



Published in final edited form as:

Psychoneuroendocrinology. 2019 August ; 106: 122–128. doi:10.1016/j.psyneuen.2019.03.021.

An Investigation of Racial/Ethnic and Sex Differences in the Association between Experiences of Everyday Discrimination and Leukocyte Telomere Length among Patients with Coronary Artery Disease

Samaah Sullivan, PhD¹, Muhammad Hammadah, MD², Ibhar Al Mheid, MD², Amit Shah, MD, MSCR^{1,2,3}, Yan V. Sun, PhD^{1,3}, Michael Kutner, PhD⁴, Laura Ward, MSPH⁴, Elizabeth Blackburn, PhD⁵, Jinying Zhao, MD, PhD⁶, Jue Lin, PhD⁵, J. Douglas Bremner, MD^{3,7}, Arshed A. Quyyumi, MD², Viola Vaccarino, MD, PhD^{1,2}, Tené T. Lewis, PhD¹

¹Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

²Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA

³Atlanta VA Medical Center, Decatur, Georgia, USA

⁴Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

⁵Department of Biochemistry and Biophysics, University of California San Francisco, San Francisco, California, USA

⁶Department of Epidemiology, College of Public Health and Health Professions and College of Medicine, University of Florida, Gainesville, Florida, USA

⁷Departments of Psychiatry and Behavioral Sciences and Radiology, Emory University School of Medicine, Atlanta, Georgia, USA

Abstract

Leukocyte telomere length (LTL) may be sensitive to psychosocial stressors such as discrimination. An inclusive examination of experiences of discrimination on LTL across racial/ethnic and sex groups is currently lacking. Baseline data were obtained from 369 White and African American patients with coronary artery disease (CAD) in the Mental Stress Ischemia

Address for Correspondence: Dr. Tené T. Lewis, PhD, Emory University, Department of Epidemiology, Rollins School of Public Health, 1518 Clifton Rd NE, Room 3027, Atlanta, GA 30322. Phone: 404-727-6706; Fax: 404-727-8737; tene.t.lewis@emory.edu.

CONTRIBUTORS
VV, AQ, JDB, AS, and TTL participated in the overall study aims, study design, and analytic methods for the Mental Stress Ischemia Mechanisms and Prognosis Study. SS developed the paper concept, drafted the manuscript, and conducted the statistical analysis. MH, IA, AS, YS, EB, JZ, and JL were involved in the data acquisition, collection, preparation, analysis, and storage of the data. LW and MK participated in data management and contributed to the analysis. All authors critically read, revised, and approved the final manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Mechanisms and Prognosis Study. LTL was measured from peripheral blood leukocytes by quantitative polymerase chain reaction and calculated in kilobase pairs. Discrimination was measured using the 10-item Everyday Discrimination Scale (EDS). Responses were rated using 4-point Likert scales ranging from never = 1 to often = 4 and summed. Regression models were stratified by race/ethnicity and sex to estimate associations between discrimination and LTL. Each 10-unit increase in experiences of everyday discrimination was associated with an average of .20 fewer kilobase pairs (or 200 base pairs) among both African American women ($\beta = -0.19$; 95% CI: $-0.35, -0.04$; p -value: 0.02) and White women ($\beta = -0.19$; 95% CI: $-0.37, -0.01$; p -value: 0.04), after adjusting for basic demographic factors. Results were similar after further adjusting for behavioral, disease, and psychosocial risk factors (depression and stress). There were no significant associations between experiences of everyday discrimination and LTL for White men or African American men. Overall, experiences of discrimination were associated with shorter LTL among women and not in men. Discrimination may be a potential source of stress associated with shorter LTL among women with CAD. Future studies should explore longitudinal associations between everyday experiences of discrimination and telomere length and also with adverse cardiovascular outcomes.

Keywords

Leukocyte telomere length; discrimination; psychosocial stressors; women

1. INTRODUCTION

Research suggests that psychosocial stress is associated with earlier onset of age-related diseases (O'Donovan et al., 2012). Telomere length, a biomarker of aging at the cellular level may illuminate potential mechanisms between stress and pathogenesis of disease (O'Donovan et al., 2012; Sanders and Newman, 2013). Telomeres, which are protective caps at the end of chromosomes composed of repeated nucleotides or base pairs of DNA, have a central role in genomic stability and chromosomal structural integrity (Blackburn, 2000, 2001). Telomere shortening is a biologically natural phenomenon that occurs over time and across the lifespan, eventually stripping the chromosome of its protective armor. Subsequently, cells become functionally impaired and are unable to proliferate, which leads to cellular senescence or cell death (Blackburn, 2000, 2001).

However, chronological age accounts for less than 10% of the variance in human telomere length (Blackburn et al., 2015). While genetic factors can influence telomere length, environmental and psychosocial determinants can also play a role. Many studies have found that greater exposure to psychosocial stressors are associated with shorter telomere length including life stress (Epel et al., 2004), low social support (Carroll et al., 2013), low socioeconomic status (Adler et al., 2013; Needham et al., 2013), and adverse, or stressful neighborhood environments (Gebreab et al., 2016). Although the majority of research in this area has focused on adults, associations between psychosocial stressors and shorter telomere length have also been observed among children (Theall et al., 2013). Similar results have also been confirmed in recent meta-analyses in adults and children (Hanssen et al., 2017; Mathur et al., 2016; Pepper et al., 2018; Schutte and Malouff, 2016).

One important, yet relatively understudied source of stress-related cellular aging is everyday discrimination, or interpersonal mistreatment. To date, only a few studies have examined the association between discrimination and telomere length (Chae et al., 2016; Chae et al., 2014; Liu and Kawachi, 2017) and while some significant associations were found, all of these studies focused on racial/ethnic discrimination alone. Research suggests; however, that experiences of discrimination may transcend experiences of mistreatment due to race/ethnicity and may include occurrences of unfair treatment related to age, sex, physical disability, or other characteristics. Further, none of the aforementioned studies explicitly examined experiences of discrimination and telomere length stratified or moderated by sex, failing to consider whether the effect of discrimination on LTL differs for women and men. Thus, an inclusive examination of experiences of discrimination on LTL across racial/ethnic and sex groups is currently lacking.

This study was designed to investigate whether experiences of everyday discrimination are associated with shorter LTL across race/ethnicity and sex among African-American and White men and women with coronary artery disease (CAD). LTL may have particular relevance for this group, as CAD is an age-related disease and shorter LTL has been associated with reduced vascular regenerative capacity and repair and a range of adverse outcomes (e.g., stroke, myocardial infarction, mortality) in this population (Hammadah et al., 2017a).

In the current analysis, we hypothesized that experiences of everyday discrimination would be associated with shorter telomere length among women, and African American women in particular. Research suggests that women may be more physiologically vulnerable to psychosocial stressors (Vaccarino and Bremner, 2017), particularly those of an interpersonal nature, compared to men (Stroud et al., 2002). We expected stronger associations among African American women because research suggests that African American women may experience greater frequency, duration, and intensity of psychosocial stressors (Geronimus et al., 2010) and are more likely to experience everyday discrimination on the basis of multiple subordinate identities (Lewis et al., 2015; Lewis and Van Dyke, 2018). Also, there is evidence that African American women are more likely than their white or male counterparts to be discriminated against in medical encounters (Schulman et al., 1999; Shaw et al., 2008), which may be especially relevant for our study population of patients with coronary artery disease.

In addition to exploring the main association between experience of everyday discrimination and telomere length, we further wanted to investigate whether the possible relationship was independent or explained by other dimensions of stressors including perceived stress and depression. Not only has prior research recommended controlling for other dimensions of stressors in discrimination research on health outcomes (Albert and Williams, 2011), perceived stress and depression have also been associated with shorter telomere length in previous studies and in recent meta-analyses (Epel et al., 2004; Lin et al., 2016; Mathur et al., 2016).

2. MATERIALS AND METHODS

2.1 Study Design

The Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS) is a prospective cohort study designed to investigate mechanisms and prognosis of mental stress-induced ischemia among patients with stable coronary artery disease (CAD). Patients were recruited from Emory University-affiliated hospitals and clinics and were eligible for the study if they were between 30–79 years of age and had documented CAD, including any 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 (MI), or 4) positive exercise or pharmacological nuclear stress test or electrocardiographic exercise stress test (Hammadah et al., 2017b). Patients were excluded from participating in the study if they were either pregnant; were hospitalized in the previous week for unstable angina, decompensated heart failure, or myocardial infarction; had severe psychiatric conditions such as schizophrenia; a history of alcohol or substance abuse; active malignancy or end stage renal disease; or other severe medical problems expected to shorten life expectancy to less than 45 years.

Between June 2011 and August 2014, 695 patients were enrolled in MIPS. During the baseline visits, patients underwent clinical evaluations including mental and physical stress testing and questionnaire assessments such as the Beck Depression Inventory and the Perceived Stress Scale. Blood samples for telomere length were collected during the baseline clinic visits. The Institutional Review Board at Emory University approved the MIPS protocol. Written informed consent was obtained from all patients. More detailed information on the MIPS objectives and study design has been described elsewhere (Hammadah et al., 2017b).

2.2 Participants

Analyses were restricted to patients who indicated that their race/ethnicity was either Non-Hispanic White or African American (n=645). Of these, 199 were missing information on everyday discrimination as the Everyday Discrimination Scale was added after the start of the study, and 76 participants did not have telomere assays because of technical difficulties in sample drawing or processing, or because the patient refused. Further, we removed observations with missing covariates of interest including income (n=15), education (n=4), and smoking history (n=2). Thus, there were 369 patients in the final analytic dataset. Participants included in the analytic dataset were not significantly different than participants who were excluded due to missing observations across demographic characteristics with the exception of age (Supplemental Table 1). Specifically, included participants were slightly younger than those with missing data (mean: 62.2; SD: 9.3 vs. 63.9; SD: 9.8; *p*-value: 0.01).

2.3 Measurements

2.3.1 Telomere Length—Leukocyte telomere length (LTL) was measured from peripheral blood leukocytes collected during the baseline examination. All LTL assays were performed by Dr. Blackburn's laboratory at the University of California, San Francisco using methods by Cawthon (2009) and Lin et al. (2010). LTL was measured as the ratio of

telomeric product/single copy gene (T/S) by quantitative PCR analyses using a serially diluted standard DNA and the standard curve method. Reference DNA (pooled samples of leukocyte genomic DNA from 100 female donors) was included in each PCR run so that the quantity of targeted templates in each research sample could be determined relative to the reference DNA sample by the standard curve method. In each batch (8 plates in total), the T/S ratio of each control DNA were divided by the average T/S for the same DNA from 10 runs to get a normalizing factor. The average normalizing factor for all 8 plates were used to correct the participant DNA samples to get the final T/S ratio. The T/S ratio for each sample was measured twice. When the duplicate T/S value and the initial value varied by more than 7%, the sample was run a third time and the two closest values were reported. The T/S ratios represent the average length of telomeres. We then converted the T/S ratios to kilobase pairs using the following equation: kilobase pairs = $[3274 + 2413 * (T/S)]/1000$. More detailed information on the LTL measurement in MIPS has been described previously (Hammadah et al., 2017a).

2.3.2 Experiences of Everyday Discrimination—Discrimination was measured using the 10-item Everyday Discrimination Scale (EDS). The EDS was adapted from the original 9-item scale developed for use in the Detroit Area Study (Williams et al., 1997). Occurrences of unfair treatment during the previous 12 months were assessed without reference to race/ethnicity, age, sex, or other demographic characteristics. Specifically, participants were asked how often during their day-to-day experiences: 1) They were treated with less courtesy than other people; 2) They were treated with less respect than other people; 3) They received poorer service than other people at restaurants or stores; 4) People acted as if they were not smart; 5) People acted as if they were afraid of them; 6) People acted as if they were dishonest; 7) People acted as if they were better than them; 8) They were called names or insulted; 9) They were threatened or harassed; and 10) People ignored them, or acted as if they were not there. Responses were rated using 4-point Likert scales ranging from never (1) to often (4) which were summed and ranged from 0 to 40 on an ordinal scale. The Cronbach α for the EDS in the MIPS study was 0.90.

2.3.3 Covariates—Demographic information was obtained using standardized questionnaires. Previous medical history (diabetes, hypertension, previous MI) were obtained by study nurses or physicians through medical history, clinical examinations and by reviewing medical records. Demographics included race/ethnicity (Non-Hispanic White or African American), sex, educational attainment, income, and marital status. Educational attainment was assessed as highest year of education (grade school, some high school, high school or GED, some college, bachelor's degree, master's, degree, or other) and recoded as either high school or less or greater than high school. Income was dichotomized as whether family income was < \$20,000 or \geq \$20,000. Marital status included 1) married, partnered living as married; or 2) single, separated, divorced, or widowed. Participants' height and weight were objectively measured during the clinic visit and used to calculate body mass index (BMI, kg/m^2).

Depressive symptomology was assessed using the Beck Depression Inventory Second Edition (BDI-II) (Beck AT et al., 1996). The BDI-II includes 21 questions which asks

participants to rate their feelings, cognitions, and physical symptoms (e.g., sadness, pessimism, guilt, fatigue) during the past two weeks. Each item contains a 4-point Likert scale to indicate the severity of each feeling, from 0 (not at all) to 3 (extreme form of each symptom) (Beck AT et al., 1996). Responses across the items were summed so that higher scores indicated greater symptoms of depression.

Perceived stress was measured using the Cohen's Perceived Stress Scale (PSS) (Cohen et al., 1983). Participants were asked to rate their feelings about situations and experiences during the past month across 10 items using 5-point Likert scale ranging from Never (0) to Very Often (4) (e.g., nervous and stressed, confident about handling personal problems, not able cope with things, angered because of things outside of control). Positively stated items were reverse coded, and items were summed so that higher scores indicated greater perceptions of stress.

2.4 Statistical Analysis

Descriptive statistics were calculated for the MIPS sample by race/ethnicity and sex. Group differences were tested using chi-squared tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Additionally, because we were interested in determining whether associations were stronger among women and especially African American women, we also ran race and sex stratified models. Using linear regression models, we tested for differences in slopes across sex and race for discrimination on telomere length by including interaction terms of discrimination-by-sex, and discrimination-by-race, race-by-sex, and discrimination-by-sex-by-race. Adjusted models further included covariates that were considered *a priori*. Model 1 was adjusted for age. Model 2 was further adjusted for income, education and marital status. Model 3 further included cardiovascular risk factors and medical history, including smoking, BMI, diabetes, hypertension, and previous MI. Model 4 added additional adjustments for psychosocial factors (depression and perceived stress) as potential mediators. The significance level for main effects was set at $p < 0.05$ while the statistical significance of interaction effects was set at $p < 0.10$. Also, to minimize any potential batch effect in telomere length, we deemed important to include telomere plate as a random effect in our models to account for any correlation of values related to how the samples were run or prepared in the laboratory. Thus, we further included plate effect as a random intercept across all models. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

3. RESULTS

Table 1 presents descriptive characteristics of the analytic sample by race/ethnicity and sex. Of the 369 participants, 13.5% were White women, 54.7% were White men, 11.7% were African American women, and 20.1% were African American men (Table 1). African American race and female sex was significantly associated with younger age, lower income, marital status of single/widowed/or divorced, diabetes, and hypertension. African American race and male sex was associated with significantly higher discrimination scores and younger age. There were also significant differences across sex within race worth noting such that White women were significantly associated with higher discrimination scores, lower

income, history of smoking, and with higher depressive and stress scores compared to White men. Bivariate correlations of LTL with discrimination, demographic, clinical, and psychosocial covariates are described in Table 2.

In a multivariable model including discrimination, race, sex, their interaction terms, there was a steeper and negative slope for discrimination on telomere length for White and African American women compared to White and African American men (Figure 1) and the interaction term of discrimination-by-sex was $p = 0.07$ (Supplemental Table 2). However, after adjusting for age and in subsequent models, there was no significant difference in the effect of discrimination on LTL between women and men.

In linear regression analyses stratified by sex and race/ethnicity (Table 3) and after adjusting for age alone, each 10-unit increase in experiences of everyday discrimination were significantly associated with shorter LTL among African American women ($\beta = -0.17$; 95% CI: $-0.33, -0.04$; p -value: 0.03). After further adjusting for basic demographic factors including income, education, and marital status (model 2), experiences of everyday discrimination were significantly associated with shorter LTL among both African American women ($\beta = -0.19$; 95% CI: $-0.35, -0.04$; p -value: 0.02) and White women ($\beta = -0.19$; 95% CI: $-0.37, -0.01$; p -value: 0.04). Specifically, greater experiences of discrimination were associated with an average of .20 fewer kilobase pairs (or 200 base pairs) in both groups. Results were similar for both African American women and White women after further adjusting for behavioral and disease risk factors in model 3, and also after adjusting for psychosocial factors in model 4. There were no significant associations between discrimination and LTL in either White or African American men in any of the regression models and effect estimates were close to the null. Alternatively, a one standard deviation increase in discrimination score for each race sex group on LTL $\{(\beta \text{ for LTL}/10) * \text{SD of discrimination score}\}$, would change LTL by -0.09 kilobase pairs (90 base pairs) for White Women, -10 kilobase pairs (100 base pairs) for African American women, -03 kilobase pairs (30 base pairs) for White men, and -0.07 kilobase pairs (70 base pairs) among African American men.

4. DISCUSSION

Although we hypothesized that associations would be most pronounced for African American women, we found that reports of everyday discrimination were significantly associated with fewer LTL among both African American and White women, but not among men in stratified models after adjusting for basic demographic factors. Results were similar after further adjusting for lifestyle/disease factors and psychosocial factors. Similar to prior studies of healthy populations (Brown et al., 2016; Fitzpatrick et al., 2011; Hunt et al., 2008), in our sample of CAD patients, African American women had longer mean LTL compared to African American men, White women and White men. Nonetheless, the association between discrimination and LTL was significant for African American and White women, and remained statistically significant after adjusting for lifestyle and disease risk factors as well as possible alternative psychosocial and mediating pathways, including depression and stress. Across stratified regression models, there were no significant associations between discrimination and LTL for either White or African American men.

Our findings suggest that there may be stronger associations between everyday discrimination and telomere length for women than for men with CAD, irrespective of racial/ethnic background. Although these findings are preliminary and should be considered exploratory given the limited number of women in our sample, it is possible that there are sex-specific differences in the mechanisms through which psychosocial stressors, such as discrimination, affect physiological processes. Research suggests that women are more vulnerable to psychosocial stress, having greater activation of stress processes (Bangasser and Valentino, 2012; Hallman et al., 2001) and thereby biological effects that may be detrimental to cardiovascular health, especially women with CAD (Vaccarino and Bremner, 2017). There are also known sex differences in *psychological* responses to stress. For example, research suggests that irrespective of race, women ruminate about stressors more than men (Nolen-Hoeksema, 2012; Shull et al., 2016) and this may be particularly true for stressors that are interpersonal in nature, such as discrimination. Rumination, in turn, has been known to impact physiological pathways that ultimately influence disease (Gerin et al., 2012; Gianferante et al., 2014; Johnson et al., 2012). Additional research on the physiological and psychological pathways linking discrimination to telomere length is needed.

The fact that our results were statistically significant in African American women but were not observed among African American men in stratified models is consistent with prior research. Across indicators, studies have observed more pronounced discrimination and health associations among African American women compared to African American men for a range of outcomes including CRP (Cunningham et al., 2012), kidney function (Beydoun et al., 2017), psychological distress (Banks et al., 2006), hypertension (Roberts et al., 2008), and health-related quality-of-life (Coley et al., 2017). Some studies suggest that this may be due to African American women having different experiences of, reactions to, and/or coping differently with experiences of discrimination compared to African American men (Coley et al., 2017; Cunningham et al., 2012). African American women also experience combined effects of discrimination as they occupy more than one social disadvantage status on the basis of race and on the basis of sex (intersectionalities) (Lewis et al., 2015; Lewis and Van Dyke, 2018). At least one other study has found that multiple types of discrimination combine, or intersect, to affect health among individuals with multiple subordinate social identities (Grollman, 2014). Our results are also similar to findings by Chae et al. (2016; 2014), who did not find a significant main effect between racial discrimination and LTL among African American men.

In our study, there are several limitations worth noting. First, we only measured discrimination at the individual-level. Institutional-level discrimination might also adversely affect the health of women and African Americans by creating disadvantage through systemic policies and practices, services, opportunities, and social norms that restrict equal opportunities in employment and education (socioeconomic), residential segregation and selection, and also in health care access and treatment (Williams, 1999). By limiting our investigation to an individual-level measure of discrimination alone, we may have underestimated the association between discrimination and telomere length, particularly among African American men and women. This is a topic worthy of exploration in future research. Second, although MIPS is a prospective cohort study, telomere length was only

collected during the baseline examination, limiting a longitudinal examination of associations between discrimination and telomere length. Since our data are cross-sectional, we are constrained from assumptions of temporality and causality. Also, we had a relatively small sample size of women across race/sex subgroups which may have limited the power for some analyses and statistical power to detect significant interactions, especially the 3-way interaction between discrimination, race, and sex. However, we were able to show some significant associations between discrimination and leukocyte telomere length in our race and sex stratified analyses despite our small sample of women. We believe this offers support for studying and presenting these results although they should be interpreted with some caution given our small sample of women. Ideally these preliminary findings will provide a foundation for other studies to investigate not only racial differences in the association between discrimination and leukocyte telomere length, but also examine differences by sex. Finally, since 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.

Nonetheless, there are several strengths of our study. To our knowledge, no previous study has investigated the association between experiences of discrimination and LTL in CAD patient samples across sex and racial/ethnic groups. Previous studies on discrimination and LTL have limited their investigations by race/ethnicity and focusing on racial discrimination, leaving an important gap in this sphere of research on whether the effect of discrimination on LTL differs for women and men, and unfair treatment related to characteristics other than race. Importantly, by stratifying our analyses by race/ethnicity and sex, and including an inclusive examination of discrimination, we bring to light associations among women that have been previously obscured. This study furthers the growing literature linking discrimination with adverse physiological associations, particularly among women.

4.1 Conclusion

In a cohort of African American and White CAD patients, experiences of discrimination were associated with shorter LTL among women and not in men. Future studies with larger sample sizes and prospective designs are warranted to determine whether discrimination-linked telomere shortening is a potential mechanism of sex-specific disparities in cardiovascular outcomes. Future studies should explore these associations and broaden the investigation to other race/ethnic groups. These findings, albeit preliminary, raise important questions and bring attention to possible sex-specific differences in stress physiology that require further exploration, particularly given the relatively poor long-term outcomes for young women with CAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health (P01HL101398, P20HL113451-01, P01HL086773-06A1, R56HL126558-01, R01HL109413, R01HL109413-02S1, R01HL125246, R01HL088726, UL1TR000454, KL2TR000455, K24HL077506, K24 MH076955, K23HL127251, T32HL130025A, and K12HD085850).

ROLE OF THE FUNDING SOURCE

The authors of this article are solely responsible for the content of this paper. The funding agency had no role in the design and conduct of this study, in the collection, analysis, interpretation of the data, or in the preparation, review or approval of this manuscript.

Abbreviations and Acronyms:

BDI	Beck Depression Inventory
BMI	Body Mass Index
CAD	Coronary Artery Disease
CRP	C-reactive protein
EDS	Everyday Discrimination Scale
IL-6	Interleukin-6
LTL	Leukocyte Telomere Length
MIPS	Mental Stress Ischemia Mechanisms and Prognosis Study
PSS	Cohen's Perceived Stress Scale

REFERENCES

- Adler N, Pantell MS, O'Donovan A, Blackburn E, Cawthon R, Koster A, Opresko P, Newman A, Harris TB, Epel E, 2013 Educational attainment and late life telomere length in the Health, Aging and Body Composition Study. *Brain Behav Immun* 27:15–21. [PubMed: 22981835]
- Albert MA, Williams DR, 2011 Invited commentary: Discrimination--an emerging target for reducing risk of cardiovascular disease? *Am J Epidemiol* 173:1240–3. [PubMed: 21354989]
- Bangasser DA, Valentino RJ, 2012 Sex differences in molecular and cellular substrates of stress. *Cell Mol Neurobiol* 32:709–23. [PubMed: 22488525]
- Banks KH, Kohn-Wood LP, Spencer M, 2006 An Examination of the African American Experience of Everyday Discrimination and Symptoms of Psychological Distress. *Community Mental Health Journal* 42:555–70. [PubMed: 16897412]
- Beck AT, Steer RA, Brown GK, 1996 BDI-II. Beck Depression Inventory, Second Edition ed. The Psychological Corporation, San Antonio, TX.
- Beydoun MA, Poggi-Burke A, Zonderman AB, Rostant OS, Evans MK, Crews DC, 2017 Perceived Discrimination and Longitudinal Change in Kidney Function Among Urban Adults. *Psychosom Med* 79:824–34. [PubMed: 28445210]
- Blackburn EH, 2000 Telomere states and cell fates. *Nature* 408:53–6. [PubMed: 11081503]
- Blackburn EH, 2001 Switching and signaling at the telomere. *Cell* 106:661–73. [PubMed: 11572773]
- Blackburn EH, Epel ES, Lin J, 2015 Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science* 350:1193–8. [PubMed: 26785477]
- Brown L, Needham B, Ailshire J, 2016 Telomere Length Among Older U.S. Adults. *J Aging Health*: 898264316661390.
- Carroll JE, Diez Roux AV, Fitzpatrick AL, Seeman T, 2013 Low social support is associated with shorter leukocyte telomere length in late life: multi-ethnic study of atherosclerosis. *Psychosom Med* 75:171–7. [PubMed: 23370895]
- Cawthon RM, 2009 Telomere length measurement by a novel monochrome multiplex quantitative PCR method. *Nucleic Acids Res* 37:e21. [PubMed: 19129229]

- Chae DH, Epel ES, Nuru-Jeter AM, Lincoln KD, Taylor RJ, Lin J, Blackburn EH, Thomas SB, 2016 Discrimination, mental health, and leukocyte telomere length among African American men. *Psychoneuroendocrinology* 63:10–6. [PubMed: 26398001]
- Chae DH, Nuru-Jeter AM, Adler NE, Brody GH, Lin J, Blackburn EH, Epel ES, 2014 Discrimination, racial bias, and telomere length in African-American men. *Am J Prev Med* 46:103–11. [PubMed: 24439343]
- Cohen S, Kamarck T, Mermelstein R, 1983 A global measure of perceived stress. *Journal of health and social behavior* 24:385–96. [PubMed: 6668417]
- Coley SL, Mendes de Leon CF, Ward EC, Barnes LL, Skarupski KA, Jacobs EA, 2017 Perceived discrimination and health-related quality-of-life: gender differences among older African Americans. *Qual Life Res*.
- Cunningham TJ, Seeman TE, Kawachi I, Gortmaker SL, Jacobs DR, Kiefe CI, Berkman LF, 2012 Racial/ethnic and gender differences in the association between self-reported experiences of racial/ethnic discrimination and inflammation in the CARDIA cohort of 4 US communities. *Soc Sci Med* 75:922–31. [PubMed: 22682683]
- Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM, 2004 Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A* 101:17312–5. [PubMed: 15574496]
- Fitzpatrick AL, Kronmal RA, Kimura M, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Hardikar S, Aviv A, 2011 Leukocyte telomere length and mortality in the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci* 66:421–9. [PubMed: 21289018]
- Gebreab SY, Riestra P, Gaye A, Khan RJ, Xu R, Davis AR, Quarells RC, Davis SK, Gibbons GH, 2016 Perceived neighborhood problems are associated with shorter telomere length in African American women. *Psychoneuroendocrinology* 69:90–7. [PubMed: 27070760]
- Gerin W, Zawadzki MJ, Brosschot JF, Thayer JF, Christenfeld NJ, Campbell TS, Smyth JM, 2012 Rumination as a mediator of chronic stress effects on hypertension: a causal model. *Int J Hypertens* 2012:453465. [PubMed: 22518285]
- Geronimus AT, Hicken MT, Pearson JA, Seashols SJ, Brown KL, Cruz TD, 2010 Do US Black Women Experience Stress-Related Accelerated Biological Aging?: A Novel Theory and First Population-Based Test of Black-White Differences in Telomere Length. *Hum Nat* 21:19–38. [PubMed: 20436780]
- Gianferante D, Thoma MV, Hanlin L, Chen X, Breines JG, Zoccola PM, Rohleder N, 2014 Post-stress rumination predicts HPA axis responses to repeated acute stress. *Psychoneuroendocrinology* 49:244–52. [PubMed: 25127082]
- Grollman EA, 2014 Multiple disadvantaged statuses and health: the role of multiple forms of discrimination. *Journal of health and social behavior* 55:3–19. [PubMed: 24578393]
- Hallman T, Burell G, Setterlind S, Oden A, Lisspers J, 2001 Psychosocial risk factors for coronary heart disease, their importance compared with other risk factors and gender differences in sensitivity. *J Cardiovasc Risk* 8:39–49. [PubMed: 11234725]
- Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Abdelhadi N, Alkhoder A, Obideen M, Pimple PM, Levantsevych O, Kelli HM, Shah A, Sun YV, Pearce B, Kutner M, Long Q, Ward L, Ko YA, Hosny Mohammed K, Lin J, Zhao J, Bremner JD, Kim J, Waller EK, Raggi P, Sheps D, Quyyumi AA, Vaccarino V, 2017a Telomere Shortening, Regenerative Capacity, and Cardiovascular Outcomes. *Circ Res* 120:1130–38. [PubMed: 27956416]
- Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Shah AJ, Sun Y, Pearce B, Garcia EV, Kutner M, Bremner JD, Esteves F, Raggi P, Sheps DS, Vaccarino V, Quyyumi AA, 2017b The Mental Stress Ischemia Prognosis Study: Objectives, Study Design, and Prevalence of Inducible Ischemia. *Psychosom Med* 79:311–17. [PubMed: 28002382]
- Hanssen LM, Schutte NS, Malouff JM, Epel ES, 2017 The Relationship Between Childhood Psychosocial Stressor Level and Telomere Length: A Meta-Analysis. *Health Psychol Res* 5:6378. [PubMed: 28603779]
- Hunt SC, Chen W, Gardner JP, Kimura M, Srinivasan SR, Eckfeldt JH, Berenson GS, Aviv A, 2008 Leukocyte telomeres are longer in African Americans than in whites: the National Heart, Lung,

and Blood Institute Family Heart Study and the Bogalusa Heart Study. *Aging cell* 7:451–8. [PubMed: 18462274]

Johnson JA, Lavoie KL, Bacon SL, Carlson LE, Campbell TS, 2012 The effect of trait rumination on adaptation to repeated stress. *Psychosom Med* 74:258–62. [PubMed: 22408131]

Lewis TT, Cogburn CD, Williams DR, 2015 Self-reported experiences of discrimination and health: scientific advances, ongoing controversies, and emerging issues. *Annu Rev Clin Psychol* 11:407–40. [PubMed: 25581238]

Lewis TT, Van Dyke ME, 2018 Discrimination and the Health of African Americans: The Potential Importance of Intersectionalities. *Current Directions in Psychological Science*: 0963721418770442.

Lin J, Epel E, Cheon J, Kroenke C, Sinclair E, Bigos M, Wolkowitz O, Mellon S, Blackburn E, 2010 Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. *J Immunol Methods* 352:71–80. [PubMed: 19837074]

Lin PY, Huang YC, Hung CF, 2016 Shortened telomere length in patients with depression: A meta-analytic study. *J Psychiatr Res* 76:84–93. [PubMed: 26919486]

Liu SY, Kawachi I, 2017 Discrimination and Telomere Length Among Older Adults in the United States. *Public Health Rep*:33354916689613.

Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, Khazeni N, 2016 Perceived stress and telomere length: A systematic review, meta-analysis, and methodologic considerations for advancing the field. *Brain Behav Immun* 54:158–69. [PubMed: 26853993]

Needham BL, Adler N, Gregorich S, Rehkopf D, Lin J, Blackburn EH, Epel ES, 2013 Socioeconomic status, health behavior, and leukocyte telomere length in the National Health and Nutrition Examination Survey, 1999–2002. *Soc Sci Med* 85:1–8. [PubMed: 23540359]

Nolen-Hoeksema S, 2012 Emotion regulation and psychopathology: the role of gender. *Annu Rev Clin Psychol* 8:161–87. [PubMed: 22035243]

O'Donovan A, Tomiyama AJ, Lin J, Puterman E, Adler NE, Kemeny M, Wolkowitz OM, Blackburn EH, Epel ES, 2012 Stress appraisals and cellular aging: a key role for anticipatory threat in the relationship between psychological stress and telomere length. *Brain Behav Immun* 26:573–9. [PubMed: 22293459]

Pepper GV, Bateson M, Nettle D, 2018 Telomeres as integrative markers of exposure to stress and adversity: a systematic review and meta-analysis. *R Soc Open Sci* 5:180744. [PubMed: 30225068]

Roberts CB, Vines AI, Kaufman JS, James SA, 2008 Cross-sectional association between perceived discrimination and hypertension in African-American men and women: the Pitt County Study. *Am J Epidemiol* 167:624–32. [PubMed: 18083714]

Sanders JL, Newman AB, 2013 Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? *Epidemiol Rev* 35:112–31. [PubMed: 23302541]

Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, Dube R, Taleghani CK, Burke JE, Williams S, Eisenberg JM, Escarce JJ, 1999 The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med* 340:618–26. [PubMed: 10029647]

Schutte NS, Malouff JM, 2016 The Relationship Between Perceived Stress and Telomere Length: A Meta-analysis. *Stress Health* 32:313–19. [PubMed: 25393133]

Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, Douglas PS, Krone RJ, McKay CR, Block PC, Hewitt K, Weintraub WS, Peterson ED, American College of Cardiology-National Cardiovascular Data Registry, I., 2008 Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation* 117:1787–801. [PubMed: 18378615]

Shull A, Mayer SE, McGinnis E, Geiss E, Vargas I, Lopez-Duran NL, 2016 Trait and state rumination interact to prolong cortisol activation to psychosocial stress in females. *Psychoneuroendocrinology* 74:324–32. [PubMed: 27716572]

Stroud LR, Salovey P, Epel ES, 2002 Sex differences in stress responses: social rejection versus achievement stress. *Biol Psychiatry* 52:318–27. [PubMed: 12208639]

- Theall KP, Brett ZH, Shirtcliff EA, Dunn EC, Drury SS, 2013 Neighborhood disorder and telomeres: connecting children's exposure to community level stress and cellular response. *Soc Sci Med* 85:50–8. [PubMed: 23540366]
- Vaccarino V, Bremner JD, 2017 Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. *Neurosci Biobehav Rev* 74:297–309. [PubMed: 27496672]
- Williams DR, 1999 Race, socioeconomic status, and health. The added effects of racism and discrimination. *Ann N Y Acad Sci* 896:173–88. [PubMed: 10681897]
- Williams DR, Yan Y, Jackson JS, Anderson NB, 1997 Racial Differences in Physical and Mental Health: Socio-economic Status, Stress and Discrimination. *J Health Psychol* 2:335–51. [PubMed: 22013026]

HIGHLIGHTS

- Discrimination is an understudied source of stress-related cellular aging.
- Investigations across racial/ethnic and sex groups is currently lacking.
- Discrimination was associated with shorter LTL among women and not in men.
- Women may be more vulnerable to psychosocial stressors such as discrimination.
- Sex-specific differences in stress physiology deserves further exploration.

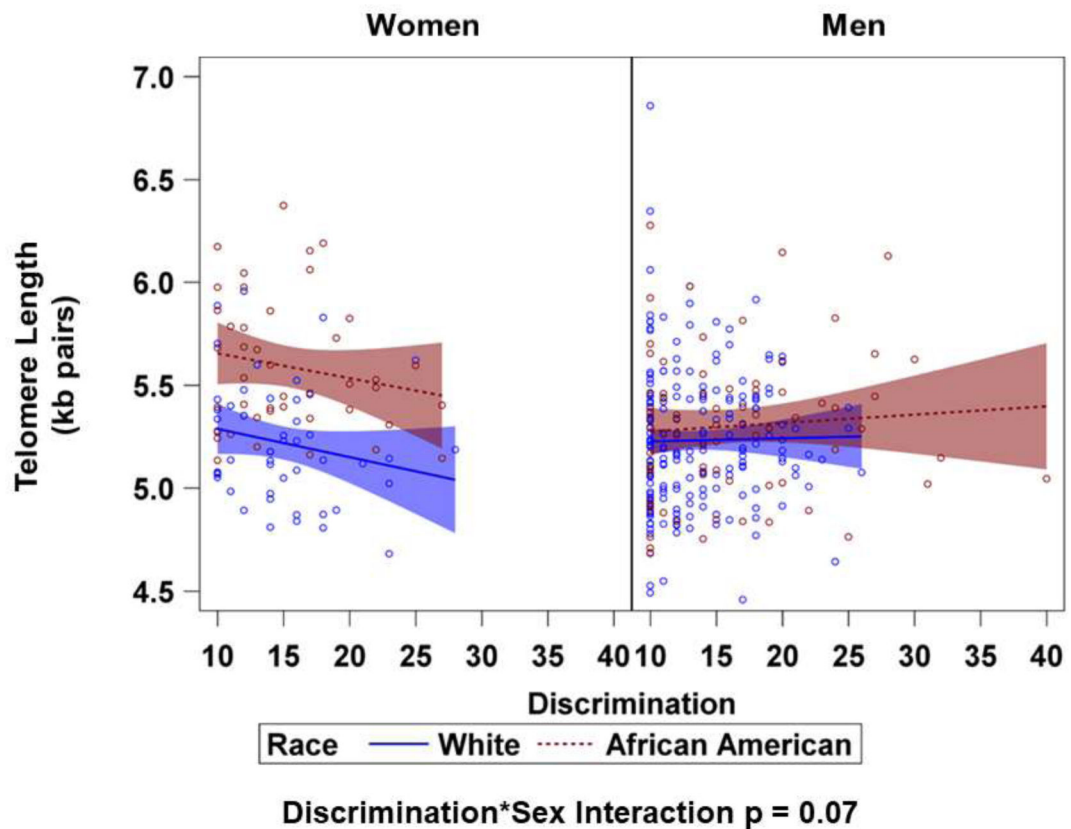


Figure 1. Regression Slopes and 95% Confidence Intervals for Discrimination across Sex and Race on Telomere Length (kilobase pairs).

Linear regression models were used to test for differences in slopes across sex and race for discrimination on telomere length by including interaction terms of discrimination-by-sex, discrimination-by-race, race-by-sex, and discrimination-by-sex-by-race. The interaction term of discrimination-by-sex was $p = 0.07$.

Table 1. Descriptive Characteristics of Participants Stratified by Race/Ethnicity and Sex (N=369) in the Mental Stress Ischemia Prognosis Study (MIPS).

	Women			Men		
	White	African American	p-value	White	African American	p-value
Total, n (%)	50 (13.5)	43 (11.7)		202 (54.7)	74 (20.1)	
Telomere Length, kilobase pairs, mean (SD)	5.2 (0.05)	5.6 (0.1)	<.0001	5.2 (0.03)	5.3 (0.04) [‡]	0.13
Discrimination Score, mean (SD)	14.9 (4.3)	15.4 (4.9)	0.55	13.5 (3.8)*	16.2 (6.6)	0.001
Age, mean (SD)	65.3 (8.8)	58.9 (8.0)	0.0003	63.5 (9.2)	58.0 (9.7)	0.0002
Income < \$20,000, n (%)	10 (20.0)	18 (41.9)	0.02	16 (7.9)*	21 (28.4)	<.0001
Education, High School or Less, n (%)	16 (32.0)	13 (30.2)	0.85	39 (19.3)	29 (39.2)	0.001
History of Smoking, n (%)	22 (44.0)	18 (41.9)	0.84	82 (40.6)*	25 (33.8)*	0.30
Married/living with partner, n (%)	26 (52.0)	13 (30.2)	0.03	157 (77.7)	41 (55.4)	0.0003
Diabetes, n (%)	12 (24.0)	19 (44.2)	0.04	56 (27.7)	30 (40.5)	0.04
Hypertension, n (%)	36 (72.0)	40 (93.0)	0.01	145 (71.8)	70 (94.6)	<.0001
Previous Myocardial Ischemia, n (%)	18 (36.0)	21 (48.8)	0.21	67 (33.2)	34 (46.0)	0.05
BMI, kg/m ² , mean (SD)	29.3 (6.7)	32.5 (7.3)	0.03	29.5 (4.8)	30.4 (4.9)	0.21
BDI total score, mean (SD)	9.4 (6.9)	10.0 (9.4)	0.76	6.7 (6.9)*	9.9 (10.1)	0.01
PSS total score, mean (SD)	13.8 (8.3)	15.1 (7.4)	0.43	10.8 (6.7)*	13.7 (7.7)	0.003

Abbreviations: BDI: Beck depression inventory; BMI: Body mass index; MIPS: Mental stress ischemia mechanisms and prognosis study; PSS: Cohen's perceived stress scale; SD: Standard deviation.

* p < 0.05 between women and men within race

[‡] p < 0.0001 between women and men within race

Bivariate Correlations of Leukocyte Telomere Length with Discrimination, Demographic, Clinical, and Psychosocial Covariates, Mental Stress Ischemia Prognosis Study (MIPS).

Table 2:

	Overall	White Women	African American Women	White Men	African American Men
Discrimination	0.03	-0.21	-0.18	0.02	0.08
Age	-0.35	-0.11	-0.59*	-0.30 [†]	-0.27*
Race/Ethnicity	0.24 [†]	--	--	--	--
Sex	-0.17*	--	--	--	--
Marital Status	-0.08	0.05	-0.03	0.06	-0.13
Income	-0.17	-0.24	-0.16	0.02	-0.19
Education	0.06	-0.08	0.03	0.11	0.19
Smoking History	-0.08	-0.10	0.20	-0.14*	-0.10
Diabetes	0.01	0.03	-0.20	-0.05	-0.01
Hypertension	0.002	-0.02	-0.43*	-0.08	0.09
Previous MI	-0.02	-0.13	0.10	-0.08	-0.04
BMI, kg/m ²	0.06	-0.11	0.06	-0.05	-0.01
BDI	0.09	0.21	0.11	-0.02	0.09
PSS	0.08	-0.16	-0.05	0.04	0.18

Abbreviations: BDI: Beck depression inventory; BMI: Body mass index; MIPS: Mental stress ischemia mechanisms and prognosis study; PSS: Cohen's perceived stress scale; SD: Standard deviation.

Pearson correlations for continuous covariates and Spearman correlations for categorical covariates. Race/ethnicity coded as 0=White, 1 = African American; Sex coded as 0=Female, 1=Male; Marital status coded as 0=Single/Separated/Divorced/Widowed, 1=Married/Living with Partner; Education coded as 0= High School or less, 1 = Greater than High School; Smoking History coded as 0=Never, 1=Current/Former; Diabetes, Hypertension, and Previous MI coded as 0=No, 1=Yes. Discrimination, age, BMI, Depression, and Stress are continuous variables.

* $p < 0.05$

[†] $p < 0.0001$

Table 3.

Adjusted Estimates for Experiences of Everyday Discrimination (per 10-unit increase) on Leukocyte Telomere Length (N=369) in the Mental Stress Ischemia Prognosis Study (MIPS) by Race/Ethnicity and Sex.

	White Women β (95% CI)	African American Women β (95% CI)	White Men β (95% CI)	African American Men β (95% CI)
Model 1				
Discrimination	-0.16 (-0.35, 0.03)	-0.17 (-0.33, -0.01)*	-0.08 (-0.21, 0.04)	-0.02 (-0.14, 0.11)
Age	-0.01 (-0.01, 0.004)	-0.02 (-0.03, -0.01) [†]	-0.01 (-0.02, -0.01) [†]	-0.01 (-0.02, -0.0004)*
Model 2				
Discrimination	-0.19 (-0.37, -0.01)*	-0.19 (-0.35, -0.04)*	-0.07 (-0.19, 0.06)	-0.04 (-0.17, 0.08)
Age	-0.003 (-0.01, 0.01)	-0.02 (-0.03, -0.01) [†]	-0.01 (-0.02, -0.01) [†]	-0.01 (-0.02, -0.002)*
Income < \$20,000	0.27 (0.05, 0.50)*	0.13 (-0.04, 0.30)	-0.06 (-0.24, 0.12)	0.16 (-0.04, 0.36)
Education HS or Less	-0.02 (-0.20, 0.15)	0.04 (-0.13, 0.20)	-0.11 (-0.22, -0.002)*	-0.21 (-0.36, -0.06)*
Single/Sep/Div/Wid	-0.09 (-0.25, 0.07)	-0.05 (-0.23, 0.13)	-0.06 (-0.17, 0.06)	-0.05 (-0.22, 0.11)
Model 3				
Discrimination	-0.19 (-0.39, 0.01)	-0.20 (-0.34, -0.06)*	-0.08 (-0.20, 0.04)	-0.08 (-0.21, 0.05)
Age	-0.004 (-0.01, 0.006)	-0.01 (-0.02, -0.01)*	-0.01 (-0.02, -0.01) [†]	-0.02 (-0.03, -0.004)*
Income < \$20,000	0.28 (0.02, 0.53)*	0.08 (-0.08, 0.24)	-0.05 (-0.22, 0.13)	0.15 (-0.05, 0.36)
Education HS or Less	-0.02 (-0.20, 0.17)	0.08 (-0.08, 0.23)	-0.09 (-0.20, 0.01)	-0.22 (-0.38, -0.06)*
Single/Sep/Div/Wid	-0.09 (-0.28, 0.09)	-0.08 (-0.25, 0.10)	-0.05 (-0.16, 0.06)	-0.05 (-0.22, 0.11)
Smoking History	-0.03 (-0.19, 0.13)	0.11 (-0.04, 0.25)	-0.10 (-0.19, -0.01)*	-0.03 (-0.21, 0.14)
Diabetes	-0.03 (-0.22, 0.16)	-0.10 (-0.25, 0.05)	-0.01 (-0.11, 0.09)	0.03 (-0.14, 0.19)
Hypertension	-0.05 (-0.24, 0.14)	-0.49 (-0.82, -0.16)*	-0.02 (-0.12, 0.07)	0.05 (-0.29, 0.40)
Previous MI	-0.04 (-0.23, 0.15)	0.07 (-0.07, 0.21)	-0.09 (-0.18, 0.003)	-0.12 (-0.29, 0.05)
BMI	0.001 (-0.01, 0.02)	0.01 (-0.004, 0.02)	0.0005 (-0.01, 0.01)	-0.008 (-0.02, 0.01)
Model 4				
Discrimination	-0.21 (-0.39, -0.02)*	-0.20 (-0.35, -0.04)*	-0.08 (-0.21, 0.05)	-0.11 (-0.25, 0.04)
Age	-0.002 (-0.01, 0.01)	-0.01 (-0.02, -0.01)*	-0.01 (-0.02, -0.01) [†]	-0.01 (-0.03, -0.003)*
Income < \$20,000	0.27 (0.04, 0.50)*	0.08 (-0.08, 0.24)	-0.05 (-0.22, 0.13)	0.15 (-0.05, 0.36)
Education HS or Less	-0.06 (-0.23, 0.12)	0.08 (-0.08, 0.24)	-0.09 (-0.20, 0.01)	-0.23 (-0.39, -0.06)*
Single/Sep/Div/Wid	-0.09 (-0.26, 0.08)	-0.08 (-0.25, 0.10)	-0.05 (-0.16, 0.06)	-0.03 (-0.20, 0.14)
Smoking History	0.004 (-0.14, 0.15)	0.11 (-0.04, 0.25)	-0.10 (-0.19, -0.01)	-0.02 (-0.19, 0.15)
Diabetes	0.02 (-0.15, 0.19)	-0.10 (-0.26, 0.06)	-0.01 (-0.11, 0.09)	0.02 (-0.14, 0.19)
Hypertension	-0.06 (-0.23, 0.10)	-0.49 (-0.83, -0.15)*	-0.02 (-0.12, 0.07)	0.03 (-0.32, 0.38)
Previous MI	-0.01 (-0.18, 0.16)	0.07 (-0.07, 0.21)	-0.09 (-0.18, 0.003)	-0.11 (-0.28, 0.05)
BMI	0.003 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.001 (-0.01, 0.01)	-0.01 (-0.03, 0.01)
BDI	0.02 (0.01, 0.03)*	-0.0004 (-0.01, 0.01)	-0.001 (-0.01, 0.01)	-0.003 (-0.01, 0.01)
PSS	-0.01 (-0.02, -0.003)*	0.0003 (-0.01, 0.01)	0.001 (-0.01, 0.01)	0.01 (-0.01, 0.02)

Abbreviations: BDI: Beck depression inventory; BMI: Body mass index; CI: Confidence interval; MIPS: Mental stress ischemia mechanisms and prognosis study; PSS: Cohen's perceived stress scale.

*
 $p < 0.05$

†
 $p < 0.0001$

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript