0.091	2.835	0.005*
Young Adulthood Poverty	-0.022	0.018	-0.04	-1.205	0.229
Mid/Late Adulthood Poverty	-0.005	0.021	-0.007	-0.237	0.813
Allostatic Load	0.034	0.009	0.115	3.843	0.000**
Gender x AL	-0.008	0.018	-0.013	-0.445	0.656
Ethnicity x AL	-0.015	0.019	-0.024	-0.771	0.441
Age x AL	-0.003	0.001	-0.107	-3.343	0.001*
Child Poverty x AL	-0.001	0.007	-0.004	-0.139	0.89

Note. * $p < .05$, ** $p < .001$, two-tailed.

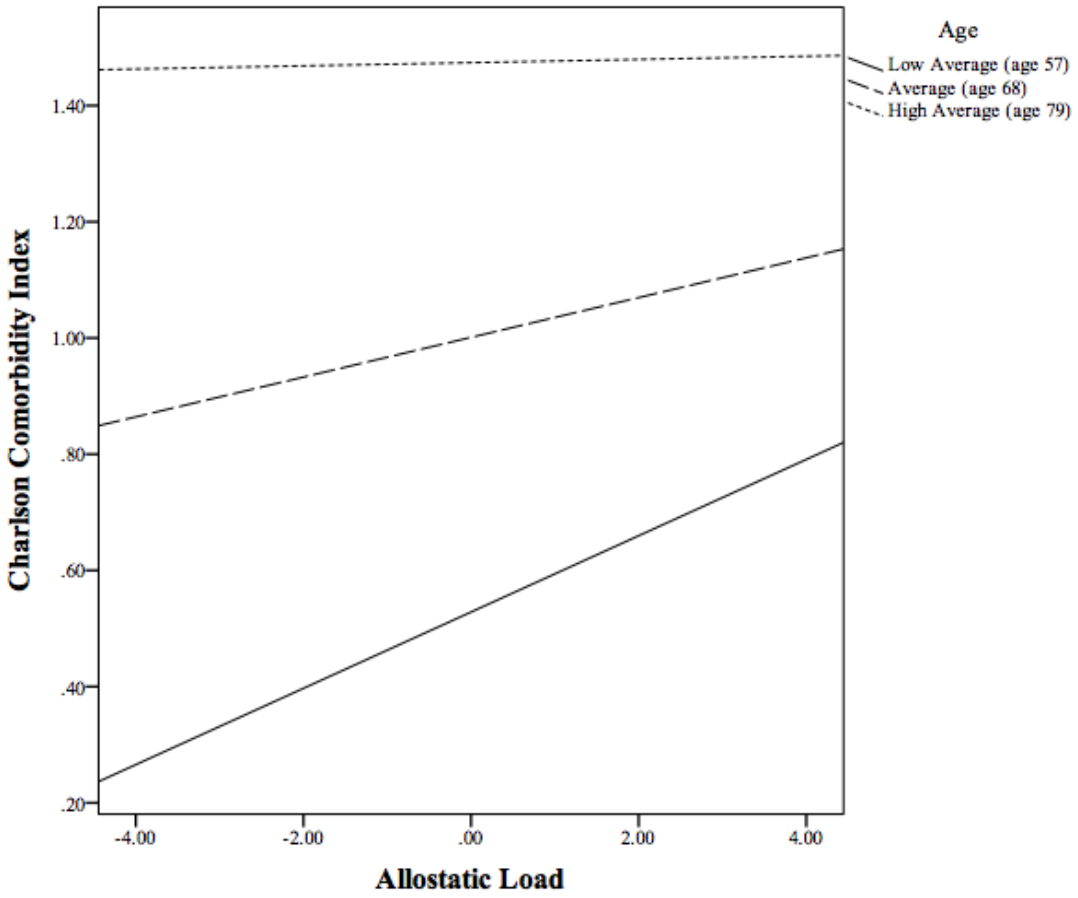

Figure 1. Relation between elevated stress biomarkers (allostatic load) and chronic disease (Charlson Comorbidity Index) for three different age groups (low, average, high).

A mediation model was tested using the SPSS PROCESS Macro (Hayes, 2012) to examine whether AL mediates the relationship between poverty and chronic disease. The results of the model suggest that AL does not mediate the relationship between poverty (childhood, young adulthood, or mid/late adulthood) and chronic disease, b = .0281, SE = .0184, 95% CI = -.0064, .0670.

Discussion

The current study examined the effects of life-course poverty on health in older Blacks and Whites via elevated chronic stress biomarkers indicating premature aging. Ample research supports that poverty in early childhood can leave lasting, devastating effects on stress regulating systems and that this dysregulation is the principle underlying mechanism for early morbidity and mortality (Evans & Kim, 2007; McEwen, 1998, 2000). The results contribute to and support this growing body of literature, further showing that poverty experienced at younger ages has a stronger effect on morbidity than poverty experienced as an adult. However, these results should be interpreted with caution and may be inconclusive due to the limited number of individuals in the sample who have experienced adulthood poverty. Further, the Charlson Comorbidity index used to measure morbidity in the study is a modified version of the full index. Therefore, we are limiting the amount of variability captured by this index because several diseases were not included in the version used in the analysis.

Literature on the use of AL as a measure of cumulative biological system dysregulation has grown in popularity due to its dynamic, flexible approach to measurement (Seeman et al., 1997, 2001, 2004; Gruenewald, 2012; Karlamangla, 2002).

AL, an indicator of elevated stress hormones and measure of cumulative physiological damage, is also associated with chronic disease severity. The results of the current study support existing literature on AL as a reliable prognosticator of morbidity risk.

Ethnicity was found to be a demographic factor that significantly influenced AL. The study suggests that Black subjects generally had higher levels of AL compared to White subjects. Previous studies have suggested that racial/ethnic differences in AL can be explained by chronic social stressors, such as discrimination (Geronimus et al., 2006). This weathering effect posits that being Black is associated with higher levels of physical health deterioration, outside of the added stressor of poverty.

The study also identifies age as a significant moderator of allostatic load for chronic disease severity. The interaction suggests that allostatic load has a greater effect on younger individuals, those whose biological systems have been less compromised by the effects of age. Conversely, older individuals who have already endured some physiological wear and tear from the normal aging process, experience less compromising effects of allostatic load on chronic disease severity although AL has a negative association with comorbidity regardless of age (see Figure 1). We were concerned for individuals born during the Great Depression era as a confounding factor for the effects found. However, individuals born during this time period did not comprise a significant proportion of the sample (20.7%).

The increasing prevalence of chronic disease is a major area of concern for the healthcare economy. Center for Disease Control and Prevention (2009) estimates that 75% of health care expenditures go toward treatment of chronic disease. Several factors that lead to chronic disease are preventable and/or manageable, therefore, it is important

for researchers to acknowledge the predictors and preclinical indicators that are present before full-blown manifestation of the chronic disease occurs.

Strengths and Limitations and Future Directions

The strengths of this study are the large sample size and the validated measures used to measure poverty at different age periods, AL, and chronic disease. The use of biomarkers to calculate AL offers a quantitative measure of cumulative stress-related physiological deterioration that reduces bias or subjectivity in self-reports. In addition, the demographics of the sample (highly educated, relatively healthy, affluent older adults) suggest findings of poverty, AL, and chronic disease on this unique population of Seventh-day Adventists likely underestimate the effects in a general population of the U.S. One of the limitations to our findings is the cross-sectional and retrospective self-report measure of poverty and chronic illness. Generalizability of the findings is limited to those of similar socioeconomic status in the United States. Another limitation of the

study is the restriction of range seen in our variables of interest. Table 1 displays the ranges of *poverty*, *AL*, and *CCI* which reflect a sample where the majority of participants, on average, have not experienced significant poverty and are relatively healthy. Future studies should aim to increase generalizability by sampling individuals across the spectrum of age, SES, education, and ethnicity to provide results more representative to the general U.S. population.

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