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Allostatic load in the association of depressive symptoms with incident coronary heart disease: The Jackson Heart Study

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ABSTRACT

African Americans are at heightened risk for coronary heart disease (CHD), with biologic pathways poorly understood. We examined the role of allostatic load (AL) in the association of depressive symptoms with incident CHD among 2,670 African American men and women in the prospective Jackson Heart Study. Depressive symptoms were quantified using the Center for Epidemiologic Studies Depression Scale (CES-D). Incident CHD was ascertained by self-report, death certificate survey, and adjudicated medical record surveillance. Baseline AL was quantified using biologic parameters of metabolic, cardiovascular, immune, and neuroendocrine subsystems and as a combined meta-factor. Sequential models adjusted for demographic, socioeconomic, and behavioral covariates, stratified to examine differences by sex. Greater depressive symptomatology was associated with greater metabolic, cardiovascular, and immune AL (p-values ≤ 0.036) and AL meta-factor z-scores ($p = 0.007$), with findings driven by observations among females. Each 1-point increase in baseline depressive symptomatology, and 1-SD increase in metabolic AL, neuroendocrine AL, and AL meta-factor z-scores was associated with 3.3%, 88%, 39%, and 130% increases in CHD risk, respectively (p-values < 0.001). Neuroendocrine AL and AL meta-factor scores predicted incident CHD among males but not females in stratified analyses. Metabolic AL partially mediated the association of depressive symptoms with incident CHD (5.79% mediation, $p = 0.044$), a finding present among females ($p = 0.016$) but not males ($p = 0.840$). Among African American adults, we present novel findings of an association between depressive symptomatology and incident CHD, partially mediated by metabolic AL. These findings appear to be unique to females, an important consideration in the design of targeted interventions for CHD prevention.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality in the U.S. (Kochanek et al., 2017), with African Americans at heightened risk for incident disease and CVD-related death compared to whites (Cunningham et al., 2017; Writing Group Members et al., 2016). Moreover, even when controlling for a number of relevant covariates, CVD presents at earlier ages, post-diagnosis survival is shortened, and risk for sudden death is heightened in African American versus white populations (Thomas et al., 2010; Thorpe et al., 2016; Zhao et al., 2019). For example, in mediation analyses of 15,069 participants, Zhao et al. (2019) found that 34.7% of the excess risk of sudden cardiac death in African Americans compared to whites remained unaccounted for after adjusting for individual socioeconomic, behavioral, clinical, and biological parameters (e.g., income, education, smoking, diabetes mellitus, body mass index, blood pressure). Racial and ethnic minorities

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with coronary artery disease are also less likely to receive effective pharmacotherapy (Tran et al., 2017). Though, racial disparities in CVD events have also been noted across treatment tiers among those with similar cardiovascular risk (e.g., greater probability of coronary heart disease [CHD] among hypertensive African Americans versus hypertensive whites receiving one, two, three, and four anti-hypertensive medications (Tajeu et al., 2017). Together, such data suggest that traditional and bias-associated risk do not fully account for racial disparities in CVD outcomes. As such, while a substantial literature outlines the presence and persistence of racial disparities in cardiovascular health, the identification of non-traditional risk factors that may contribute to CVD among African Americans remains an important area of inquiry.

In this regard, depressive symptoms have been increasingly recognized as a non-traditional risk factor that may contribute to the development and progression of poor cardiovascular health (Eurelings et al., 2018; Wandell et al., 2018; Wu et al., 2018). For example, depressive symptoms have been shown to precede incident CVD during follow-up periods of 5–15 years (Eurelings et al., 2018; Wandell et al., 2018). Recent work suggests that depressive symptoms may be a particularly salient predictor of CHD among African Americans compared to non-Hispanic whites (O'Brien et al., 2015). Despite such findings and those suggesting that African Americans may bear a disproportionate burden of depressive symptomatology (Mukherjee et al., 2016), including as a function of racial discriminatory exposures (Paradies et al., 2015), studies explicating the link between depressive symptoms and CHD among African Americans have received relatively little attention.

Moreover, depressive symptoms have been linked to dysregulation across a number of biological parameters, namely obesity (Ambrosio et al., 2018; Srinivas et al., 2018), high blood pressure (Srinivas et al., 2018), and inflammation (Ambrosio et al., 2018), including the new onset or progression of biological dysregulation in prospective investigations. In fact, when such parameters are held constant in aggregate, the magnitude of racial disparities in CVD-related mortality is significantly attenuated (Duru et al., 2012), suggesting dysregulation of key biological parameters may help explain the association between depressive symptoms and CHD. However, the mediational role of biological subsystems of potential importance in the association between depressive symptoms and CHD among African Americans remains understudied. Similarly, the prevalence of depression is known to differ among men and women and the structure of psychological stress-responsive biological dysregulation appears to differ by sex (Buckwalter et al., 2016; Labaka et al., 2018). For example accumulating evidence suggests that women are more likely to exhibit an inflammatory phenotype than men in the context of major depressive disorder (Labaka et al., 2018). The identification of sex differences in the pathways linking depressive symptoms to incident CHD could provide new opportunity to design tailored preventive interventions.

To address these knowledge deficits and identify novel targets in the prevention of CHD among African Americans, we draw upon the allostatic load (AL) model, which posits that the repeated application of adaptive responses to psychological stress or distress leads to cumulative and quantifiable wear and tear on the body (McEwen, 1998). AL can be estimated as a composite meta-factor (an aggregate measure of underlying subsystems) and partitioned into subsystems (i.e., metabolic [waist circumference, triglyceride/high density lipoprotein ratio, low density lipoprotein, hemoglobin A1c], cardiovascular [heart rate, systolic blood pressure, diastolic blood pressure), immune [high sensitivity C-reactive protein], neuroendocrine [cortisol, aldosterone] (e.g., Seeman et al., 2008, 1997)), providing a framework from which to examine the relative importance of biological dysregulation across and within subsystems in the association of depressive symptoms with incident CHD. Specifically, we examined associations among depressive symptoms and AL indices assessed at baseline and incident CHD over a period of approximately 10 years among the adults participating in the prospective Jackson Heart Study (JHS). Given the extant literature, we hypothesized that greater depressive symptomatology at baseline would predict heightened risk for incident CHD and that this association would be partially mediated by the AL meta-factor. We also hypothesized that subscale analyses would reveal metabolic and cardiovascular AL subsystem contributions among the full sample with the potential for unique immune AL subsystem contributions among women in the development of depressive symptom-associated CHD.

2. Methods

2.1. Study design

The JHS is a prospective study of risk factors for the development and progression of CVD in a cohort of 5,306 African American adults, aged 21–94 years at baseline from the tri-county area (Hinds, Madison, Rankin counties) of metropolitan Jackson, Mississippi. Details about the study design have been described elsewhere (Taylor et al., 2005). Briefly, JHS participants were enrolled and followed longitudinally at three examinations occurring from 2000 to 2004 (i.e., baseline), 2005–2008 (i.e., examination 2), and 2009–2013 (i.e., examination 3) and through annual phone calls. In the current analyses, participants were excluded if they had baseline CHD (n = 400), if CES-D score was missing (n = 1713), if baseline or follow-up CHD data was missing (n = 117), or if covariates were missing (n = 406). After exclusions, the analytic cohort included 2,670 adults (mean age 53.4 $\pm$ 12.5 years; 66% female). Demographic and clinical summaries for excluded versus included JHS participants are presented in Supplemental Table 1. Excluded JHS participants were older, more likely to be male, had less education, were less likely to report a management or professional occupation, were more likely to smoke, were less likely to engage in physical activity, were more likely to be taking medications, and exhibited less favorable biological parameters (e.g., greater waist circumference, heart rate, systolic blood pressure, triglycerides, triglyceride/high density lipoprotein ratio, hemoglobin A1c, serum cortisol) than included JHS participants (p values $\leq$ 0.05). Both groups had 4% incident CHD among those with available data. The JHS was approved by the institutional review boards of the University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All participants provided informed consent.

2.2. Depressive symptoms

Depressive symptoms over the last week were quantified at baseline using the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report measure (Radloff, 1977). Participants were asked to indicate whether each item (e.g., "I had trouble keeping my mind on what I was doing") was experienced rarely or none of the time (score = 0), some or a little of the time (score = 1), occasionally or a moderate amount of time (score = 2), or most or all of the time (score = 3) during the past week (some items reverse coded). CES-D scores range from 0 to 60, with higher scores indicative of greater depressive symptomatology and scores $\geq$16 indicative of clinically significant depressive symptomatology (Thomas et al., 2001). The scale has been extensively used and validated, including among African American community-dwelling populations (Atkins, 2014). Internal reliability was high in this sample (α = 0.82).

2.3. Coronary heart disease

Incident CHD served as the outcome of interest. Methods for ascertaining cardiovascular events in the JHS cohort have been described previously (Keku et al., 2005). Briefly, CVD events were ascertained through a combination of active and passive surveillance. Annual follow-up included interviews with participants and next of kin to ascertain health events, such as cardiac events, hospitalizations, or death, and through questionnaires completed by physicians and medical

examiners or coroners and reviewed by the medical record abstraction unit to generate diagnosis information. These diagnoses were reviewed and adjudicated by trained medical personnel. Cardiovascular illness hospitalizations were identified and adjudicated as described previously (Keku et al., 2005). Hospitalization data were obtained from the hospital discharge index from all catchment area hospitals and annual follow-up data and data from non-catchment area hospitals were obtained after patient consent. Death certificates from state vital statistics offices were surveyed for potential CVD events. The self-reported data from annual follow-up were reconciled with the hospital discharge index data. The primary diagnoses based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were reviewed and adjudicated by trained medical personnel. For the current analyses, we assessed the CHD occurrence between 2000 and 2011.

2.4. Allostatic load

Baseline AL was quantified according to biological parameters in one of four AL subsystems: 1) metabolic (i.e., waist circumference, triglyceride/high density lipoprotein [HDL] ratio, low density lipoprotein [LDL], hemoglobin A1c [HbA1c]), 2) cardiovascular (i.e., heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP]), 3) immune (i.e., high sensitivity C-reactive protein [hs-CRP]), and 4) neuroendocrine (i.e., serum cortisol, serum aldosterone). The continuous scores for each biological parameter were transformed into standardized z-scores. The standardized z-scores for each biological parameter were then averaged within each respective AL subsystem to create a subsystem score. The AL subsystem scores were then averaged to create a composite AL meta-factor.

AL subsystem parameters were chosen to reflect the secondary markers (i.e., metabolic, cardiovascular, immune) and primary mediators (i.e., neuroendocrine) of AL commonly assessed in the AL literature (e.g., Seeman et al., 2008, 1997) and available for use in the JHS dataset. We generated z-scores, which are indicative of individual differences from the sample mean for each parameter. Calculation of z-scores allows for examination of incremental effects across diverse parameters and appears to show slightly improved predictive power for health outcomes than alternative AL indices (Seplaki et al., 2005). Employing an approach used previously (e.g., Friedman et al., 2015), we averaged AL subsystem scores to allow for the creation of an AL meta-factor that is not unduly influenced by the number of biological parameters in each AL subsystem.

Certified technicians and nurses measured participants' waist circumference (average of two measurements around the umbilicus) and resting seated blood pressure, the average of two measurements at 5-minute intervals using an appropriately sized cuff with standard Hawksley random-zero instruments.

Fasting blood samples were drawn at baseline in the supine position and processed using a standardized protocol. Plasma and serum were prepared from samples by sedimentation in a refrigerated centrifuge within two hours of blood collection, stored at −70 °C, and sent to central laboratories (University of Minnesota) (Carpenter et al., 2004; Taylor et al., 2005). Fasting serum LDL (mg/dL [Friedewald equation]), HDL, and triglycerides were assayed using standard techniques (Carpenter et al., 2004). HbA1c concentrations were measured as previously described (Joseph et al., 2016). Using a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN), hs-CRP was measured by the immunoturbidimetric CRP-Latex assay (Kamiya Biomedical Company, Seattle, WA) (Effoe et al., 2015). Measurement was done in duplicate, and any duplicates that were not within a 3 assay SD from one another were rerun. The interassay coefficient of variation on control samples was 4.5% (at an hs-CRP level of 0.45 mg/L) and 4.4% (at an hs-CRP level of 1.56 mg/L). Serum aldosterone was measured by radioimmunoassay (Siemens) and the intra-assay coefficients of variation were 8.7% and 6.2% for low and high concentrations. Morning serum cortisol was measured by chemiluminescent immunoassay performed on an immunoassay system (ADVIA Centaur; Siemens). Intra-assay coefficients of variation, were 9.1% and 7.7% for high and low cortisol concentrations, respectively.

2.5. Covariates

Baseline information was obtained during clinic visits or at home using standardized questionnaires including: demographics (age, sex), occupation (management/professional versus not), level of education (≥ Bachelor's degree versus < Bachelor's degree), current smoking status, and physical activity assessed using an interviewer-administered physical activity questionnaire, modified from the Baeke physical activity survey (Baecke et al., 1982). This instrument was identical to the one used during the Kaiser Physical Activity survey, which showed good validity and reliability in a multiethnic sample (Ainsworth et al., 2000). Physical activity was categorized according to the American Heart Association 2020 cardiovascular health guidelines as poor, intermediate, or ideal health, as described previously (Joseph et al., 2016).

2.6. Statistical analyses

Baseline characteristics of participants are presented by CES-D less than versus greater than or equal to 16 (at risk for clinical depression), using two-sample t-tests for normally distributed continuous variables (mean, standard deviation), Wilcoxon two-sample nonparametric tests for non-normally distributed continuous variables (median, interquartile range), or Chi-square tests for categorical variables as appropriate.

Multivariable regression models examined associations between baseline depressive symptoms and AL at baseline. Cox proportional hazard models were built to examine associations among baseline depressive symptoms and incident CHD and baseline AL and incident CHD, run in separate models. Hazard ratios (HR, 95% confidence interval-CI) were calculated per 1-point increment for depressive symptomology and per 1-standard deviation (SD) increment of continuously-measured AL. The mediational role of AL in the association between depressive symptoms and incident CHD was also assessed through formal mediation analyses (R package 'mediation') (Imai et al., 2010; Tingley et al., 2014). The average indirect effects of the exposure (i.e., depressive symptoms) on the outcome (i.e., CHD) through the mediating variables (i.e., AL subsystem and meta-factor z-scores) and proportions mediated were quantified.

For all analyses, sequential modeling was performed to adjust for potentially confounding variables as follows: Model 1: unadjusted; Model 2: Model 1 + demographic variables (age, sex); Model 3: Model 2 + socioeconomic variables (education, occupation); and Model 4: Model 3 + behavioral variables (smoking status, physical activity). For all models, interaction effects by sex were examined and the sample was stratified to examine differences by sex. For models assessing AL, subscale analyses were performed, with metabolic, cardiovascular, immune, and neuroendocrine subsystem scores serving as independent variables. The proportional hazards assumption was assessed using Schoenfeld residuals and no significant violations were noted. Statistical significance was defined as two-sided alpha = 0.05 for the primary outcome, the main mediation analysis. The association of baseline depressive symptoms and AL and the association of baseline depressive symptoms with incident CHD, are estimated separately to establish the foundation for the main mediation analysis. The sex-stratified and AL subscale findings were exploratory in nature and p-values were reported at a nominal level. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Table 1
Baseline Characteristics of Participants in the Jackson Heart Study by CES-D < versus ≥ 16.

Baseline Characteristics*	< 16 (*n* = 2112)	≥16 (*n* = 558)	Total (*n* = 2670)	P-value
Age (years)	53.8 (12.4)	51.8 (13.0)	53.4 (12.5)	0.001
Sex (female)	1335 (63%)	414 (74%)	1749 (66%)	< .001
High school or greater education (yes)	1857 (88%)	452 (81%)	2309 (86%)	< .001
Management/Professional occupation (yes)	948 (45%)	153 (27%)	1101 (41%)	< .001
Smoking status (yes)	191 (9%)	94 (17%)	285 (11%)	< .001
Physical activity				< .001
Poor	900 (43%)	286 (51%)	1186 (44%)	
Intermediate	722 (34%)	191 (34%)	913 (34%)	
Ideal	490 (23%)	81 (15%)	571 (21%)	
Waist circumference (cm)	99.7 (16.1)	101.4 (16.9)	100.1 (16.3)	0.033
Triglycerides (mg/dL)	100.5 (52.7)	104.6 (61.4)	101.3 (54.7)	0.113
High-density lipoprotein (mg/dL)	52.2 (14.6)	51.9 (13.9)	52.1 (14.4)	0.661
Low-density lipoprotein (mg/dL)	127.7 (35.8)	121.3 (35.4)	126.4 (35.8)	< .001
Triglyceride/HDL ratio†	1.7 (1, 2.7)	1.8 (1, 2.8)	1.7 (1, 2.7)	0.605
Hemoglobin A1c (%)	5.8 (1.1)	5.9 (1.2)	5.8 (1.1)	0.401
Heart rate	63.8 (10)	64.7 (10.5)	64 (10.2)	0.062
Systolic blood pressure (mmHg)	125.9 (15.7)	126.1 (16.3)	125.9 (15.8)	0.739
Diastolic blood pressure (mmHg)	76 (8.5)	76.3 (8.5)	76 (8.5)	0.446
High-sensitivity C-reactive protein (mg/L)†	0.25 (0.1, 0.5)	0.33 (0.1, 0.7)	0.26 (0.1, 0.6)	< .001
Cortisol (ug/dL)	9.6 (4)	9.4 (4)	9.6 (4)	0.309
Plasma aldosterone (ng/dL) †	4.5 (3, 7.3)	4.1 (2, 7.4)	4.4 (3, 7.3)	0.062
Allostatic load metabolic Z-score	−0.02(0.6)	−0.02 (0.6)	−0.02 (0.6)	0.976
Allostatic load cardiovascular Z-score	−0.04 (0.7)	0.01 (0.7)	−0.03 (0.7)	0.147
Allostatic load immune Z-score	−0.06 (1)	0.14 (1)	−0.01 (1)	< .001
Allostatic load neuroendocrine Z-score	−0.007 (0.8)	−0.07 (0.8)	−0.02 (0.8	0.110
Allostatic load meta-factor Z-score	−0.03 (0.5)	0.01 (0.5)	−0.02 (0.5)	0.038
Incident coronary heart disease (yes)	75 (4%)	31 (6%)	106 (4%)	0.031

Note: p values of < 0.05 considered statistically significant.
* Mean (SD) or percentages are listed, p-values calculated using chi-square (categorical variables) and two sample *t*-test (parametric continuous variables).
† Median (IQR), p-values calculated using Wilcoxon two sample nonparametric test (non-parametric continuous variables).

3. Results

3.1. Participant characteristics

Among 2670 adults mean age 53.4 ± 12.5 years, 66% female, during a median follow-up period of 9.9 years (IQR 9, 10.7), 106 CHD events occurred. Table 1 shows the profile of participants stratified by clinically non-significant (CES-D < 16) versus significant (CES-D ≥ 16) depressive symptomatology. Among the full cohort, the prevalence of clinically significant depressive symptoms was 20.9%. Women were more likely to exhibit significant depressive symptoms than men (23.7% vs. 15.6%; $p < 0.001$). Compared to those with a CES-D score < 16, participants with a CES-D score ≥16 were also younger and more likely to report current smoking, less than a high school education, non-professional occupations, and poor physical activity (p-values < 0.050). In regards to AL biological parameters, participants with CES-D scores ≥16 had a greater waist circumference, hs-CRP, and immune, and meta-factor AL z-scores and lower LDL than participants with CES-D scores < 16 (p-values < 0.050). CHD incidence was 6% vs. 4% among participants with CES-D ≥16 vs. < 16 ($p = 0.031$).

3.2. Depressive symptoms and allostatic load

The sequentially adjusted associations among depressive symptoms and AL indices at baseline are presented in Table 2. Among the full cohort, the fully adjusted models revealed that 1-point greater CES-D score was associated with a 0.003 unit positive difference in metabolic AL z-score ($p = 0.036$), a 0.004 unit positive difference in cardiovascular AL z-score ($p = 0.031$), and a 0.007 unit positive difference in immune AL z-score ($p = 0.009$). The association of CES-D with the AL meta-factor z-score, which serves as a composite index of all AL subsystems, was also statistically significant (B = 0.003, $p = 0.007$). Depressive symptomatology was not associated with neuroendocrine subsystem dysregulation (B = −0.0007, $p = 0.737$).

A statistically significant interaction effect by sex was also noted in examining the association between CES-D scores and AL metabolic subsystem z-scores ($p = 0.048$), with CES-D scores significantly associated with metabolic AL among women ($p = 0.005$) but not men ($p = 0.590$) in stratified analyses. Interaction effects by sex approached but did not reach statistical significance in examining associations among depressive symptoms, cardiovascular AL, and the AL meta-factor ($p = 0.068$ and $p = 0.054$, respectively), with results stratified by sex shown in Table 2. For these AL parameters, significant associations with depressive symptoms were witnessed among women but not men.

3.3. Depressive symptoms, allostatic load, and coronary heart disease

The sequentially adjusted associations of depressive symptoms and AL with CHD are presented in Table 3. Among the full cohort, in the fully adjusted models, each 1-point increase in CES-D score was associated with a 3.3% higher risk of CHD (p = 0.007). Each 1-unit increase in metabolic AL subsystem z-score was associated with an 88% higher risk of CHD ($p < 0.001$). Each 1-unit increase in neuroendocrine AL subsystem z-score was associated with a 39% higher risk of CHD ($p = 0.008$). When AL was examined as a meta-factor, each 1-unit increase in AL z-score was associated with a 130% higher risk of CHD ($p < 0.001$).

Associations among depressive symptoms, AL, and CHD did not significantly differ by sex in examining interaction effects in the fully adjusted models ($p \geq 0.082$). However, given the sex differences noted in the associations among depressive symptoms and AL, we also provide these results stratified by sex (Table 3). Point estimates for the association of depressive symptoms with CHD were similar among males and females and was significant among females (HR 1.044, 95%CI 1.015, 1.073). Stratifying by sex also revealed higher HRs for males versus females for the metabolic AL subsystem z-score though, as noted, these differences were not statistically significant (Males: HR 2.02, 95%CI 1.27, 3.21; Females: HR 1.78, 95%CI 1.21, 2.63). The neuroendocrine AL subsystem (Males: HR 1.86, 95%CI 1.25, 2.76; Females: HR 1.18, 95%CI 0.86, 1.62) and AL meta-factor (Males: HR 3.33, 95%CI

Table 2
The association of depressive symptoms (CES-D Score) with allostatic load subsystem and meta-factor scores in the Jackson Heart Study.

AL Z-Scores	Model	Overall (n = 2,670)		Women (n = 1,749)		Men (n = 921)	
		Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
Metabolic	1	0.002 (−0.001, 0.005)	0.210	0.005 (0.001, 0.008)	0.009	−0.001 (−0.007, 0.004)	0.702
	2	0.004 (0.001, 0.007)	0.005	0.006 (0.003, 0.009)	0.001	−0.0006 (−0.006, 0.005)	0.840
	3	0.004 (0.0006, 0.006)	0.018	0.005 (0.002, 0.009)	0.002	−0.001 (−0.007, 0.004)	0.681
	4	0.003 (0.0002, 0.006)	0.036	0.005 (0.001, 0.008)	0.005	−0.002 (−0.007, 0.004)	0.590
Cardiovascular	1	0.004 (0.0007, 0.007)	0.018	0.006 (0.002, 0.010)	0.003	0.00008 (−0.006, 0.006)	0.980
	2	0.005 (0.002, 0.008)	0.003	0.007 (0.003, 0.010)	0.001	0.0004 (−0.006, 0.007)	0.897
	3	0.005 (0.001, 0.008)	0.007	0.006 (0.002, 0.010)	0.001	0.00,003 (−0.006, 0.006)	0.992
	4	0.004 (0.0003, 0.007)	0.031	0.005 (0.002, 0.009)	0.005	−0.001 (−0.007, 0.005)	0.705
Immune	1	0.012 (0.007, 0.017)	< .001	0.010 (0.004, 0.015)	0.001	0.006 (−0.003, 0.016)	0.161
	2	0.009 (0.005, 0.014)	< .001	0.011 (0.005, 0.016)	< .001	0.007 (−0.002, 0.016)	0.138
	3	0.008 (0.003, 0.013)	0.002	0.009 (0.003, 0.015)	0.002	0.005 (−0.004, 0.014)	0.275
	4	0.007 (0.002, 0.011)	0.009	0.008 (0.002, 0.013)	0.008	0.003 (−0.006, 0.012)	0.474
Neuroendocrine	1	−0.003 (−0.006, 0.001)	0.190	−0.0002 (−0.005, 0.004)	0.933	−0.001 (−0.008, 0.006)	0.756
	2	0.0002 (−0.003, 0.004)	0.909	0.0006 (−0.004, 0.005)	0.783	−0.0008 (−0.007, 0.006)	0.820
	3	−0.0001 (−0.004, 0.004)	0.940	0.0003 (−0.004, 0.005)	0.905	−0.001 (−0.008, 0.006)	0.731
	4	−0.0007 (−0.004, 0.003)	0.737	−0.0001 (−0.005, 0.004)	0.951	−0.002 (−0.009, 0.005)	0.577
Meta-factor	1	0.004 (0.002, 0.006)	< .001	0.005 (0.002, 0.008)	< .001	0.001 (−0.003, 0.005)	0.618
	2	0.005 (0.002, 0.007)	< .001	0.006 (0.003, 0.009)	< .001	0.001 (−0.003, 0.006)	0.496
	3	0.004 (0.002, 0.006)	0.001	0.005 (0.003, 0.008)	< .001	0.0007 (−0.004, 0.005)	0.757
	4	0.003 (0.0008, 0.005)	0.007	0.004 (0.002, 0.007)	0.001	−0.0004 (−0.005, 0.004)	0.869

Note: p values of < 0.05 considered statistically significant; multivariable regression models examined associations among baseline depressive symptoms and AL at baseline; Model 1 unadjusted; Model 2 includes model 1 plus age, sex; Model 3 includes Model 2 plus education, occupation; Model 4 includes Model 3 + smoking, physical activity; AL = allostatic load.

1.71, 6.49; Females: HR 1.77, 95%CI 1.00, 3.14) associations failed to reach statistical significance in females but were predictive of incident CHD in males.

3.4. Allostatic load in the association of depressive symptoms with coronary heart disease

The fully adjusted model for testing mediation by AL in the association of depressive symptoms with incident CHD is presented in Table 4. In examining the AL meta-factor z-score among the full cohort, there was a significant mediation effect, with percent mediation estimated at 7.55% (p = 0.016). In examining the AL subsystem scores, metabolic AL was found to mediate 5.79% of the association between depressive symptoms and incident CHD (p = 0.044). No additional indirect effects were supported according to the alternative AL subsystems.

Next, given the aforementioned results, tests of mediation were repeated stratifying by sex. Metabolic AL significantly mediated the association between depressive symptoms and incident CHD among females (6.18% mediated, p = 0.016). In contrast, there was no support for a mediated effect of metabolic AL in the association between CES-D score and CHD risk among males (−2.16% mediated, p = 0.840). The AL meta-factor also failed to reach statistical significance as a mediator among either group alone (p values $\geq$ 0.116). Consistent with our previous findings, the direct effect of depressive symptoms on incident CHD could also be detected among females (p = 0.010) but not males (p = 0.420) in the metabolic AL mediational model.

4. Discussion

This study provides evidence that, among a diverse cohort of African American adults, each 1-point increase in baseline depressive

Table 3
The Association of Depressive Symptoms and Allostatic Load with Coronary Heart Disease in the Jackson Heart Study.

	Predictor	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Overall	CES-D	1.025 (1.00, 1.05)*	1.036 (1.01, 1.06)*	1.034 (1.01, 1.06)*	1.033 (1.01, 1.06)*
(n = 2,670)	Metabolic AL z-score	2.01 (1.53, 2.64)*	1.90 (1.41, 2.55)*	1.88 (1.40, 2.53)*	1.88 (1.39, 2.53)*
	Cardiovascular AL z-score	1.26 (0.95, 1.67)	1.23 (0.93, 1.63)	1.21 (0.92, 1.61)	1.20 (0.90, 1.60)
	Immune AL z-score	1.14 (0.94, 1.38)	1.17 (0.95, 1.43)	1.16 (0.95, 1.43)	1.16 (0.94, 1.42)
	Neuroendocrine AL z-score	1.47 (1.17, 1.83)*	1.40 (1.09, 1.78)*	1.40 (1.10, 1.79)*	1.39 (1.09, 1.78)*
	AL meta-factor z-score	2.45 (1.64, 3.68)*	2.35 (1.53, 3.63)*	2.32 (1.51, 3.58)*	2.30 (1.49, 3.57)*
Women	CES-D	1.033 (1.01, 1.06)*	1.047 (1.02, 1.08)*	1.044 (1.02, 1.07)*	1.044 (1.02, 1.07)*
(n = 1,749)	Metabolic AL z-score	1.95 (1.38, 2.77)*	1.81 (1.23, 2.67)*	1.79 (1.22, 2.65)*	1.78 (1.21, 2.63)*
	Cardiovascular AL z-score	1.27 (0.87, 1.85)	1.24 (0.74, 1.82)	1.21 (0.83, 1.78)	1.20 (0.82, 1.76)
	Immune AL z-score	1.06 (0.83, 1.36)	1.07 (0.83, 1.37)	1.05 (0.82, 1.36)	1.05 (0.81, 1.36)
	Neuroendocrine AL z-score	1.32 (0.99, 1.76)	1.19 (0.87, 1.63)	1.18 (0.86, 1.62)	1.18 (0.86, 1.62)
	AL meta-factor z-score	2.03 (1.20, 3.44)*	1.84 (1.05, 3.23)*	1.78 (1.01, 3.15)*	1.77 (1.00, 3.14)
Men	CES-D	1.017 (0.98, 1.06)	1.017 (0.98, 1.06)	1.014 (0.97, 1.06)	1.014 (0.97, 1.06)
(n = 921)	Metabolic AL z-score	2.04 (1.30, 3.20)*	2.03 (1.28, 3.24)*	2.01 (1.27, 3.19)*	2.02 (1.27, 3.21)*
	Cardiovascular AL z-score	1.22 (0.80, 1.86)	1.22 (0.81, 1.84)	1.22 (0.81, 1.84)	1.20 (0.79, 1.82)
	Immune AL z-score	1.48 (1.08, 2.05)*	1.37 (0.98, 1.91)	1.38 (0.99, 1.92)	1.37 (0.97, 1.92)
	Neuroendocrine AL z-score	1.74 (1.17, 2.57)*	1.86 (1.25, 2.76)*	1.88 (1.26, 2.79)*	1.86 (1.25, 2.76)*
	AL meta-factor z-score	3.31 (1.75, 6.28)*	3.36 (1.72, 6.55)*	3.35 (1.73, 6.51)*	3.33 (1.71, 6.49)*

Note: p values of < 0.05 considered statistically significant; Models run separately for each listed predictor; Model 1 unadjusted; Model 2 includes model 1 plus age, sex; Model 3 includes Model 2 plus education, occupation; Model 4 includes Model 3 + smoking, physical activity; AL = allostatic load; *statistically significant association.

Table 4
Percent Mediation of Allostatic Load on the Association of Depressive Symptoms with Incident Coronary Heart Disease in the Jackson Heart Study.

	Overall (n = 2,670)		Women (n = 1,749)		Men (n = 921)	
	% Mediated	p	% Mediated	p	% Mediated	p
Metabolic AL z-score	5.79	0.044	6.18	0.016	−2.16	0.840
Cardiovascular AL z-score	1.78	0.254	1.54	0.500	−0.19	0.920
Immune AL z-score	2.29	0.256	0.17	0.934	1.66	0.810
Neuroendocrine AL z-score	−0.57	0.744	−0.03	0.952	−2.95	0.780
AL Meta-factor z-score	7.55	0.016	4.94	0.116	−0.20	0.990

Note: p values of < 0.05 considered statistically significant; Models adjusted for age, sex, education, occupation, smoking and physical activity; AL = allostatic load.

symptoms is associated with a 3.3% greater risk of incident CHD and is partially mediated by greater overall AL and metabolic AL. This report expands important literature demonstrating (Brown et al., 2011; O'Brien et al., 2015; Sims et al., 2015) but also refuting (Moise et al., 2016) an association between depressive symptoms and CHD-related outcomes in studies with significant African American representation. Extending prior work, we present findings produced from formal mediation analyses suggesting a key biologic pathway (i.e., metabolic) by which depressive symptomatology may be linked to CHD in African Americans. Findings from tests of mediation are of particular importance considering that there is biologic plausibility for a number of correlates of depressive symptomatology to play a role in cardiovascular risk. A more complete understanding of CHD risk pathways serves as a critical foundation toward progress in targeted CHD prevention.

The metabolic AL subsystem score found to mediate the association between depressive symptoms and incident CHD was composed of abdominal adiposity (i.e., waist circumference), cholesterol (i.e., triglyceride/HDL ratio, LDL), and blood glucose (i.e., HbA1c) markers. In the context of depressive symptoms, we observed less favorable waist circumference, in particular. The observed associations are in line with prior literature, particularly among African Americans (Beydoun et al., 2016; Grossniklaus et al., 2012), with some data suggesting that this relationship is not due to increased depression-associated dietary energy density (Grossniklaus et al., 2012). It is also important to consider that, with increased abdominal adiposity, use of fat stores as a source of energy has been increasingly appreciated as resulting in increased hepatic triglyceride production within very LDL particles and the accumulation of small HDL particles (which fail to offer the expected protection) and small LDL particles (which result in lower measured LDL levels) (Bosomworth, 2013). The triad of high triglyceride levels, low HDL levels, and increased LDL particle number (termed "atherogenic dyslipidemia") is thought to be particularly detrimental to the health of the coronary arteries (Bosomworth, 2013), with the findings from this report suggesting that this may be a particularly important pathway in the development of depressive symptom-associated CHD.

We also noted associations among depressive symptoms and immune AL (i.e., hs-CRP). This finding is in line with prior psychoneuroimmunologic studies linking depressive symptoms and markers of inflammation, with inflammation increasingly implicated in chronic disease (reviewed by Kiecolt-Glaser et al., 2015). In fact, some evidence suggests the presence of an inflammatory subtype of depression more likely to demonstrate resistance to traditional pharmacotherapies (Beijers et al., 2019; Jeng et al., 2018), prompting pursuit of adjuvant or alternative treatment approaches among these individuals (reviewed by Ionescu and Papakostas, 2017).

In the current study, hs-CRP did not predict CHD in the assessed sample, which is interesting considering that hs-CRP has been considered for inclusion in predictive models of CVD (US Preventive Services Task Force et al., 2018). Though, the usefulness of hs-CRP as a reflection of chronic, low-grade inflammation has been debated and the U.S. Preventive Services Task Force recently determined that the current evidence is insufficient to warrant recommendation of hs-CRP testing, calling for high-quality prospective studies among diverse populations (US Preventive Services Task Force et al., 2018). While the current study suggests minimal predictive value of a single assessment of hs-CRP for CHD among a large African American cohort, more work is needed to determine the potential for incremental predictive value when hs-CRP is added to traditional risk scoring systems.

We also showed that, overall, depressive symptoms were not associated with neuroendocrine AL (i.e., cortisol and aldosterone) but neuroendocrine AL predicted increased risk for CHD. In fact, participants with clinically significant depressive symptoms showed marginally lower aldosterone levels versus those without depressive symptoms. This finding is unexpected, as multiple studies (e.g., Segeda et al., 2017) have implicated higher aldosterone burden in the context of depressive symptoms, with increased activity of the renin-angiotensin-aldosterone system (RAAS) implicated in hypertension and CVD (Joseph et al., 2017). This discrepancy may be related to methodological differences (e.g., population, sampling) but may also reflect the mounting of a compensatory response among those combatting depressive symptoms. For example, De Vos et al. (2018) reported that, among African Americans (n = 68) but not non-Hispanic whites (n = 127), chronic depression predicts elevations in DBP and concomitant reductions in renin over a 3-year follow-up period. The authors posited that renin suppression reflected an unsuccessful defense against volume-loading hypertension, as aldosterone levels and estimated glomerular filtration rate remained unchanged. The role of the RAAS in CHD in the context of depression warrants further exploration.

Importantly, this report reveals differences by sex in the role of AL in the association of depressive symptoms with CHD. In fact, among males (n = 921), baseline depressive symptoms failed to predict incident CHD, AL as a meta-factor, or any AL subsystem score. Though, in males, metabolic and neuroendocrine AL and the AL meta-factor were associated with CHD. In females (n = 1,749), baseline depressive symptoms predicted CHD risk and greater AL (metabolic, cardiovascular, immune, and meta-factor). Greater metabolic AL, in particular, predicted CHD, with support for the variable as a mediator. This suggests that findings related to the metabolic pathway in depressive symptom-associated CHD were driven by females and highlight the benefit of AL subsystem analyses. Moreover, the menopausal transition and greater severity of menopausal symptoms (including depressed mood) have been linked to dysregulation across several metabolic parameters (Cengiz et al., 2019; Gurka et al., 2016), which may to help to explain the findings of the current study and highlight the importance of continued work in this area.

Pathways linking neuroendocrine AL and CHD may also show differences by sex, with future studies focusing on more nuanced depictions of neuroendocrine function having potential to shed light on this possibility. Specifically, while a single morning serum cortisol value holds strong potential for clinical translation, correlates well with alternative indices (e.g., salivary cortisol (Restituto et al., 2008)), and predicts concurrent metabolic dysregulation (e.g., higher fasting plasma glucose, HbA1c (Ortiz et al., 2019)), in-depth assessments of diurnal patterns or total output over a period of time may provide additional insight.

Similarly, there remains a need for explication of pathways,

mechanisms, and biology underlying sex differences in CVD as well as clinical translation for diagnosis and treatment, evolving due to increased inclusivity of females in cardiovascular research demonstrating sex differences in aging, cardiac function, coronary artery anatomy, and blood pressure regulation (Taqueti, 2018). Here, we add to the body of literature identifying sex-specific cardiovascular outcomes in response to depressive symptoms and AL among African Americans. Consistent with our hypothesis, AL contributions to CHD risk differed by sex, which mirrors work from others who have identified higher AL among African American women associated with metabolic atherogenic dyslipidemia (Chyu and Upchurch, 2018).

Strengths of this report include the assessment of a large, socioeconomically diverse, contemporary, African American community-based cohort with rigorously ascertained physiologic and laboratory measures and over a decade of follow-up of adjudicated CHD outcomes. The availability of CES-D data also provided the opportunity to assess associations among continuously estimated depressive symptoms, AL parameters, and incident CHD, which is not possible when relying solely on the presence or absence of a clinical diagnosis of depression. This being said, the CES-D is well-validated but relies on self-report. Data on clinical diagnosis or treatment of depression at baseline exam were not available, prohibiting their examination. Some evidence does suggest that antidepressants alter risk for CVD (Coupland et al., 2016; Hamer et al., 2011). Individuals with self-reported CHD at baseline were excluded from analyses. Therefore, the current report provides estimates of associations among depressive symptoms, AL indices, and incident CHD diagnosis. Though, the potential for unrecognized pathophysiologic features of CHD among analyzed individuals must also be recognized (Vigili de Kreutzenberg et al., 2017).

Despite these and other strengths, there are some additional potential limitations. First, the participants in the JHS are from one geographic area in the southeastern U.S. and may not be representative of all African Americans. A number of JHS participants were also excluded from analyses due to baseline CHD (n = 400) or data missingness for CES-D scores (n = 1713), CHD data (n = 117), or covariates (n = 406), producing an analytical sample that was generally of higher socioeconomic status and healthier than the excluded sample. The generalizability of this report and potential for selection bias must be considered with this in mind. Second, CES-D and AL were analyzed according to baseline measures only. As such, while a growing literature suggests that depressive symptoms are capable of contributing to the progression or even establishment of dysregulation in the biological systems under investigation (Ambrosio et al., 2018; Niles and O'Donovan, 2019; Srinivas et al., 2018), the cross-sectional nature of this data must be fully acknowledged and highlights the importance of future longitudinal investigations of detailed AL indices and incident CVD over lengthy follow-up periods. Third, exploratory analyses of AL subscale and sex-stratified statistical associations were interpreted without correction for multiple comparisons and require verification in future studies. Therefore, some caution is warranted in the interpretation of results.

In conclusion, this report provides data indicating that depressive symptom-associated CHD risk is partially mediated by greater metabolic AL burden among African American adults, with stratified analyses suggesting that this mediational pathway is unique to females. We also identified concurrent associations among depressive symptoms and AL (metabolic, cardiovascular, immune, meta-factor) among females only and predictive value of neuroendocrine AL for incident CHD among males only. These findings suggest that application of the AL framework may be particularly fruitful in elucidation of biologic pathways linking psychological parameters to CHD. In particular, determination of the clinical significance of the statistically significant associations noted in the present analyses will be an important area of future inquiry. Similarly, future studies examining risk factors and mechanisms underlying CHD should carefully consider time-varying depressive symptoms and potential differences by sex, which is critical to the design of interventions for the targeted prevention and treatment of CHD among African American men and women.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.06.020.

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