ABSTRACT

Title of thesis: ASSOCIATION BETWEEN ALLOSTATIC LOAD AND ARTHRITIS IN NHANES ADULTS

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Objective: To examine the cross-sectional association between allostatic load and arthritis using data from the National Health and Nutrition Examination Survey (NHANES). Methods: Complete data on 7,714 adults were included in the analysis. An allostatic load (AL) index, comprising of multiple regulatory systems, was calculated from 11 biomarkers. Multivariate logistic regression was used to estimate the odds ratio (OR) for the association between allostatic load and arthritis, while accounting for confounders. Results: Significant positive associations were found between both continuous allostatic load (OR=1.12, 95% CI= 1.08-1.17) and the two highest quartile categories of AL and arthritis compared to the lowest quartile (quartile 3: OR=1.73, 95% CI=1.38-2.17, quartile 4: OR=1.79, 95% CI=1.41-2.26), after adjusting for confounders. The subscales of the inflammatory (OR=1.27, 95% CI=1.15-1.40) and metabolic system (OR=1.20, 95% CI=1.13-1.28) were also significant predictors. Conclusions: Cumulative biological risk is a plausible mechanism that is associated with arthritis.

ASSOCIATION BETWEEN ALLOSTATIC LOAD AND ARTHRITIS IN NHANES ADULTS

By

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Chapter 1: Background

Arthritis

Arthritis is a rheumatic disease that is characterized by joint inflammation as its primary distinguishing symptom. Rheumatic diseases are a large group of inflammatory diseases that have loss of function of connecting or supporting structures of the body including joints, tendons, ligaments, bones, and muscles. Arthritis creates a large burden on the United States affecting more than 46 million people and incurring medical costs of $321.8 billion in 2003.[1] The two major types of arthritis are rheumatoid and osteoarthritis which affect 1.3 million people and 27 million people respectively.[1] Osteoarthritis damages the cartilage in joints leading to less cushioning in the joints, and over time leads to damage to the bone structure. Rheumatoid arthritis is a systemic dysfunction in the immune system that causes inflammation and damage to the joint. The causes of arthritis are largely unknown, but it is clear that the inflammatory system is involved. Several risk factors are established: arthritis is positively associated with increasing age and tends to affect more women than men.[2-4] The increased risk in women has been unexplained by research, so far. Some studies have also shown associations between arthritis and race/ethnicity and socioeconomic factors[2] as well as health behaviors such as smoking[5].

Allostatic Load

Inflammation is largely controlled by the body's immune system which is affected by the stress response system in the form of the sympathetic nervous system

(SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, a part of the neuroendocrine system. The body's response to stress is meant to be an adaptive adjustment to allow enhanced coping with stressors; however, exposure to chronic stress over extended periods of time can be maladaptive and even damaging to the body. The concept of allostatic load (AL) is that physiological burdens amount due to repeated exposure to the body's natural stress response and inefficient turning on or shutting off of these responses.[6] This causes wear and tear and affects multiple physiological systems in the body and may increase the risk of various health conditions and diseases. Allostatic load (AL) is typically operationalized as measuring physiological markers of the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, cardiovascular system, and metabolic processes[7] and creating a summary measure of the markers that are out of normal range. The markers can generally be divided into mediators and outcomes. The primary mediators include norepinephrine, epinephrine, cortisol, and dehydropiandrosterone sulfate (DHEA-S), which are hormones released by the body in response to stress.[8] The second category of markers, outcomes, are measuring the effects of the primary mediators on various systems in the body and include elevated blood pressure, body mass index (BMI; kg/m^2), cholesterol, glycohemoglobin, and others.[8] Over time, authors have added additional biomarkers as research has showed their significance in the AL process.

The theory of allostatic load emphasizes that markers out of normal range can indicate high risk of disease. To measure this high risk, authors have used a variety of cut-offs to determine the high-risk category including: clinical guidelines, quartiles based on the sample distribution, deciles based on the sample distribution, z scores, and/or

considering both above and below normal range as high risk if applicable to the specific biomarker. AL has been shown to increase risk of cardiovascular disease, cognitive decline, physical decline, and mortality.[7] It has also been positively associated with older age,[9] black race,[8] number of psychological stressors,[10] low neighborhood socioeconomic status,[11] and negatively with positive social relationships, number of social ties,[9] income, and education.[12] Allostatic load has also been shown to vary by gender[8, 9] and smoking status.[12]

Arthritis and Allostatic Load

Research has shown that stress can worsen the symptoms of rheumatic diseases, and recently, mounting evidence suggests that it may play a role in the etiology or pathogenesis of these diseases, particularly in arthritis.[13] Patients with arthritis, particularly rheumatoid arthritis have abnormal stress responses in the form of a dampened HPA axis where they have inadequate cortisol and adrenocorticotropic hormone responses to stress[13]. There is a shift from beta receptors to alpha receptors, which causes increased secretion of pro-inflammatory cytokines and causes stress hormones to lack their normal immunosuppressive actions[13]. They also have decreased sympathetic nerve fibers in the affected tissues; together these changes stimulate a proinflammatory environment.[13, 14] A dampened HPA axis can cause increased susceptibility to autoimmune or inflammatory disease such as rheumatic diseases[15] because the normal hormones released by the HPA axis and sympathetic nervous system, which are immunosuppressive, are present in insufficient levels. It is possible that this dysfunction of the stress response is related to a larger dysfunction in the body's

physiology in the form of allostatic load. McEwen and Seeman consider this hypoactive state of the HPA axis to be a form of AL that causes the immune mediators to overreact and increase the risk of autoimmune and inflammatory disorders.[6]

As of yet, no study has looked at an association between allostatic load and arthritis. Research has however, laid a foundation for such work by studying the stress response in those with arthritis and stress as a risk factor for arthritis. The primary aim of this research is to assess if there is a cross-sectional association between allostatic load and arthritis using a large, nationally representative study. This aim will be investigated through the following research questions: 1) is there a significant association between a cumulative score of allostatic load and arthritis; 2) is there a significant association between each of the three subscales of allostatic load (inflammatory, metabolic, and cardiovascular) and arthritis; 3) is there a significant interaction present between total allostatic load and gender in the association between allostatic load and arthritis. The third research question is based on the unexplained increased risk of arthritis in women, and looks to see if allostatic load could be related to this gender-based risk. The hypothesis of this research is that there will be a positive association between a higher allostatic load score and risk of arthritis, and that the AL subscale of inflammation will be the only subscale with a significant relationship with arthritis.

Chapter 2: Methods

The sample includes participants from NHANES 2003-2004 and 2005-2006, conducted by the National Center for Health Statistics (NCHS), a part of the Centers for Disease Control and Prevention (CDC). A nationally representative sample of about 5,000 people is surveyed for NHANES each year, and data is released in 2 year cycles. The survey consists of an interview portion with demographic, socioeconomic, dietary, and health-related questions, a physical examination with physiological measurements and laboratory tests. The survey uses multistage stratified clustered probability samples selected to be representative of the national population. Subjects are civilian, non-institutionalized household populations of all ages with oversampling of African Americans, Mexican Americans, people over the age of 60, low income persons, adolescents aged 12-19, and pregnant women.

Study Sample

The sample included participants of NHANES 03-06 (N=20,470). Subjects were excluded if they were under the age of 20 since normal biomarker levels vary between adults and children (n=10,450), were pregnant or possibly pregnant at the time of interview or exam since pregnancy alters biomarker levels (determined by urine test at exam; n=834), if they were missing any of the 11 biomarkers for AL (n=1,439), if they were missing doctor diagnosed arthritis (not asked, refused to respond, or responded "don't know"; n=21), or if they were missing education or smoking status information (n=12). The final analytic sample included 7,714 participants, 37.7% of the full sample

and 73.8% of the adult sample. See table 1 for complete demographic information and distribution.

Table 1. Demographic Characteristics of Analytic Sample (Weighted) (N=7714)

Variable	N (%)	Variable	N (%)
Age		**Annual Family Income Cont.**	
20-85 years	Mean: 46.8 Std Dev: 0.5	$35,000-44,999	767 (10.1%)
Gender		$45,000-54,999	667 (9.6%)
Male	4011 (50.1%)	$55,000-74,999	752 (12.4%)
Female	3703 (49.9%)	$75,000 or more	1425 (25.9%)
Race/Ethnicity		Missing	383 (4.3%)
Non-Hispanic White	4062 (73.3%)	**Poverty to Income Ratio (PIR)**	
Non-Hispanic Black	1588 (10.5%)	Below poverty line (PIR<1.0)	1205 (10.5%)
Hispanic	1760 (11.1%)	Near poverty (1.0≤ PIR <2.0)	1924 (19.3%)
Multiracial or Other	304 (5.1%)	2.0≤ PIR <3.0	1191 (15.5%)
Education		3.0 or above	2966 (50.0%)
Less than high school graduate	2163 (17.4%)	Missing	428 (4.75)
High school graduate or GED	1908 (26.1%)	**Smoking Status**	
Associates degree or some college	2170 (31.6%)	Never Smoker	3868 (49.7%)
College degree	1473 (24.9%)	Current Smoker	1788 (25.1%)
Annual Family Income		Past Smoker	2058 (25.2%)
Less than $9,999	646 (5.9%)		
$10,000-19,999	1412 (12.8%)	**Arthritis**	
$20,000-24,999	690 (7.2%)	Yes	2148 (25.0%)
$25,000-34,999	972 (11.8%)	No	5566 (75.0%)

Variables

Independent Variable

The independent variable was allostatic load which is a summary index created by the number of biomarkers for which the subject falls into the high-risk category. Based on allostatic load literature and availability, 11 biomarkers were used: C-reactive protein (CRP), glycohemoglobin (glycosylated hemoglobin), homocysteine, total triglycerides,

serum albumin, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, diastolic blood pressure, resting heart rate, and body mass index (see table 2 for list and definitions and table 3 for distribution). Each biomarker was based on a single measurement taken at the examination portion of NHANES, except for systolic and diastolic blood pressure. Both systolic and diastolic blood pressure were measured between one and four times on each participant, and the mean of all available measurements were used to estimate average blood pressure. CRP, glycohemoglobin, homocysteine, triglycerides, albumin, total cholesterol, and HDL cholesterol were all based on blood drawn at the exam.

The laboratory used for measuring serum glycohemoglobin was changed between study years 2004 and 2005 so the glycohemoglobin levels from 2005-2006 were transformed based on NHANES recommendation to increase compatibility with 2003-2004 levels[16]. Body mass index was calculated as the measured the measured weight in kilograms divided by the measured height in meters squared. Some studies that have used CRP as a biomarker in allostatic load have excluded participants with values over 10 mg/dL since their high values could indicate a systemic infection. However, this is not appropriate to do when considering an outcome of arthritis which characteristically has high levels of CRP during preclinical and clinical manifestation. Studies show that mean CRP levels in a sample of rheumatoid arthritis patients had a median of 5.3 and a mean of 11.4, with a standard deviation of 21.1[17]. Therefore in this sample, levels of CRP over 10 could be a natural state of inflammation and not due to infection.

The high risk categories were defined as those that fall into the high risk quartile based on the sample's distribution of that variable; this was the 75th percentile for all

biomarkers except for albumin and HDL cholesterol which was the 25th percentile. For each subject the number of biomarkers that were in the high risk group was summed to create the total allostatic load value (range of 0-11). This variable was analyzed both as a continuous variable and as a categorical variable with the approximate quartiles of the distribution serving as the categories (Q1: 27%, values 0-1, n=2101; Q2: 18%, value 2, n=1349, Q3: 33%, values 3-4, n=2572; Q4: 21%, values 5-11, n=1692). Exact quartiles could not be used due to the fact that only integers are valid scores for the AL scale.

Three subscales were created out of these biomarkers, inflammatory (CRP and albumin; range 0-2), metabolic (glycohemoglobin, total cholesterol, HDL cholesterol, triglycerides, BMI; range 0-5), and cardiovascular (systolic blood pressure, diastolic blood pressure, resting heart rate, homocysteine; range 0-4) by totaling the biomarkers for each that was in the high risk category. Each subscale was separately used as a continuous independent variable to see which had associations with arthritis.

Table 2. Allostatic Load Biomarkers and Descriptions

Variable (units)	Description	Subgroup of AL
C-Reactive Protein (mg/dL)	Protein produced by liver, indicates inflammation	Inflammatory
Serum Albumin (g/dL)	Protein made by the liver, can indicate kidney or liver function or protein malabsorption	Inflammatory
Glycohemoglobin (%)	Glucose bound to hemoglobin, indicates long-term control of blood glucose levels	Metabolic
Body Mass Index (kg/m^2)	Index of height compared to weight, indicates overweight or obesity	Metabolic
Triglycerides (mg/dL)	Lipoprotein associated with cardiovascular disease	Metabolic
Total Cholesterol (mg/dL)	Lipoprotein made by liver, contributes to atherosclerosis	Metabolic
HDL Cholesterol (mg/dL)	Type of cholesterol that is believed to remove cholesterol from arteries, reduces risk of heart disease	Metabolic
Homocysteine (umol/L)	Amino acid associated with atherosclerosis and cardiovascular disease	Cardiovascular

Systolic Blood Pressure Average (mm Hg)	Maximum pressure exerted when heart contracts, with DBP indicates high blood pressure	Cardiovascular
Diastolic Blood Pressure Average (mm Hg)	Minimum pressure in arteries when heart is relaxed, with SBP indicates high blood pressure	Cardiovascular
Resting Heart Rate (bpm)	Heart beats per minute when at rest, indicates heart conditions and general efficiency of heart	Cardiovascular

Table 3. Allostatic Load Biomarker Distribution in Analytic Sample (Weighted) (N=7714)

Variable (units)	Mean	Range	Std Error	High Risk*
C-Reactive Protein (mg/dL)	0.41	0.01-25.40	0.01	≥0.43
Albumin (g/dL)	4.27	1.90-5.50	0.01	<4.00
Glycohemoglobin (%)	5.52	4.00-18.00	0.02	≥5.60
Body Mass Index (kg/m^2)	28.28	13.36-130.21	0.15	≥31.56
Triglycerides (mg/dL)	146.79	20.00-5210.00	1.95	≥175.56
Total Cholesterol (mg/dL)	202.22	81.00-712.00	0.66	≥226.85
HDL Cholesterol (mg/dL)	54.13	17.00-188.00	0.26	<41.63
Homocysteine (µmol/L)	8.82	2.92-145.00	0.09	≥9.89
Systolic Blood Pressure Average (mm Hg)	123.18	73.00-270.00	0.36	≥131.92
Diastolic Blood Pressure Average (mm Hg)	70.75	0.00-124.00	0.26	≥77.94
Resting Heart Rate (bpm)	72.27	32.00-220.00	0.27	≥78.76

*This is the definition of high risk for the biomarker based on the analytic sample distribution; it is determined by the 75th percentile for all biomarkers except for HDL and albumin which use the 25th percentile.

For comparative analysis, the z score method of calculating allostatic load was also used. For this method, each biomarker distribution was transformed to the standard normal table and the participants' value was transformed to a z score. Subjects with outlier values at or beyond five standard deviations from the mean were excluded based on methods described by Seplaki and colleagues as a means of removing outliers[18]. The absolute value of the z scores were taken so that both directions of values from the mean were considered higher risk for all biomarkers except for HDL cholesterol since there has

been no research showing that high levels of HDL can be harmful (all z value more than zero were assigned a value of zero). The z scores of the 11 biomarkers were then summed to create the total allostatic load score and the subscale scores. Each of these scales were used as predictors in age-adjusted and multivariate regression models and these results were compared to the count method of calculating allostatic load.

Dependent Variable

The dependent variable was self-reported doctor diagnosed arthritis (yes/no). All those with missing values and reporting "don't know" or "refused" were treated as missing for diagnosis of arthritis and were excluded as explained above. The sample has 2,148 cases of arthritis (25%).

Covariates

Covariates included age, gender, race/ethnicity, income and poverty level, education, and smoking status. Each of these covariates have been shown to have a direct association with allostatic load and a direct or indirect association with arthritis.

Age was the participant's age in years at the time of the screening interview calculated from the respondent's actual or imputed date of birth. Imputed dates of birth were calculated by NAHNES if missing based on the reported age. All adults over the age of 85 were given values of 85 by NHANES due to the fact that few participants were in this category and reporting specific ages could risk their anonymity. Gender was self

reported as either male or female. Race/ethnicity was coded based on both reported race and ethnicity and includes the following categories: Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other race including multiracial individuals. Mexican American and other Hispanic were collapsed into one category of Hispanic due to small a sample size.

Socioeconomic status was assessed by both education and income variables. Education was the reported highest grade or level of education completed and was categorized as: less than 9^{th} grade, $9\text{-}12^{th}$ grade and no high school diploma, high school graduate/GED, some college or associates degree, and college graduate or higher. The categories of less than 9^{th} grade and $9\text{-}12^{th}$ grade but no high school diploma were collapsed due to high similarity and small sample size. If the participant was missing education (n=9) then they were excluded from the sample. Income was the total annual family income reported including wages, retirement income, disability payments, interest income, and assistance programs. Those who did not know the exact amount selected a range and the midpoint of the range was used as the value. The categories created by NHANES were slightly collapsed due to small numbers in some categories. The final categorization was: less than $9,999, $10,000-19,999, $20,000-24,999, $25,000-34,999, $35,000-44,999, $45,000-54,999, $55,000-74,999, $75,000 or more, and missing income.

The poverty income ratio (PIR) was calculated from the family income and was the ratio of the income to the family's appropriate poverty threshold based on the family size. Values of 1.0 are at the federal poverty threshold, those below 1.0 are considered poor, and values of above 1.0 indicate income above the poverty level (all above 5.0 were top coded at 5.0 by NHANES since disclosing their information is a risk to their

anonymity). This variable was categorized based on poverty groupings. The first category was those with PIR less than 1.0 since they are below the official federal poverty line and will generally qualify for all government assistance programs. The next category was the near poor at PIR greater than or equal to 1.0 and less than 2.0. These individuals may qualify for many state government programs such as Medicaid or State Children's Health Insurance Program (SCHIP), that often have eligibility for those up to 200% of the Federal Poverty Line (FPL). Some states have eligibility that expends up to 300% FPL, so the next group was those with PIR greater than or equal to 2.0 and up to 3.0. The last group generally will not qualify for any assistance programs (PIR≥3.0). A missing category was also created for those without PIR.

Smoking status was categorized based on self-report as a never smoker, current smoker, or if one had previously smoked and quit, then as a former/past smoker. Those missing smoking status (n=3) were excluded from the sample.

Statistical Analysis

Descriptive statistics assessed the general distribution of each variable. Each parameter for AL was divided into quartiles based on the sample/population distribution, a high risk quartile was identified for each parameter, and the number of parameters that each subject falls into the high risk quartile were summed for the total AL score. Simple age-adjusted logistic regression examined the relationship between continuous allostatic load score and arthritis and to assess the relationship of each covariate and arthritis. Multivariate logistic regression analyses estimated the odds ratio for the association

between continuous allostatic load and arthritis, while accounting for confounders. To determine the final multivariate model, each covariate was added to the univariate model one at a time and then in pairs, trios, and quads until all combinations of covariates were considered. The model with the lowest Akaike's Information Criterion (AIC) was taken. Tests for multicollinearity were run on this model to ensure that the variables were not collinear and could be run in the same regression model. Collinearity based on the variance inflation factor (VIF) was present between annual family income and poverty to income ratio, so one of these variables needed to be removed from the model. To determine which to remove, a model with income but not PIR and a model with PIR but not income was run and the AIC was compared. The model with income and not PIR had the lowest AIC out of all models and no longer violated collinearity.

The total allostatic load score was divided into quartiles based on the sample distribution, and this served as a categorical version of total AL score. The age-adjusted model and multivariate model were rerun using total allostatic load score as this categorical variable. Separate age-adjusted and multivariate logistic regressions were run using each subscale of allostatic load (continuous) and arthritis. The final model of continuous total allostatic load and arthritis was tested for an interaction between allostatic load and gender by adding an interaction term to the model. The interaction term was not significant, so this avenue was not pursued further. All models were also stratified by gender and age groups to look at effect modification by these variables. Two age groupings were used for stratification: 1) less than 50 years old and 50 years old or older, and 2) less than 40, 40 to 59 years old, and 60 years old or older. All models accounted for the survey's complex sampling design using the statistical procedure

PROC SURVEYLOGISTIC using SAS 9.2 (Cary, North Carolina). Each age-adjusted and multivariate model was rerun with the z score method allostatic load variables and subscales and compared to the count method.

Chapter 3: Results

Table 1 shows the distribution of the sample based on key sociodemographic characteristics. The mean age of the sample was approximately 47 years (standard deviation= 0.5 years) and the sample was evenly distributed on gender. The sample was 73% Non-Hispanic White, 11% Hispanic, 11% Non-Hispanic black, and 5% multiracial or other race/ethnicity. The educational level was fairly evenly distributed across the categories with less having less than a high school degree and more having an associate's degree or some college. The majority of the sample were at 300% or more of the federal poverty threshold and were never smokers. The sample was fairly evenly distributed across the income categories with the exception of $75,000 or more which had a larger proportion (26%) of the participants and less than $9,999 which had a smaller proportion (6%) of the participants than other categories. Approximately 25% of the sample had arthritis; this is slightly higher than the prevalence estimate of 21% found by Helmick and colleagues using national surveys including NHANES and the National Health Interview Survey[19].

Age adjusted models showed that the continuous total allostatic load score was a statistically significant predictor of self-reported doctor diagnosed arthritis, where each one unit increase in the allostatic load score (one additional high risk biomarker) resulted in 1.13 increased odds of having arthritis (95% CI=1.09-1.17). See Table 4 for complete results. Age was also a statistically significant predictor of arthritis with each one year increase in age having a 1.06 increased odds of having arthritis (95% CI= 1.05-1.06). In the fully adjusted model, total allostatic load score had a statistically significant association with arthritis (OR=1.12, 95% CI= 1.08-1.17) when controlling for all other

variables. The other variables that were statistically significant predictors of increased odds of arthritis were age, being female compared to male, being a high school graduate or less than a high school graduate compared to having a college degree, being a current or former smoker compared to never smoking, and having an income of less than $9,999 compared to those with an income of $75,000 or more. The only statistically significant predictor that was associated with a reduced odds of having arthritis is being Non-Hispanic black (OR=0.75, 95% CI= 0.65-0.86) or Hispanic (OR= 0.42, 95% CI= 0.33-0.52) compared to being Non-Hispanic White.

Table 4. Odds Ratios and 95% Confidence Intervals for Association between Total Allostatic Load and Arthritis

	Age adjusted Model		Fully Adjusted Model	
Variable	**Odds Ratio**	**P Value**	**Odds Ratio**	**P Value**
Total AL	1.13 (1.09-1.17)	<.0001	1.12 (1.08-1.17)	<.0001
Age (yrs)	1.06 (1.05-1.06)	<.0001	1.05 (1.05-1.06)	<.0001
Gender				
Male			1.00	
Female			1.67 (1.42-1.95)	<.0001
Race				
Non-Hispanic White			1.00	
Non-Hispanic Black			0.75 (0.65-0.86)	<.0001
Hispanic			0.42 (0.33-0.52)	<.0001
Multiracial or Other			0.83 (0.57-1.21)	0.326
Education				
College Degree			1.00	
Associates Deg. or Some College			1.12 (0.94-1.35)	0.211
High School Graduate			1.24 (1.00-1.54)	0.052
No High School Degree			1.50 (1.14-1.98)	0.003

	Age adjusted Model		Fully Adjusted Model	
Variable	**Odds Ratio**	**P Value**	**Odds Ratio**	**P Value**
Smoking Status				
Never Smoker			1.00	
Current Smoker			1.33 (1.11-1.60)	0.002
Former Smoker			1.29 (1.10-1.50)	0.001
Annual Family Income				
$75,000 or more			1.00	
$55,000-74,999			1.12 (0.90-1.39)	0.296
$45,000-54,999			1.29 (1.00-1.66)	0.0497
$35,000-44,999			1.20 (0.92-1.56)	0.174
$25,000-34,999			1.18 (0.90-1.55)	0.232
$20,000-24,999			1.16 (0.89-1.49)	0.274
$10,000-19,999			1.20 (0.91-1.60)	0.204
<$9,999			1.44 (1.08-1.92)	0.014
Missing			1.28 (0.89-1.83)	0.187

In order to aid in translating the research to public health significance, a categorical variable was created based on quartiles of total allostatic load score, using the lowest quartile as the reference group. In the age-adjusted model, quartile 3 and quartile 4 each had a statistically significant positive association with odds of arthritis (quartile 2 was not statistically significant). See table 5 for complete results. Participants with total allostatic load scores in the third quartile had an increased odds of arthritis of 76 percent compared to those in the lowest quartile (OR=1.76, 95% CI=1.42-2.19). Participants with total allostatic load scores in the top quartile had an increased odds of arthritis of 80 percent compared to those in the lowest quartile (OR=1.80, 95% CI=1.43-2.25). In the multivariate model, the odds ratios were similar but slightly attenuated by controlling for

confounders at 1.73 (95% CI=1.38-2.17) for quartile 3 and 1.79 (95% CI=1.41-2.26) for quartile 4 compared to the lowest quartile.

Table 5. Odds Ratios and 95% Confidence Intervals for Association between Total Allostatic Load and Arthritis with Allostatic Load Categorized into Quartiles

	Age Adjusted Model		Multivariate Model	
Variable	**OR**	**P Value**	**OR**	**P Value**
AL Quartiles				
Quartile 1 (score 0-1)	1.00		1.00	
Quartile 2 (score 2)	1.12 (0.90-1.40)	0.292	1.14 (0.90-1.43)	0.274
Quartile 3 (score 3-4)	1.76 (1.42-2.19)	<.0001	1.73 (1.38-2.17)	<.0001
Quartile 4 (score 5-11)	1.80 (1.43-2.25)	<.0001	1.79 (1.41-2.26)	<.0001
Age (Yrs)	1.06 (1.05-1.06)	<.0001	1.05 (1.05-1.06)	<.0001
Gender				
Male			1.00	
Female			1.66 (1.42-1.95)	<.0001
Race				
Non-Hispanic White			1.00	
Non-Hispanic Black			0.74 (0.65-.85)	<.0001
Hispanic			0.42 (0.34-0.52)	<.0001
Multiracial or Other			0.82 (0.56-1.19)	0.299
Education				
College Degree			1.00	
Associates Deg. or Some College			1.48 (1.13-1.94)	0.004
High School Graduate			1.23 (0.98-1.53)	0.070
No High School Degree			1.11 (0.93-1.33)	0.252
Smoking Status				
Never Smoker			1.00	
Current Smoker			1.34 (1.13-1.61)	0.001

	Age Adjusted Model		Multivariate Model	
Variable	**OR**	**P Value**	**OR**	**P Value**
Former Smoker			1.28 (1.10-1.50)	0.001
Annual Family Income				
$75,000 or more			1.00	
$55,000-74,999			1.12 (0.90-1.40)	0.301
$45,000-54,999			1.27 (0.98-1.64)	0.072
$35,000-44,999			1.19 (0.92-1.53)	0.194
$25,000-34,999			1.18 (0.90-1.55)	0.240
$20,000-24,999			1.16 (0.89-1.51)	0.285
$10,000-19,999			1.20 (0.90-1.60)	0.211
<$9,999			1.42 (1.06-1.90)	0.018
Missing			1.25 (0.87-1.81)	0.226

Analysis of the subscales of allostatic load gave additional insight to the relationship between AL and arthritis. Subscales were left as continuous variables due to their small range and total AL was used as a continuous variable to compare to the subscales. See table 6 for complete results. The inflammatory subscale was a statistically significant predictor of arthritis with each one unit increase in the scale being associated with 1.35 increased odds of arthritis in the age-adjusted model (95% CI=1.23-1.49). The fully adjusted model had a slightly attenuated, but still highly significant association of 1.27 when controlling for all confounders (95% CI=1.15-1.40). The metabolic subscale of AL was significantly associated with an increased odds of arthritis of 1.18 (95% CI= 1.11-1.25) in the age-adjusted model and 1.20 (95% CI= 1.13-1.28) in the fully adjusted model. The cardiovascular subscale had a significant association with arthritis in the age-adjusted model (OR=1.07, 95% CI= 1.00-1.14), but marginally significant association in

the full-adjusted model (OR=1.06, 95% CI= 0.99-1.13). The subscale analysis shows that both the inflammatory and metabolic subscales have stronger associations based on the odds ratios with arthritis than the total allostatic load subscale, and that the cardiovascular subscale is weakly associated with arthritis.

Table 6. Odds Ratios and 95% Confidence Intervals for Association with Arthritis, Comparing Total Allostatic Load to Allostatic Load Subscales

	Age adjusted Model		Fully Adjusted Model	
Variable	**Odds Ratio**	**P Value**	**Odds Ratio**	**P Value**
Total AL	1.13 (1.09-1.17)	<.0001	1.12 (1.08-1.17)	<.0001
Inflammatory Subscale	1.35 (1.23-1.49)	<.0001	1.27 (1.15-1.40)	<.0001
Metabolic Subscale	1.18 (1.11-1.25)	<.0001	1.20 (1.13-1.28)	<.0001
Cardiovascular Subscale	1.07 (1.00-1.14)	0.041	1.06 (0.99-1.13)	0.074

To further assess the possibility of effect modification, stratified analysis was completed on all models. Results were stratified by gender to test if this was having an impact on the models using total allostatic load or any of the subscales. Similar to the interaction test run, there was no difference in the association by gender. To test for effect modification by age, results were stratified by two different age groupings. First the sample was stratified into being 1) less than 50 year old and 2) being 50 years old or older. This age cut-point was chosen since this is when there is a large increase in incidence of arthritis. Regression results did not show any differences by this age grouping. Next, the sample was stratified into being 1) less than 40 years old, 2) between 40 and 59 years old, and 3) being 60 years old or older. This grouping captures the fact

that there is a slight rise in incidence of arthritis around age 40. However, again regression results did not show differences by age groups.

Finally, the z score method was used to calculate total allostatic load and each subscale and compare to the count method of calculation. As stated in the methods, both high and low ends of the distribution were considered "at risk" for all biomarkers except HDL cholesterol. The age-adjusted and multivariate results were compared to the count method results, and all results were similar and showed consistent trends. Due to the similarity, results were not presented here.

Chapter 4: Discussion

The main finding of this study using NHANES 2003-2006 data was a statistically significant positive association between allostatic load and odds of arthritis. This is one of the first studies that examined the association between allostatic load and arthritis. This association was moderate when using total allostatic load as a continuous variable and stronger when categorizing it into quartiles. Those in the two highest quartiles had an increased odds of arthritis of 73 and 79 percent respectively when compared to the lowest quartile. While the second quartile was not statistically significant, the overall trend suggests a dose-response relationship, indicating higher levels of total allostatic load is associated with higher odds of arthritis.

One of the main strengths of this study was the ability to elucidate the relationship between allostatic load and arthritis using the subscale analysis. The subscales of the inflammatory system, measured by CRP and albumin levels, and the metabolic system, measured by glycohemoglobin, total cholesterol, HDL cholesterol, triglycerides, and BMI, were associated with an increased odds of arthritis of 27 percent for the former subscale and 20 for the latter, with each additional high risk biomarker, when controlling for all confounders. These odds ratios were stronger than the odds ratio of the continuously measured total allostatic load score. The cardiovascular subscale was marginally significantly associated with odds of having arthritis. The association was somewhat weak. These results suggest that the metabolic regulatory system, the inflammatory regulatory system, and the cardiovascular system may be involved in the mechanisms connecting cumulative biological dysfunction and arthritis.

Prior research has looked at the association between certain biomarkers of the inflammatory, metabolic, and cardiovascular systems and arthritis. All but one of these studies have also been cross-sectional, which fail to give additional insight to the direction of the associations. The one longitudinal study used serial blood samples to measure CRP levels in blood donors who subsequently developed rheumatoid arthritis from 0.4 to 14.5 years after blood donation[20]. These levels were compared to controls matched for age, sex, and year of blood donation[20]. The patient group had statistically significant higher concentrations of CRP for periods 0-1 year, 1-2 years, and 4-5 years before the onset of symptoms compared to the control group[20]. The control group had a constant mean CRP level over time, while the patient group had a mean that increased over time and was highest at the time of symptom onset[20]. This study suggests that CRP as a measure of inflammation is elevated prior to disease onset in patients that develop rheumatoid arthritis. This study is consistent with present research findings that there is an association between the inflammatory system and arthritis, and may suggest that dysfunction in the inflammatory system could be present before disease onset.

Existing research also suggests that there might be a connection between the elevated inflammatory system and the stress response system in patients with rheumatoid arthritis. Davis and colleagues studied fifty-eight patients with physician confirmed rheumatoid arthritis and found that those who reported higher chronic interpersonal stress, as measured by daily ratings of an abbreviated Inventory of Small Life Events scale over one month, had significantly higher levels of interleukin-6 (IL-6) production and increased resistance to the inhibiting effects of glucocorticoid doses given compared to patients with low chronic stress[21]. In contrast, CRP was not related to chronic stress in

the study[21]. IL-6 is a cytokine that is produced primarily by immune cells and stimulates inflammation through increasing production of CRP and other proteins[21]. Normally in response to stress, the HPA axis releases cortisol which suppresses inflammation and reduces production of IL-6[21]. The study supports the theory that exposure to chronic stress may cause the anti-inflammatory reactions of the stress-response system to be ineffective. It is difficult to directly compare the study to the present research due to different biomarker measurements; however, it is generally consistent with the theory of allostatic load in that exposure to the stress response system over time can cause dysfunction in the regulatory systems, such as the ineffectiveness of the HPA axis to control inflammation through IL-6. One limitation to the study is its lack of longitudinal design, so it is unclear if the elevated allostatic load in people with arthritis is a consequence of the disease or was present before disease onset.

Prior research has also found associations between certain biomarkers of the metabolic system and arthritis. Chung and colleagues studied 154 patients with rheumatoid arthritis (RA) and 85 matched controls without any inflammatory diseases and found that the RA patients had significantly lower levels of HDL, higher rates of hypertension, and higher rates of metabolic syndrome (consisting of central obesity, high triglycerides, high blood pressure, high fasting glucose, and high insulin resistance)[22]. These associations are consistent with this study's findings, but because of the cross-sectional study design, they do not grant insight to the direction of the association. Dessein and colleagues studied 79 RA patients and 39 matched controls with osteoarthritis (OA) and found that these groups were similar in terms of their rates of hypertension, BMI, total cholesterol, and triglycerides, but statistically significant

differences in their levels of diabetes and HDL cholesterol[23]. Patients with RA had significantly lower HDL levels, and higher rates of diabetes than patients with OA[23]. The study is also cross-sectional so it cannot provide insight to the direction of the association, but it indicates that some markers of the metabolic system are related to arthritis, and the type of arthritis may also be important in associations between arthritis and biomarkers since the study found different associations by type of arthritis (OA compared to RA).

In regards to the cardiovascular system, patients with arthritis are shown to have increased rates of cardiovascular disease. The studies by Dessein and Chung both showed increased rates of high blood pressure[22, 23] and Chung also found increased levels of homocysteine[22] in patients with rheumatoid arthritis. These studies are consistent with the present research, which found a marginally significant association with arthritis using the cardiovascular subscale.

Existing research supports the results found in this study in that most of the individual biomarkers included in the allostatic load scale and subscales have been previously established as having an association with arthritis. However, most of these studies have been conducted cross-sectionally in patients with existing arthritis; like the present research, they do not provide evidence of the direction of the association. It could be possible that changes in the stress-response system occur first with dysfunction in multiple regulatory systems (allostatic load), and these changes create a pro-inflammatory environment that increases the risk for developing arthritis. In contrast, it is possible that the physiological changes that cause arthritis also cause dysfunction in other regulatory systems of the body, creating a larger state of allostatic load. More

research is needed to clarify the direction of the relationship and to confirm the results in other populations.

Limitations and Strengths

This research is a secondary analysis of an existing dataset, limiting the analysis to the availability of variables in the NHANES dataset. For this reason, the hormones of the stress response system, cortisol, norepinephrine, epinephrine, and DHEA-S were not included into the AL measure. Also, additional confounders such as genetic testing for genes that increase disease risk, family history of arthritis, and systemic infections could not be assessed. Both the dependent and independent variables were assessed only once and at the same time, so the direction of the association cannot be determined by this analysis. Analysis by type of arthritis could not be completed due to a majority of missing types of arthritis. Another limitation is the use of self-reported doctor diagnosed arthritis as the outcome without objective confirmation; however, studies of validity and reliability find that self-reported arthritis diagnosis is highly reliable when compared to objective measures[24].

Despite these limitations, the present research has many strengths as well. This is the first study that has studied the association between allostatic load and the odds of a rheumatic disease such as arthritis. The present study uses a large sample with diverse racial and economic characteristics. The large and diverse sample increases the natural distribution of the biomarkers and increases the generalizability of the study. Each of the biomarkers are measured through blood samples or physical exams which enhances

accuracy of the data and reduces self-report bias. Two methods of calculating allostatic load scores were used including the traditional count method and a z score method that retains the continuous nature of the original biomarker variables and considers both high and low ends of the distribution as "at risk." Another strength of this study is the ability to give additional insight to the relationship between AL and arthritis by looking at the individual subscales of AL and give some insight to the main regulatory systems playing a role in the relationship.

Conclusion

Despite the high prevalence and significant impact that arthritis has on health, its etiology is not fully understood. With the age distribution of the United States population shifting to older cohorts, the prevalence of arthritis is expected to greatly increase as well as the impact that the disease has on our society. Establishing the relationship between a measure of cumulative biological risk such as allostatic load and arthritis grants insight into the causes, risk factors, and initiation of the disease, and possibly other rheumatic and/or inflammatory autoimmune diseases. This research can also expand the concept of allostatic load, which is a relatively new theory, by finding new means of increasing disease risk. More research is needed to establish the causal relationship and the direction of the association. Given that allostatic load has been associated with so many chronic diseases, and the large societal impact that arthritis has, longitudinal studies are needed that measure biomarkers repeatedly over time and that focus on various chronic disease outcomes such as arthritis.

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