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Neighborhood Poverty and Hemodynamic, Neuroendocrine, and Immune Response to Acute Stress among Patients with Coronary Artery Disease

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Abstract

Living in neighborhoods characterized by poverty may act as a chronic stressor that results in physiological dysregulation of the sympathetic nervous system. No previous study has assessed neighborhood poverty with hemodynamic, neuroendocrine, and immune reactivity to stress. We used data from 632 patients with coronary artery disease. Patients' residential addresses were geocoded and merged with poverty data from the 2010 American Community Survey at the census-tract level. A z-transformation was calculated to classify census tracts (neighborhoods) as

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CONTIBUTORS

VV, AQ, JDB, and TTL participated in the overall study aims, study design, and analytic methods for the Mental Stress Ischemia Mechanisms and Prognosis Study. SS, HMK, and VV developed the paper concept. SS geocoded participant addresses, drafted the manuscript, and conducted the statistical analysis. VV, HMK, MH, MT, BDP, SH, AH, and MRK contributed to the analysis, interpretation of the data, and critically revised the manuscript. MH, KW, RR, BDP, AS, BBL, JWK, OL, MO, BK, and AH were involved in the data acquisition, collection, preparation, and storage of the data. LW, MK, and YAK participated in data management and contributed to the analysis. All authors critically read, revised, and approved the final manuscript.

DISCLOSURE STATEMENT AND CONFLICT OF INTEREST

either having ‘high’ or ‘low’ poverty. Systolic blood pressure, diastolic blood pressure, heart rate, rate-pressure product, epinephrine, interleukin-6, and high-sensitivity C-reactive protein were measured before and after a public speaking stress task. Multilevel models were used for repeated measures and accounting for individuals nested within census tracts. Adjusted models included demographics, lifestyle and medical risk factors, and medication use. Another set of models included propensity scores weighted by the inverse probability of neighborhood status for sex, age, race, and individual-level income. The mean age was 63 years and 173 were women. After adjusting for potential confounders, participants living in high (vs. low) poverty neighborhoods had similar hemodynamic values at rest and lower values during mental stress for systolic blood pressure (157 mmHg vs. 161 mmHg; $p = 0.07$), heart rate (75 beats/min vs. 78 beats/min; $p = 0.02$) and rate-pressure product (11839 mmHg x beat/min vs 12579 mmHg x beat/min; $p = 0.01$). P-values for neighborhood poverty-by-time interactions were < 0.05. Results were similar in the propensity weighted models. There were no significant differences in inflammatory and epinephrine responses to mental stress based on neighborhood poverty status. A blunted hemodynamic response to mental stress was observed among participants living in high poverty neighborhoods. Future studies should explore whether neighborhood poverty and blunted hemodynamic response to stress translate into differences in long-term cardiovascular outcomes.

Keywords

Mental stress; sympathetic nervous system; blood pressure; hemodynamics; inflammation; neuroendocrine

1. INTRODUCTION

Living in low-income neighborhoods characterized by poverty and socioeconomic disadvantage is an important predictor for developing coronary artery disease (CAD) (Diez Roux et al., 2001; Nordstrom et al., 2004; Sundquist et al., 2004) as well as poorer prognosis and decreased survival among patients with CAD (Engstrom et al., 2000; Tonne et al., 2005). There is growing interest in disentangling the physiological pathways through which the neighborhood environment, such as living in low income neighborhoods, may affect cardiovascular outcomes. However, the underlying mechanisms are not well understood.

One hypothesis is that living in socially-and physically-disordered neighborhood environments characterized by poverty may act as a chronic stressor that results in physiological dysregulation of the body’s reactivity to stress, such as through the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) (Augustin et al., 2008; Broyles et al., 2012; Dulin-Keita et al., 2012; Hajat et al., 2015; Le-Scherban et al., 2018). Exposure to acute emotional stress, and stress-induced physiological perturbations are associated with cardiometabolic risk and events (Chida and Steptoe, 2010). An altered reactivity to stress, either in the direction of exaggerated reactivity or diminished reactivity, may signal a dysregulation of systems intended to maintain homeostasis (Phillips et al., 2013). Enhanced responsivity to stress provocation such as through hemodynamic, immune, and neuroendocrine responses regulated by the SNS, may serve as mechanisms for the development or exacerbation of CAD (Hammadah et al., 2017; Ramadan et al., 2013;

Vaccarino, 2016). However, there is growing recognition that even low cardiovascular reactivity to stress, as well as low cortisol reactivity, may index a dysregulation of the stress response systems and may have adverse consequences for health and behavior including obesity, depression, poorer cognitive function, and poor lung function (de Rooij, 2013; Lovallo, 2013; Phillips et al., 2013).

To date, limited research has assessed the association between neighborhood poverty with hemodynamic, neuroendocrine, and immune reactivity to stress. Furthermore, most research in this area has focused on hemodynamic response to stress among children with chronic stressors or measures of disadvantage other than the neighborhood environment (Brenner et al., 2013; Evans et al., 2013; Hackman et al., 2012; Lovallo, 2013; Lovallo et al., 2012). Virtually no data have been published on individuals with CAD, a group at high risk for subsequent adverse events. Thus, the objective of the current study was to comprehensively assess SNS reactivity to acute mental stress, including hemodynamic, neuroendocrine, and immune responses, among patients with CAD living in high (vs. low) poverty neighborhoods. To provide further validation of the phenomena of mental stress and SNS reactivity among patients living in high poverty neighborhoods, we contrasted results to hemodynamic reactivity during exercise stress testing. We hypothesized that patients in high poverty neighborhoods would have an abnormal (either enhanced or blunted) SNS response to acute mental stress but not to exercise stress.

2. MATERIALS AND METHODS

2.1 Study Design and Participants

The Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS) is a prospective study designed to investigate mechanisms and prognosis of mental stress-induced ischemia among patients with stable coronary artery disease (CAD) (Hammadah et al., 2016). Patients from Emory University-affiliated hospitals and clinics with documented CAD were eligible for the study if they were between 30–79 years of age. Criteria for documented CAD included at least one of the following: 1) abnormal coronary angiography or intravascular ultrasound demonstrating atherosclerosis with at least luminal irregularities; 2) previous percutaneous or surgical coronary revascularization; 3) documented myocardial infarction; or 4) positive exercise or pharmacological nuclear stress test or electrocardiographic exercise stress test. Patients were excluded from the study if they were pregnant; if they were hospitalized in the previous week for unstable angina, decompensated heart failure, or myocardial infarction; if they had severe psychiatric conditions such as schizophrenia or a history of alcohol or substance abuse; or if they had active malignancy, end stage renal disease, or other severe medical problems expected to shorten life expectancy to less than 5 years.

Between June 2011 and August 2014, 695 patients were enrolled in MIPS. Baseline studies were performed during two visits within a week. At the initial visit (visit 1), patients were consented and underwent a medical history and psychosocial/psychiatric assessments, blood draw, baseline vascular function testing, and either a conventional (exercise or pharmacological) stress test or a mental stress test as described below. During visit 2, they had the other stress test performed. The sequence of the two stressors was randomly assigned. The present analysis was restricted to 632 patients with available geocoded

addresses. The Institutional Review Board at Emory University approved the MIPS research protocol. Written informed consent was obtained from all patients enrolled in the study. More detailed information on the MIPS objectives and study design has been described elsewhere (Hammadah et al., 2016; Vaccarino et al., 2016).

2.2 Measurements

2.2.1 Mental Stress Testing Procedure—Mental stress testing in the laboratory setting is an established experimental approach to elicit sympathetic nervous system responses to emotional challenges and evaluate disturbances of stress mechanisms including cardiac and hemodynamic functions, especially in relation to myocardial ischemia and cardiovascular disorders (Steptoe and Vogele, 1991) (Ramachandruni et al., 2006; Strike and Steptoe, 2003; Vaccarino, 2016). The mental stress protocol we used has been validated and widely used in CAD patients (Goldberg et al., 1996; Kim et al., 2003; Ramachandruni et al., 2006; Sheps et al., 2002), and has been found to be highly reproducible and predictive of mental stress induced myocardial-ischemia and of hemodynamic and vascular responses to stress in our laboratory (Hammadah et al., 2017; Sullivan et al., 2018).

Patients were tested using a standardized public speaking task after a 30-minute rest period, in a temperature controlled, quiet, and dimly lit room, as previously described (Goldberg et al., 1996; Kim et al., 2003; Sullivan et al., 2018; Vaccarino et al., 2014; Vaccarino et al., 2016). Cardiovascular medications, including beta-blockers, calcium-channel blockers, long-acting nitrates, and other anti-ischemic medications, as well as xanthine derivatives and caffeine-containing products were withheld for approximately 24 hours prior to stress testing. Briefly, patients were asked to imagine a real-life stressful situation, in which a close relative had been mistreated in a nursing home and asked to make up a realistic story around this scenario. Patients were given two minutes to prepare a statement and then three minutes to present it in front of a video camera and an audience wearing white coats. Participants were told that their speech would be evaluated by the laboratory staff for content, quality, and duration. We recorded blood pressure and heart rate at five-minute intervals during the resting phase and at one-minute intervals during the mental stress task, and calculated the rate-pressure product.

2.2.2 Conventional Stress Testing—On a separate day, and within one week of the mental stress test, patients underwent treadmill exercise stress testing using the standard Bruce Protocol (Bruce, 1971; Fletcher et al., 2001; Gibbons et al., 2002), or, when contraindicated, pharmacologic testing with regadenoson (Lexiscan; Astellas Pharma US, Inc., Northbrook, IL). The treadmill test is clinically used in patients with CAD to detect myocardial ischemia due to supply-demand mismatch. According to the Bruce protocol, the test is administered in three-minute stages with gradual increases in treadmill speed and incline until the participant reaches 85% of their predicted heart rate according to sex and age. As exercise gradually increases, cardiac output is increased and the blocked arteries are not able to supply enough blood to the heart resulting in a mismatch in demand and supply leading to myocardial ischemia. Heart rate and blood pressure normally increase rapidly in response to exercise (Fletcher et al., 2001). The electrocardiogram (MAC 1600 device, GE),

blood pressure (Omron HEM-907XL IntelliSense Professional Digital Blood Monitor), and heart rate were continuously monitored with a physican present during the study.

2.2.3 Hemodynamic Monitoring—Hemodynamic parameters, including systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and heart rate (HR, beats/min), were recorded every 5 minutes during the resting period, every 1 minute during mental stress, and every 5 minutes during the recovery period. The rate-pressure product (RPP, beats x mmHg/min) was calculated as SBP (mmHg) x HR (beats/min).

2.2.4 Inflammatory Measurements—Inflammatory biomarkers were measured from venous blood samples from indwelling catheters, collected at rest and 90-minutes post mental stress testing, including Interleukin-6 (IL-6, pg/mL) and high-sensitivity C-reactive protein (hsCRP, mg/L). Plasma collection time points were selected based on prior studies of mental stress testing, and our own pilot testing, indicating that inflammatory response to stress becomes more apparent one hour or later post-mental stress (Edwards et al., 2006; Marsland et al., 2017; Mendham et al., 2011; Moldoveanu et al., 2000; Rooks et al., 2016; Steptoe et al., 2001). Venous blood was collected into ice-cooled citrate tubes and immediately centrifuged at 4°C; obtained plasma was snap-frozen at −70°C until further processing. We employed high sensitivity assays using the MesoScale system (Meso Scale Diagnostics Rockville, Maryland) using the SECTOR Imager 2400 to quantitate IL-6 and hsCRP according to the protocols supplied by the manufacturer. The Mesoscale multiplex assay system uses electrochemiluminescence for high sensitivity and broad dynamic range. Lower limits of detection were 0.06 pg/mL for IL-6 and 1.33 pg/mL for hsCRP. The inter-assay coefficient of variations for mid-point standards were 5.78% for IL-6 and 3.06% for hsCRP. The intra-assay coefficients of variations were 3.29% for IL-6 and 2.33% for hsCRP. IL-6 and hsCRP values were log transformed in all analyses and presented as geometric means. More detailed information about inflammatory measurements in MIPS has been previously published (Hammadah et al., 2018).

2.2.5 Epinephrine Measurements—Heparinized plasma samples were obtained at rest and 2 min after the mental stress test for measurement of epinephrine levels (EIA Kit; 2-CAT ELISA, Labor Diagnostika Nord as supplied by Rocky Mountain Scientific, Centennial, Co). We routinely assay catecholamines on this platform, and include externally-validated high and low control samples on each run. A run is rejected if these control samples do not conform to the pre-specified limits (according to the manufacturer's recommendations). Our inter-assay coefficient of variations for epinephrine were 19.72% and 18.00%, and the intra-assay coefficient of variations were 11.97% and 10.52%, for our low and high controls, respectively. This assay has an analytical sensitivity of 7 pg/mL. There were 2 samples at rest and 2 samples post mental stress test that were below the range of detection; these were assigned a value of zero in all analysis. Due to the skewed distribution of epinephrine levels, data were log transformed throughout all analyses.

2.2.6 Neighborhood Poverty—Participants' residential addresses at their baseline visit were geocoded using latitude and longitude coordinates with ArcMap 10.2 (Environmental Systems Research Institute (ESRI), Inc., Redlands, California) using 2010 U.S. Census

TIGER/Line Shapefiles based on the North American Industry Classification. Neighborhoods were defined at the census-tract level. Using the geocoded coordinates, data from the 2010 United States Census Bureau's American Community Survey (ACS) 5 –year estimates were merged with MIPS data at the census-tract level. Using previously established methods (Brody et al., 2014; Robinette et al., 2016), the economic and housing data were used to determine the percentage of the population whose income was below poverty level in each census tract. The Census Bureau uses a set of money income thresholds that vary by size and composition to determine poverty status. If a family's income is less than the poverty threshold for that family, then they are considered "in poverty". We used a z-score transformation to standardize the percentage of the population below poverty level with a mean of 0 and standard deviation of 1 so that participants' neighborhoods that were above the mean represented 'high' poverty neighborhoods while scores that were below the mean represented 'low' poverty neighborhoods.

2.2.7 Other Measurements—Demographic information was obtained using standardized questionnaires during the baseline visit of the study. Previous medical history (diabetes, hypertension, previous MI, heart failure, revascularization procedures) and medication use (e.g. beta blockers) were obtained by study nurses or physicians through medical history, clinical examinations, and by reviewing medical records. Depressive symptomology was assessed using the Beck Depression Inventory Second Edition (BDI-II) (Beck AT et al., 1996). Functional capacity was assessed using the Duke Activity Status Instrument (DASI) (Hlatky et al., 1989). The DASI is a 12-item, self-administered questionnaire used to determine patient's ability to perform common activities (i.e., personal care, household tasks, and recreational activities). Items are weighted using the known metabolic cost of each activity in metabolic energy expenditure (MET) units. Weighted scores range from 0 to 58, with higher scores representing better cardiac function status. Height and weight were objectively measured during the clinical exam and used to calculate body mass index (BMI, kg/m^2).

2.3 Statistical Analysis

Descriptive statistics were calculated for the MIPS sample and by neighborhood poverty status. Group differences were tested using chi-squared tests for categorical variables and analysis of variance (ANOVA) or Wilcoxon Mann-Whitely test for continuous variables. Hemodynamic parameters (SBP, DBP, HR, and RPP), neuroendocrine (epinephrine), and inflammatory measures (hsCRP and IL-6) were compared by neighborhood poverty status across phases of mental stress testing, using multilevel models for repeated measures and accounting for individuals nested within census tracts. Due to the non-normal distribution of epinephrine, hsCRP, and IL-6, these variables were log transformed throughout all analyses and results presented as geometric means.

To test for differences in hemodynamic (rest, preparation, speech, and recovery), neuroendocrine (rest and post-stress), and inflammatory measures (rest and post-stress) by neighborhood poverty status across time, we included neighborhood poverty, time, and the neighborhood poverty-by-time interaction term. To test the hypotheses that neighborhood poverty may be associated with hemodynamic, neuroendocrine, and inflammatory measures,

even after individual-level factors are taken into account, adjusted models further included age, sex, race, and individual-level income, as well as covariates that that were considered *a prior* and found to be different by neighborhood poverty status in bivariate analyses, including lifestyle and medical risk factors (smoking status, BMI, hypertension, diabetes, heart failure, revascularization, functional capacity, and previous MI), and medication use (beta-blockers and ACE inhibitors). The significance level for main effects was set at $p < 0.05$; while the statistical significance of interaction effects was set at $p < 0.10$.

A third set of regression models were also conducted to strengthen the validity of the results, using propensity scores weighted by the inverse probability of "treatment," or IPT (i.e. low vs. high poverty neighborhood). IPT weighting uses propensity scores to create a sample in which the distribution of measured covariates is independent of neighborhood classification (low vs. high poverty neighborhood). First, a propensity score (as a continuous variable) for the probability of living in a low versus high poverty neighborhood was estimated for each individual using variables that may contribute to selection of participants into neighborhoods, and shown to be significantly different by neighborhood group, including age, sex, race, and individual-level income. More specifically, we constructed a logistic regression model in which neighborhood status was predicted by the identified covariates that may bias the selection of participants into neighborhood groups. We then used the estimated probabilities of neighborhood membership to derive weights for IPT, i.e., predicted neighborhood status, for each person (Austin, 2011; D'Agostino, 1998; Heinze and Juni, 2011; Newgard et al., 2004). That is, participants in the high poverty neighborhoods received a weight of $1/P(Z=1|X)$ and participants in the low poverty neighborhoods received a weight of $1/(1-P(Z=1|X))$ where P is the probability, Z is the binary treatment indicator for neighborhood classification, and X is a vector of all observed covariates (Austin, 2011; Thoemmes and Ong, 2016). Next, the multilevel regression models were fitted to compare neighborhood poverty status on the outcomes of interest (i.e., hemodynamics, neuroendocrine, and inflammatory biomarkers) and adding a weight statement in the analysis step using the IPT variable that was created in the aforementioned steps (Austin, 2011). The propensity weighting scheme transforms the covariate distributions of the sample population so that the weighted covariate distributions of the group across neighborhood levels become comparable. We used this approach to help reduce selection bias due to differences between groups of people living in different neighborhood groups.

For sensitivity analyses, we also compared an alternative cut-point for 'high' poverty by using absolute values of 20% poverty to categorize 'high' poverty neighborhoods and also using percent poverty as a continuous exposure variable. Since results were similar, these data are only shown in the On-line Data Supplement. In exploratory analyses, we also attempted to further validate the results of mental stress and SNS reactivity among patients who lived in high poverty neighborhoods, by contrasting results of 425 patients who also completed conventional stress testing with a treadmill task. All analyses were conducted using SAS statistical software (SAS Inc., Cary, NC).

3. RESULTS

3.1 Sample characteristics

Of the 632 participants included in the analytic dataset, 173 were women. The mean age was 63 years and 17% had a household income below the federal poverty level (< $20,000/year) at the individual-level. As expected, given that underlying CAD was required for inclusion in the study, a large proportion of participants had concurrent comorbidities including diabetes (31%), hypertension (76%), and dyslipidemia (76%), and were taking medications including aspirin (86%), beta blockers (75%), ACE inhibitors (45%), and statins (86%). Participants represented 390 different census tracts (neighborhoods) in Georgia. The mean percentage of the population whose income was below poverty level at the census-tract level was 14%.

Three hundred seventy-five participants were living in low poverty neighborhoods, while 257 were living in high poverty neighborhoods (41%). Participants living in high poverty neighborhoods were younger, less likely to be male and White, and more likely to have a household income below poverty compared to those who lived in low poverty neighborhoods (Table 1). They also had more adverse behavioral factors than participants living in low poverty neighborhoods, including a higher BMI, a greater prevalence of smoking, greater depression scores, and lower functional capacity. SBP, DBP, and hsCRP were higher at rest in participants from high poverty neighborhoods compared with those from low poverty neighborhoods, while resting epinephrine was lower. However, there were no significant differences in previous medical history.

3.2 Hemodynamic response to stress

After adjusting for demographics (age, sex, race, and individual-level income), lifestyle and disease risk factors (smoking status, BMI, functional capacity, depression, hypertension, diabetes, heart failure, revascularization, and previous MI), and medication use (beta-blockers and ACE inhibitors), participants living in high (vs. low) poverty neighborhoods had similar hemodynamic values for SBP, DBP, HR, and RPP at rest and a blunted hemodynamic response to stress with lower values during the speaking task for SBP (157; 95% CI: 146, 155 mmHg vs. 161; 95% CI: 157, 165 mmHg; $p = 0.07$), HR (75; 95% CI: 72, 77 beats/min vs. 78; 95% CI: 75, 80 beats/min; $p = 0.02$) and RPP (11839; 95% CI: 11302, 12376 mmHg x beat/min vs 12579; 95% CI: 12077, 13082 mmHg x beat/min; $p = 0.01$). Recovery values were similar between participants living in high compared to low poverty neighborhoods. The p-values for neighborhood poverty-by-time interactions were < 0.05 (Table 2; Figure 1) indicating that participants' hemodynamic reactivity to mental stress across time (i.e., in the various phases of the mental stress test) was different between those who lived in high vs. low poverty neighborhoods. Results were similar in the IPT models, although somewhat attenuated for SBP (Table 2).

We also attempted to further validate the results of mental stress reactivity among patients who lived in high poverty neighborhoods, by contrasting results of 425 patients who also completed exercise stress testing (Figure 2). During exercise stress testing, participants who lived in high poverty neighborhoods (vs. low poverty neighborhoods) had higher values of

SBP, DBP, HR, and RPP, rather than a blunted response, with significantly higher values at exercise stages 1, 2, and 3 for SBP and stages 2 and 3 for RPP.

3.3 Inflammatory and Neuroendocrine response to stress

In the unadjusted model (model 1), participants living in high (vs. low) poverty neighborhoods had higher concentrations of hsCRP at rest (1.87; 95% CI: 1.57, 2.23 mg/L vs. 1.43; 95% CI: 1.23, 1.65 mg/L) and post-stress (1.80; 95% CI: 1.51, 2.14 mg/L vs. 1.42; 95% CI: 1.23, 1.63 mg/L). However, these differences were attenuated in models 2 and 3 (Table 3, Figure 3). At rest, concentrations of IL-6 were similar in the unadjusted model but tended to be lower in model 2 for participants living in high poverty neighborhoods (1.55; 95% CI: 1.34, 1.79 pg/mL) compared to those living in low poverty neighborhoods (1.75; 95% CI: 1.51, 2.02 pg/mL); however, levels of IL-6 were not significantly different after mental stress. Consistent with these results, the neighborhood poverty-by-time interactions were not statistically significant in the models for hsCRP or IL-6, indicating that the response to stress for inflammatory factors was similar. Results were similar in the IPT weighted models.

Concentrations of epinephrine were lower among individuals living in high (vs. low) poverty neighborhoods at rest (16.9; 95% CI: 15.1, 19.0 pg/mL vs. 17.8; 95% CI: 14.7, 21.7 pg/mL) and post-stress (26.6; 95% CI: 23.2, 30.6 pg/mL vs. 35.2; 95% CI: 31.4, 39.6 pg/mL) (Table 3). The neighborhood poverty-by-time interaction term was also marginally significant (p 0.07), denoting a tendency for a blunted epinephrine response in participants living in high poverty neighborhoods compared to those living in low poverty neighborhoods. Results were similar in the covariate adjusted model (Figure 3) and in the IPT weighted model; however, the interaction term was no longer statistically significant (p = 0.37).

3.4 Sensitivity Analyses

For sensitivity analyses, we also compared an alternative cut-point for ‘high’ poverty by using absolute values of 20% poverty within each census tract to categorize ‘high’ poverty neighborhoods and also percent poverty as a continuous exposure variable (On-line only data supplement). Results were similar when using absolute values of 20% poverty although showed an exaggerated blunted response for hemodynamic measures (Online Table 3; Online Figure 1). Using this alternative cut-point, neither hsCRP or IL-6 were significantly different between individuals living in the two neighborhood categories, while epinephrine was significantly lower after mental stress among participants who lived in high vs. low poverty neighborhoods (Online Table 3 and Online Figure 3). Similarly, when using percent poverty as a continuous exposure variable in our regression models, results showed that SBP, HR, RPP, and epinephrine significantly decreased during the speaking task as percent poverty increased (Online Tables 4 and 5).

4. DISCUSSION

In this study, we found that participants living in high poverty neighborhoods had a blunted hemodynamic response to mental stress compared to participants in neighborhoods with low levels of poverty. These results were independent of individual-level risk factors, and were

relatively unchanged in propensity weighted models that accounted for individual-level variables that may contribute to selection of participants into high poverty neighborhoods (age, sex, race, and individual-level income). Notably, this blunted response only applied to mental stress. Participants living in high poverty neighborhoods did not show a blunted hemodynamic response to exercise stress testing, and actually tended to show higher blood pressure and heart rate in response to exercise than those living in low-poverty neighborhoods. These findings highlight the presence of physiological perturbations of hemodynamic reactivity in response to mental stress via the SNS, as opposed to increased workload provoked by a physical stress. The fact that we did not observe an exaggerated inflammatory or neuroendocrine response for participants living in high poverty neighborhoods after mental stress, with a tendency for epinephrine to be actually lower post-stress in patients from disadvantaged neighborhoods compared with patients from the other neighborhoods, is consistent with a blunted SNS activation with stress which may be driving the attenuated hemodynamic response. Because a blunted hemodynamic response to mental stress was observed among participants living in high poverty neighborhoods, but not during physical stress suggests that chronic exposure of living in economically disadvantaged neighborhoods may lead to maladaptation of the body's hemodynamic response to psychological stress through the SNS.

Our findings were particularly robust after reducing the imbalance in distribution of the characteristics between high and low poverty neighborhoods by using a propensity weighting scheme to account for differences in the probability of living in a low versus a high poverty neighborhood. As a result of using propensity scores, it is unlikely that differences in the outcomes are due to age, sex, race, or individual-level income, but due to the treatment (neighborhoods), since these covariates across neighborhoods were balanced by the propensity scoring method, thereby distinguishing associations attributable to neighborhood context rather than individual composition of neighborhoods.

Living in poor neighborhood environments, characterized by socioeconomic disadvantage and poverty, may act as a chronic stressor that results in physiological dysregulation of the body's reactivity to stress through the SNS and the HPA axis (Augustin et al., 2008; Broyles et al., 2012; Dulin-Keita et al., 2012; Hajat et al., 2015) even after adjusting for individual-level factors. A plausible explanation that support the association between neighborhood poverty and stress systems dysregulation is that people who live in impoverished neighborhoods may confront more physical and social challenges than people who live in more affluent neighborhoods (Evans and Kim, 2007; Taylor et al., 1997). Neighborhood-income related physical risks include sub-standard housing, low neighborhood quality, toxins, noise, and crowding (Evans and Kim, 2007). Also, impoverished neighborhoods have higher crime rates and less access to social resources, health care, and employment opportunities, thereby creating a resource depleted social environment predisposing to chronic stress (Evans and Kim, 2007). Research has shown that psychosocial hazards in neighborhood environments such as violent crime, abandoned buildings, and signs of incivility give a heightened state of vigilance, alarm, and threat (Augustin et al., 2008; Glass et al., 2006; Ross and Mirowsky, 2001). Daily exposure to psychosocial hazards in the neighborhood environment is known to activate a physiological stress response and that may in turn lead to dysregulation of the physiological stress response (Augustin et al., 2008;

Taylor et al., 1997). Consistent with this model are also data showing that individuals who live in neighborhood environments with greater psychosocial hazards have a higher odds of cardiovascular disease including myocardial infarction, stroke, and transient ischemic attack (Augustin et al., 2008). Previous research has also shown that psychosocial stress is associated with increased cardiovascular risk and all-cause mortality in persons with low socioeconomic status, but not high socioeconomic status (Sumner et al., 2016). Although socioeconomic status was measured at the individual-level, these data support the importance and confluent role of low SES and psychosocial stress on cardiovascular outcomes.

To our knowledge, only one previous study with a relatively small sample of 82 patients (71 men and 11 women) investigated neighborhood measures of SES in relation with stress reactivity among adults with CAD. Similar to our study, Suchday et al. (2005) found that participants who lived in lower SES neighborhoods had a blunted hemodynamic (SBP and DBP) response to stress. We confirmed and expanded these findings by adding additional measures (immune and neuroendocrine) of the SNS, using a larger sample of participants, and using multilevel analytical methods that incorporate IPT to control for selection bias of participants into neighborhoods.

The finding that those who lived in lower SES neighborhoods have a lower, as opposed to higher, stress reactivity, may seem counterintuitive. However, evidence is accumulating to show that low cardiovascular reactivity to stress, as well as low cortisol reactivity, may actually have serious adverse consequences for a number of health and behavioral outcomes (de Rooij, 2013; Lovallo, 2013; Phillips et al., 2013). Previous research found a blunted hemodynamic response to stress among children living in low SES neighborhoods (Evans et al., 2013) as well as for other stressors including lifetime adversity (Lovallo et al., 2012). Most previous studies, however, have focused on HPA responses to chronic stress (Elzinga et al., 2008; Le-Scherban et al., 2018; Lovallo et al., 2012; Voellmin et al., 2015). Our data suggest that a blunted SNS response can also be a consequence of chronic adversity.

An altered reactivity to stress, either in the direction of exaggerated reactivity or diminished reactivity, may signal a dysregulation of systems intended to maintain homeostasis (Phillips et al., 2013). While an increase in epinephrine may influence the development of atherosclerosis through metabolic effects (e.g., by promoting hyperglycemia and insulin resistance) and through pro-inflammatory responses and their action on the endothelium (Pickering, 1999), the exact mechanisms underlying a blunted response to stress and its link with long-term health outcomes, remains unclear, especially as it relates to CAD. Yet there are several possibilities which may involve personal and behavior components including reduced awareness and perceptions of stressor task difficultly, system exhaustion or burn-out, motivational dysregulation within the brain, and also a stifling or titration of the blood pressure response for competing demand (Phillips et al., 2013). A blunted hemodynamic response in particular may operate through a disruption in dyad between the cardiac and peripheral vascular systems (James et al., 2012), for example when changes in cardiac output are compensated by inverse changes in total peripheral resistance without elevating systolic or diastolic blood pressure (James et al., 2012). However, more research is needed in

this arena to understand complex interactions between biological, psychological, and social factors on stress reactivity.

There are several strengths and limitations of our study worth noting. First, the MIPS study provides one of the largest and most comprehensive studies of mental stress-related responses in CAD patients to date. The diverse sample size, including a sizable number of women, along with a wide range of stress reactivity measures collected in the laboratory setting are also strengths worth noting. The experimental manipulation of the exposure (mental stress) allows a controlled assessment of the effects of stress on hemodynamic, immune, and neuroendocrine changes across time. Further, we have used statistical methods to control for clustering and selection bias of participants in neighborhoods, a limitation not always addressed in prior studies. However, our study also had limitations. First, we cannot rule out the possibility of unmeasured confounding, which may bias effect estimates toward or away from the null. While the use of inverse probability weighting to minimize selection bias does not rule out selection bias completely, and the precision varies based on the variables included in the model. Additionally, since contextual measures of the neighborhood environment using Census data have been aggregated from individual-level characteristics of residents, there are concerns whether the two can be separated empirically when adjusting for individual-level characteristics as confounders, especially in regards to socioeconomic characteristics (Diez Roux and Mair, 2010). However, we observed contextual (neighborhood) associations even after adjusting for individual-level income and other sociodemographic factors. Another disadvantage of using Census measures is that they are limited to the neighborhood characteristics available in the database for given time periods and may not accurately align to dates of data collection. While patients were enrolled in MIPS between June 2011 and August 2014, we retrospectively geocoded patients' addresses using 2010 shape files to get geographic information codes which were then merged with corresponding geographic data at the census-tract level from the 2010 United States Census Bureau's American Community Survey (ACS) 5-year estimates. The United States Department of Agriculture (which uses census-tract level poverty data from the ACS to measure food deserts in the United States), showed that the number of census tracts classified as low income (poverty rates at least 20 percent) or median family income (at or below 80% of the percent of the metropolitan area or State median income) between 2010 and 2015 showed relatively small changes (increase of 5.41%) (Rhone et al., January 2017). Additionally, we further compared the reliability of the poverty data from the 2010 and 2015 ACS for census tracts in Georgia using a Bland-Altman plot in exploratory analyses. The mean difference between the percent below poverty between 2010 and 2015 ACS was 2.7%. Of 1,969 census tracts in Georgia, only 109 (5.5%) were outside the 95% limits of agreement, showing good reliability of the data between 2010 and 2015 ACS poverty estimates. Finally, we studied a sample of patients with CAD; whether these associations can be generalizable to healthy populations is unknown, but serves as rationale for further exploration.

4.1 Conclusion

In conclusion, we found that adults with CAD who lived in low SES neighborhoods have blunted hemodynamic responses to psychological stress compared with those living in

higher SES neighborhoods, suggesting that an impoverished neighborhood environment may affect individual differences in reactivity to stress. These findings further implicate the role of contextual influences of the neighborhood environment in shaping stress response patterns, independent of individual-level income. Our results identify a possible mechanism by which living in impoverished neighborhoods may affect physiological perturbations of the stress systems that may further relate to health outcomes. Future studies should explore whether neighborhood poverty and blunted hemodynamic response to stress translate into differences in long-term cardiovascular outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

BDI-II	Beck depression inventory second edition
BMI	body mass index
CAD	coronary artery disease
DASI	Duke activity status instrument
DBP	diastolic blood pressure
HR	heart rate
HsCRP	high-sensitivity C-reactive protein
HPA	hypothalamic-pituitary-adrenal axis
IL-6	interleukin-6
MIPS	Mental Stress Ischemia Mechanisms and Prognosis Study
RPP	rate pressure product
SBP	systolic blood pressure
SNS	sympathetic nervous system

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HIGHLIGHTS

- Patients in high poverty neighborhoods had a blunted sympathetic stress response.
- Results were specific to reactivity to mental stress challenge.
- A blunted hemodynamic stress response was not observed during exercise stress.
- Neighborhood poverty may lead to poor health through a blunted stress response.

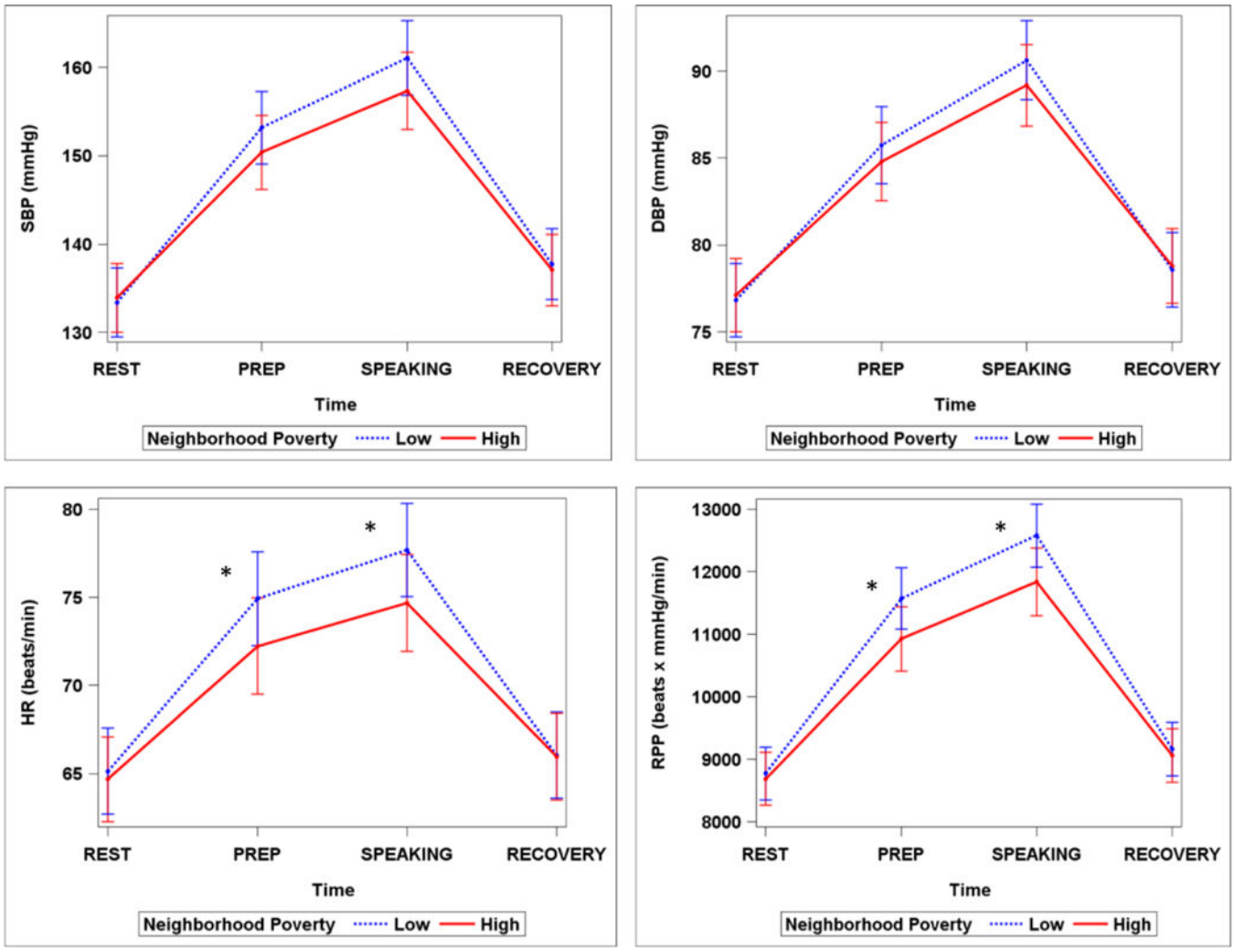

Figure 1. Comparison of changes in hemodynamic responses to mental stress among participants living in neighborhoods with low and high levels of neighborhood poverty.

Hemodynamic changes measured as systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and rate pressure product (RPP). All measurements are adjusted for demographics (age, sex, race, and individual-level income), lifestyle and disease risk factors (smoking status, BMI, functional capacity, depression, hypertension, diabetes, heart failure, revascularization, and previous MI), and medication use (beta-blockers and ACE inhibitors. Error bars represent 95% confidence intervals. * denotes p-value < 0.05.

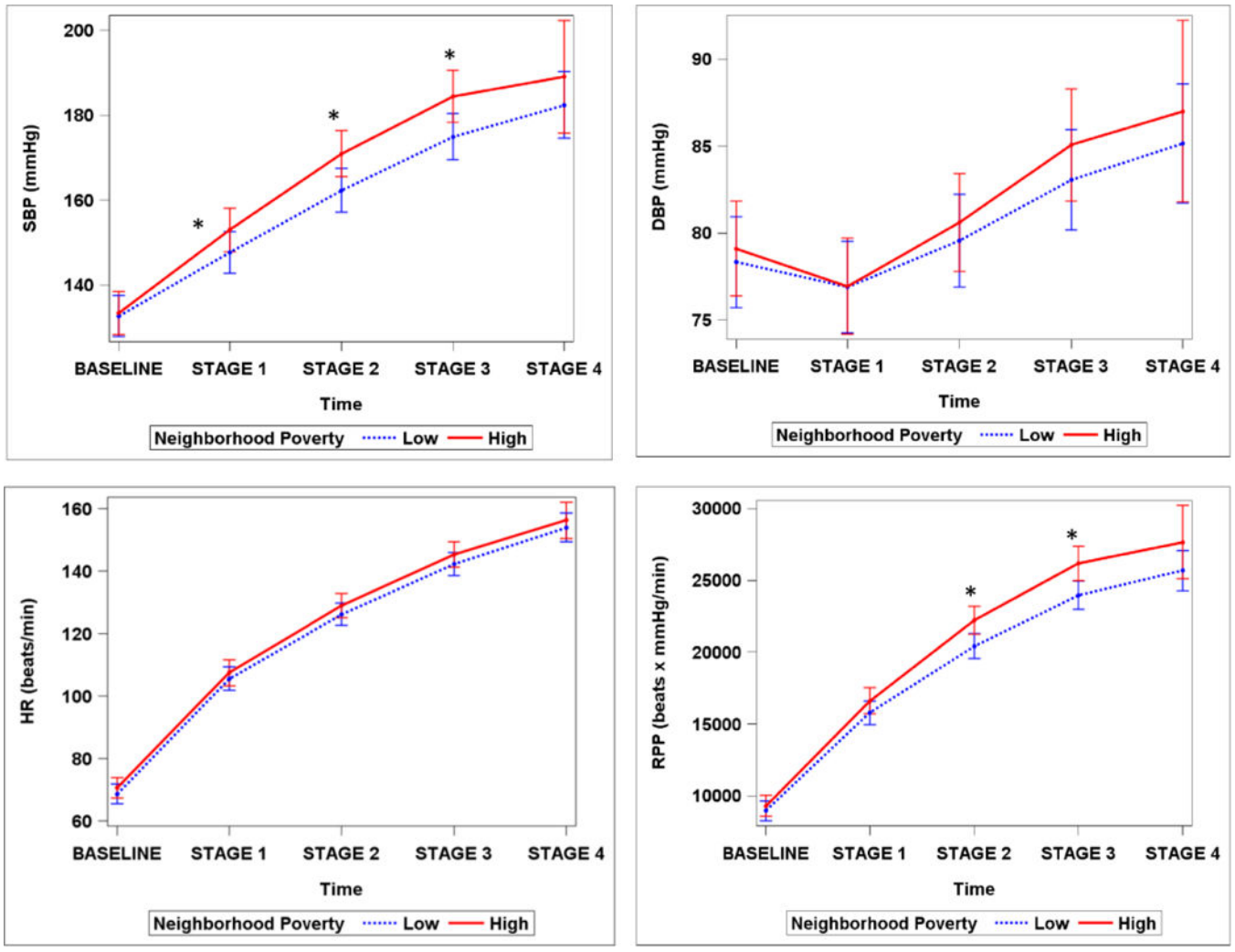

Figure 2. Comparison of changes in hemodynamic responses to exercise stress among participants living in neighborhoods with low and high levels of neighborhood poverty.

Hemodynamic changes measured as systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and rate pressure product (RPP). All measurements are adjusted for demographics (age, sex, race, and individual-level income), lifestyle and disease risk factors (smoking status, BMI, functional capacity, depression, hypertension, diabetes, heart failure, revascularization, and previous MI), and medication use (beta-blockers and ACE inhibitors). Error bars represent 95% confidence intervals. * denotes p-value < 0.05.

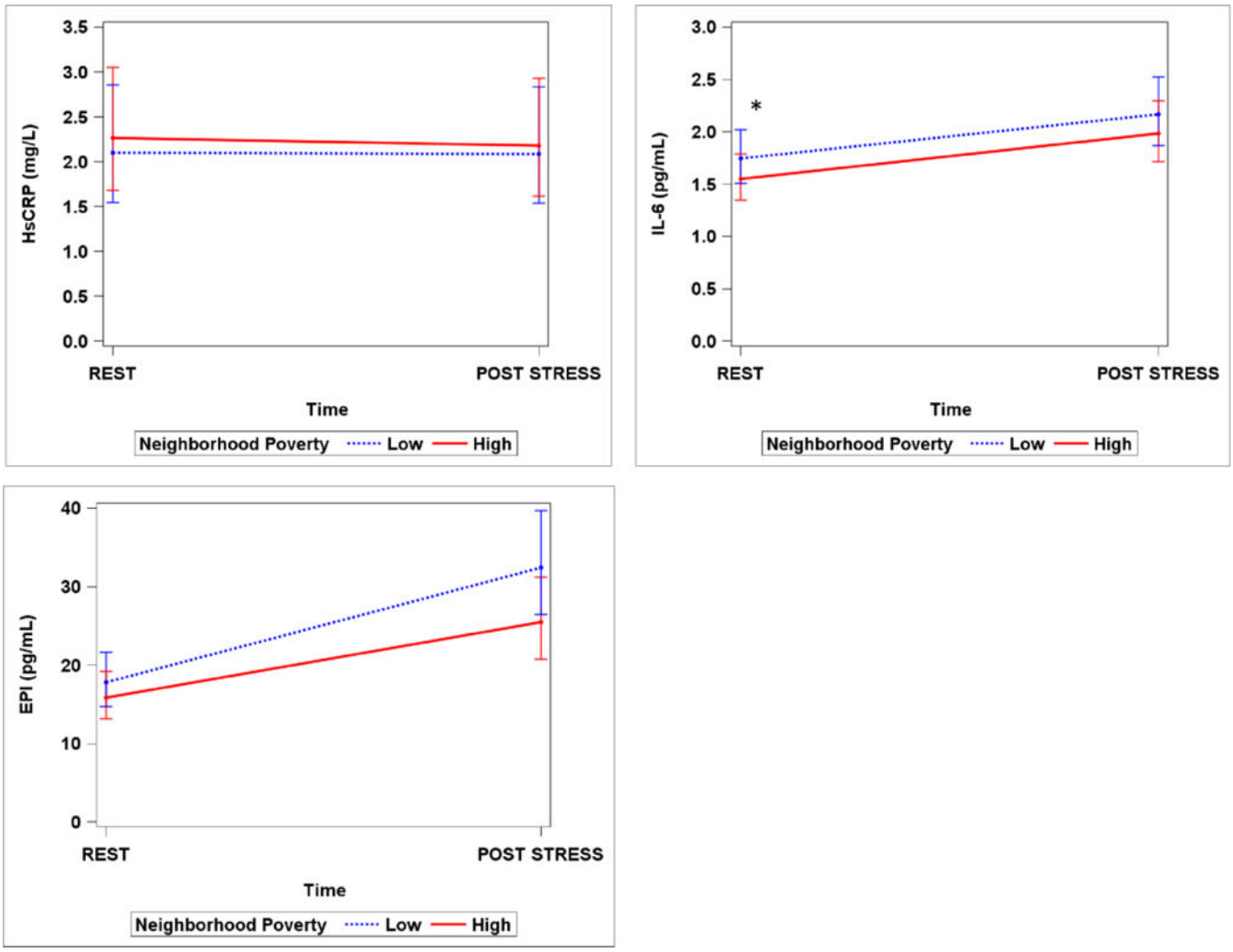

Figure 3. Comparison of changes in hsCRP (mg/L), IL-6 (pg/mL), and epinephrine (pg/mL) levels in response to mental stress among participants living in neighborhoods with low and high levels of neighborhood poverty.

Results are presented as geometric means, adjusted for demographics (age, sex, race, and individual-level income), lifestyle and disease risk factors (smoking status, BMI, functional capacity, depression, hypertension, diabetes, heart failure, revascularization, and previous MI), and medication use (beta-blockers and ACE inhibitors). * denotes p-value < 0.05.

Table 1.

Descriptive Statistics for Participants Living in Neighborhoods with Low and High Levels of Poverty.

	Low Neighborhood Poverty	High Neighborhood Poverty	*P*-Value
Participants, Total N	375	257	
Demographics			
Age, years, mean (SD)	64.3 (8.8)	61.0 (9.3)	<.0001
Age > 50 years, n (%)	351 (93.6)	221 (86.0)	0.001
Male, n (%)	289 (77.1)	170 (66.2)	0.003
White, n (%)	269 (71.7)	130 (50.6)	<.0001
Individual Household Income Below Poverty, n (%)	39 (11.0)	61 (25.2)	<.0001
Education, high school or less, n (%)	69 (18.9)	98 (38.6)	<.0001
Medical and Lifestyle Factors			
BMI, kg/m^2, mean (SD)	29.1 (4.8)	30.1 (5.9)	0.02
Depression (BDI), mean (SD)	7.2 (7.0)	10.4 (10.1)	<.0001
Function Capacity (DASI), mean (SD)	42.6 (14.0)	38.4 (15.0)	0.001
Current Smoker, n (%)	41 (11.0)	47 (18.3)	0.01
Diabetes, n (%)	115 (30.7)	83 (32.3)	0.66
Hypertension, n (%)	285 (76.0)	197 (76.7)	0.85
Dyslipidemia, n (%)	307 (81.9)	210 (81.7)	0.96
Myocardial Infarction, n (%)	140 (37.3)	99 (38.5)	0.76
Heart Failure, n (%)	85 (22.7)	68 (26.5)	0.27
Revascularization, n (%)	295 (78.7)	188 (73.2)	0.11
Medications			
Aspirin, n (%)	323 (86.1)	222 (86.7)	0.83
Beta Blocker, n (%)	273 (72.8)	202 (78.9)	0.08
ACE Inhibitors, n (%)	157 (41.9)	128 (50.0)	0.04
Anti-Depressant, n (%)	78 (20.8)	65 (25.4)	0.18
Statins, n (%)	323 (86.1)	219 (85.6)	0.84
Resting Hemodynamics			
SBP, mmHg, mean (SD)	134.6 (17.3)	137.2 (19.4)	0.08
DBP, mmHg, mean (SD)	77.7 (9.7)	79.7 (10.9)	0.02
HR, beats/min, mean (SD)	63.1 (11.0)	63.8 (10.8)	0.40
RPP, beat x mmHg/min, mean (SD)	8514.2 (1986.0)	8757.0 (1965.2)	0.14
Inflammatory Markers			
HsCRP, mg/L, median (IQR)	1.4 (0.6, 3.2)	1.9 (0.7, 4.5)	0.02
IL-6, pg/mL, median (IQR)	1.4 (1.0, 2.1)	1.4 (0.9, 2.2)	0.28
Catecholamines			
Epinephrine, pg/mL, median (IQR)	21.1 (11.7, 34.9)	17.8 (10.7, 29.2)	0.03
Neighborhood			
Length of Residence, yrs, n (%)			<.0001
<1–4	46 (14.2)	63 (29.2)	

	Low Neighborhood Poverty	High Neighborhood Poverty	*P*-Value
5–10	76 (23.5)	37 (17.1)	
11–15	56 (17.3)	21 (9.7)	
16–20	55 (17.0)	27 (12.5)	
> 20	90 (27.9)	68 (31.5)	

Abbreviations: BDI: Beck depression inventory; BMI: body mass index; DASI: Duke activity status instrument; DBP: diastolic blood pressure; HR: heart rate; HsCRP: high-sensitivity C reactive protein; IL-6; interleukin-6; RPP: rate pressure product SBP: systolic blood pressure.

Statistical tests: Categorical variables: Chi-square; continuous variables: Student's t test or Wilcoxon-Mann Whitley U Test when appropriate.

Table 2.

Comparison of Changes in Hemodynamic Responses to Mental Stress among Participants Living in Neighborhoods with Low and high Levels of Neighborhood Poverty.

		Low Neighborhood Poverty	High Neighborhood Poverty		
Model	**Time**	**Mean (95% CI)**	**Mean (95% CI)**	***P*-value**	***P*-value of poverty*time interaction**
		SBP (mmHg)			
Model 1*					0.004
	Rest	135 (133, 136)	137 (135, 139)	0.08	
	Prep	154 (152, 156)	153 (151, 156)	0.63	
	Speaking	162 (160, 164)	160 (157, 163)	0.34	
	Recovery	139 (137, 141)	140 (138, 143)	0.38	
Model 2†					0.01
	Rest	133 (130, 137)	134 (130, 138)	0.73	
	Prep	153 (149, 157)	150 (146, 155)	0.14	
	Speaking	161 (157, 165)	157 (153, 162)	0.07	
	Recovery	138 (134, 142)	137 (133, 141)	0.69	
Model 3‡					0.15
	Rest	132 (129, 136)	133 (130, 136)	0.73	
	Prep	152 (148, 155)	150 (147, 154)	0.49	
	Speaking	160 (156, 163)	158 (154, 161)	0.25	
	Recovery	137 (134, 140)	136 (133, 139)	0.64	
		DBP (mmHg)			
Model 1*					0.03
	Rest	77.8 (76.7, 78.8)	79.7 (78.4, 80.9)	0.03	
	Prep	86.6 (85.4, 87.9)	87.2 (85.7, 88.7)	0.59	
	Speaking	91.5 (90.2, 92.9)	91.6 (90.0, 93.2)	0.97	
	Recovery	79.6 (78.4, 80.7)	81.3 (80.0, 82.7)	0.05	
Model 2†					0.07

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Model	Time	Low Neighborhood Poverty Mean (95% CI)	High Neighborhood Poverty Mean (95% CI)	*P*-value	*P*-value of poverty * time interaction
	Rest	76.8 (74.7, 78.9)	77.1 (75.0, 79.2)	0.73	
	Prep	85.7 (83.5, 88.0)	84.8 (82.5, 87.1)	0.35	
	Speaking	90.6 (88.4, 92.9)	89.2 (86.8, 91.5)	0.18	
	Recovery	78.6 (76.4, 80.7)	78.8 (76.6, 80.9)	0.80	
Model 3‡					0.16
	Rest	77.8 (76.0, 79.5)	77.9 (76.1, 79.6)	0.88	
	Prep	86.5 (84.6, 88.5)	85.6 (83.7, 87.5)	0.35	
	Speaking	91.5 (89.5, 98.5)	90.1 (88.1, 92.1)	0.20	
	Recovery	79.7 (77.9, 81.5)	79.4 (77.6, 81.2)	0.69	
		HR (beats/min)			
Model 1*					0.0003
	Rest	63.1 (62.0, 64.3)	63.9 (62.5, 65.3)	0.40	
	Prep	72.6 (71.1, 74.1)	71.3 (69.5, 73.1)	0.28	
	Speaking	75.4 (73.9, 76.8)	73.6 (71.8, 75.4)	0.13	
	Recovery	64.0 (62.8, 65.2)	65.2 (63.8, 66.6)	0.20	
Model 2†					0.001
	Rest	65.1 (62.7, 67.6)	64.7 (62.3, 67.1)	0.63	
	Prep	74.9 (72.3, 77.6)	72.2 (69.5, 75.0)	0.03	
	Speaking	77.7 (75.0, 80.3)	74.7 (71.9, 77.4)	0.02	
	Recovery	66.1 (63.6, 68.5)	66.0 (63.5, 68.4)	0.93	
Model 3‡					0.004
	Rest	66.1 (64.0, 68.1)	65.8 (63.8, 67.9)	0.84	
	Prep	76.0 (73.7, 78.4)	73.8 (71.4, 76.1)	0.09	
	Speaking	78.6 (76.3, 81.0)	76.3 (73.9, 78.6)	0.08	
	Recovery	66.9 (64.9, 69.0)	67.1 (65.0, 69.2)	0.88	
		RPP (beats * mmHg /min)			
Model 1*					0.002

Model	Time	Low Neighborhood Poverty Mean (95% CI)	High Neighborhood Poverty Mean (95% CI)	*P*-value	*P*-value of poverty*time interaction
	Rest	8536 (8326, 8747)	8758 (8505, 9011)	0.19	
	Prep	11257 (10951, 11563)	10945 (10575, 11314)	0.20	
	Speaking	12270 (11945, 12595)	11829 (11438, 12221)	0.09	
	Recovery	8915 (8696, 9134)	9130 (8867, 9393)	0.22	
Model 2†					0.005
	Rest	8775 (8353, 9196)	8689 (8269, 9109)	0.61	
	Prep	11570 (11081, 12059)	10925 (10407, 11443)	0.01	
	Speaking	12579 (12077, 13082)	11839 (11302, 12376)	0.01	
	Recovery	9167 (8740, 9594)	9062 (8634, 9491)	0.56	
Model 3≠					0.04
	Rest	8827 (8469, 9185)	8783 (8423, 9143)	0.81	
	Prep	11617 (11174, 12061)	11139 (10692, 11586)	0.07	
	Speaking	12624 (12157, 13091)	12065 (11594, 12535)	0.05	
	Recovery	9224 (8860, 9588)	9154 (8788, 9519)	0.71	

Abbreviations: DBP: diastolic blood pressure; HR: heart rate; CL: confidence limit; SPB: systolic blood pressure; RPP: rate pressure product.

*Model 1 included neighborhood poverty, time, and neighborhood poverty-by-time interaction term.

†Model 2 included model 1 covariates + age (continuous), sex, race, income, smoking status, hypertension, diabetes, heart failure, revascularization, beta-blockers, ACE Inhibitors, previous MI, and BMI (continuous), functional capacity, and depression.

≠Model 3 used inverse probability weighted regression using propensity score to account for differences between patients living in neighborhoods with high and low poverty (estimated for age, sex, race, and income) and also adjusted for smoking status, hypertension, diabetes, heart failure, revascularization, beta-blockers, ACE Inhibitors, previous MI, and BMI (continuous), functional capacity, and depression.

Statistical tests: Interactions: Type 3 Tests of Fixed Effects: Pr>F; Differences of Least Square Means: Pr>|t|.

Table 3.

Comparison of Changes in Immune and Neuroendocrine Responses to Mental Stress among Participants Living in Neighborhoods with Low and high Levels of Neighborhood Poverty.

Model	Time	Low Neighborhood Poverty Mean (95% CI)	High Neighborhood Poverty Mean (95% CI)	*P*-value	*P*-value of poverty*time interaction
		HsCRP (mg/L)			
Model 1*					0.15
	Rest	1.43 (1.23, 1.65)	1.87 (1.57, 2.23)	0.02	
	Post Stress	1.42 (1.23, 1.63)	1.80 (1.51, 2.14)	0.04	
Model 2†					0.18
	Rest	2.10 (1.55, 2.86)	2.26 (1.68, 3.05)	0.53	
	Post Stress	2.08 (1.53, 2.83)	2.17 (1.62, 2.93)	0.71	
Model 3‡					0.25
	Rest	2.05 (1.60, 2.62)	2.23 (1.76, 2.83)	0.47	
	Post Stress	2.01 (1.58, 1.58)	2.13 (1.68, 2.70)	0.61	
		IL-6 (pg/mL)			
Model 1*					0.39
	Rest	1.49 (1.39, 1.60)	1.43 (1.31, 1.55)	0.44	
	Post Stress	1.84 (1.71, 1.98)	1.82 (1.66, 1.90)	0.84	
Model 2†					0.44
	Rest	1.75 (1.51, 2.02)	1.55 (1.34, 1.79)	0.04	
	Post Stress	2.17 (1.87, 2.52)	1.98 (1.71, 2.30)	0.15	
Model 3‡					0.90
	Rest	1.81 (1.60, 2.04)	1.64 (1.45, 1.84)	0.08	
	Post Stress	2.26 (1.99, 2.56)	2.05 (1.81, 2.32)	0.12	
		Epinephrine (pg/mL)			
Model 1*					0.07
	Rest	19.7 (17.9, 21.8)	16.9 (15.1, 19.0)	0.05	

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Model	Time	Low Neighborhood Poverty Mean (95% CI)	High Neighborhood Poverty Mean (95% CI)	*P*-value	*P*-value of poverty*time interaction
	Post Stress	35.2 (31.4, 39.6)	26.6 (23.2, 30.6)	0.002	
Model 2†					0.09
	Rest	17.8 (14.7, 21.7)	15.9 (13.1, 19.2)	0.16	
	Post Stress	32.4 (26.4, 39.7)	25.5 (20.8, 31.2)	0.06	
Model 3≠					0.37
	Rest	20.6 (17.4, 24.3)	17.8 (15.1, 20.9)	0.05	
	Post Stress	36.7 (30.7, 43.9)	29.6 (24.8, 35.4)	0.02	

Abbreviations: HsCRP: high sensitivity C-reactive protein; IL-6: interleukin-6; CL: confidence limit.

*Model 1 included neighborhood poverty, time, and neighborhood poverty-by-time interaction term.

†Model 2 included model 1 covariates + age (continuous), sex, race, income, smoking status, hypertension, diabetes, heart failure, revascularization, beta-blockers, ACE Inhibitors, previous MI, and BMI (continuous), functional capacity, and depression.

≠Model 3 used inverse probability weighted regression using propensity score to account for differences between patients living in neighborhoods with high and low poverty (estimated for age, sex, race, and income) and also adjusted for smoking status, hypertension, diabetes, heart failure, revascularization, beta-blockers, ACE Inhibitors, previous MI, and BMI (continuous), functional capacity, and depression.

Statistical tests: Interactions: Type 3 Tests of Fixed Effects: Pr>F; Differences of Least Square Means: Pr>|t|.