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Cortisol Regulation, Perceived Discrimination, and Ethnic Differences in Pain Responses among Persons with Knee Osteoarthritis

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CORTISOL REGULATION, PERCEIVED DISCRIMINATION, AND ETHNIC DIFFERENCES IN PAIN RESPONSES AMONG PERSONS WITH KNEE OSTEOARTHRITIS

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ABSTRACT

Plasma cortisol concentrations obtained directly after the Trier Social Stress test are negatively associated with subsequent pain tolerances during the cold pressor task (CPT) among healthy non-Hispanic whites (NHWs), but not healthy African Americans (AAs). It is possible frequent exposure to perceived discrimination, a marker of chronic stress, explains this lack of association between cortisol regulation and pain tolerances among AAs. Our aim was to determine if 1) ethnic differences in pain sensitivity during the CPT could be partially explained by differences in cortisol regulation among persons with knee osteoarthritis (OA), 2) perceived discrimination was related to cortisol dysregulation, which was in turn related to greater pain sensitivity among African Americans with knee OA, and 3) the relationship between perceived discrimination and pain sensitivity depends on socioeconomic status (SES). Participants were 91 (47 AA; 44 NHW) community-dwelling adults between the ages of 45 to 85 with symptomatic knee OA. Cortisol was measured at three time points: 1) baseline, 2) immediately after the CPT, and 3) 20 min after the CPT. Although AAs exhibited greater pain sensitivity during the CPT than NHWs, cortisol did not mediate this relationship. However, baseline cortisol was positively associated with pain tolerances (a non-verbal pain behavior) in NHWs, while post-CPT cortisol was negatively associated with pain ratings (a verbal pain behavior) in AAs. Opposite of predictions, perceived discrimination was related to

lower pain ratings during the CPT, and cortisol regulation did not help explain this relationship. Finally, the relationship between perceived discrimination and pain ratings was only found among AAs of relatively SES. Post-hoc analyses showed that compared to AAs with relatively low incomes, AAs with relatively high incomes were more likely to report an active coping style toward discrimination. These results suggest that verbal pain reports are important for understanding the relationship between cortisol and pain among AAs. Further, perceived discrimination may serve a protective role for AAs with knee OA, particularly those earning relatively high incomes. Future work is needed to determine if AAs reporting an active coping style toward discrimination also report an active coping style during exposure to noxious stimulation.

DEDICATION

This dissertation is dedicated to my family. My mother, father, and brother have all helped shape the person I am in their own unique way, and I will be forever grateful for their loving support of my endeavors.

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by

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SPECIFIC AIMS AND HYPOTHESES

Healthy African American (AA) adults, compared to non-Hispanic whites (NHWs), consistently exhibit greater pain sensitivity to experimental noxious stimuli (1). Among persons with arthritis, AAs report greater arthritis-related pain and disability than their NHW counterparts (2, 3). However, little is known regarding the biopsychosocial variables that may contribute to enhanced experimental and clinical pain responses among AAs. It has been hypothesized that prolonged exposure to chronic stressors among AAs, such as perceived racial discrimination, may alter endogenous stress regulatory systems that eventually contribute to enhanced pain sensitivity (4, 5). Indeed, perceived racial discrimination is associated with chronic stress among AAs (6). In addition, among AAs, perceived racial discrimination is associated with greater body pain (7) and back pain (8), as well as greater heat pain sensitivity in individuals with symptomatic knee osteoarthritis (OA) (4). The present study focused exclusively on persons with knee OA because knee OA is a highly prevalent condition with high direct and indirect costs (3).

The relationship between biomarkers of stress exposure, such as cortisol, and ethnic differences in pain sensitivity has never been specifically examined in healthy persons or individuals with knee OA. Mechlin and colleagues (5), however, showed that healthy AAs, relative to their NHW counterparts, exhibit lower basal cortisol levels, as well as lower cortisol levels after exposure to the Trier Social Stress Test (TSST). Also, post-stressor levels of cortisol among NHWs, but not AAs, were correlated with greater

pain tolerance levels during a subsequent cold pressor task (CPT). Given that increases in cortisol after noxious stimulation is associated with pain reduction in healthy adults (9), we determined whether a) ethnic differences in responses to painful stimulation could be explained in part by differences in cortisol regulation in persons with knee OA, and b) perceived racial discrimination was associated with alterations in cortisol regulation in response to noxious laboratory stimulation, particularly among AAs with knee OA. Because previous studies of cortisol and pain have used the CPT as a pain stimulus (5), we similarly used the CPT in order to compare our results with knee OA patients to those obtained with healthy controls.

The present study also determined if the relationship between perceived racial discrimination and pain sensitivity varies as a function of socioeconomic status (SES). SES is an important variable to consider in the context of perceived racial discrimination because AAs of lower SES are more likely to experience racial discrimination (10) and have fewer resources to cope with perceived racial discrimination compared to AAs of higher SES (11). Therefore, the relationship between perceived racial discrimination and pain sensitivity may be more pronounced among AAs of lower SES compared to those of higher SES.

The overall aims of the proposed investigation were to replicate previous findings showing AAs demonstrate greater experimental pain sensitivity compared to NHWs, and to determine whether ethnic differences in responses to noxious stimulation could be partially explained by differences in cortisol regulation. Further, we determined whether cortisol regulation was negatively associated with perceived racial discrimination, and

whether SES moderated the relationship between perceived racial discrimination and pain sensitivity.

Aim 1: Assess ethnic group differences in response to noxious stimulation.

Hypothesis 1: Compared to NHWs, AAs will produce greater ratings of pain unpleasantness, and exhibit lower pain tolerance levels during the CPT.

Aim 2: Determine if the relationship between ethnic group and pain sensitivity is mediated by basal cortisol levels and/or cortisol release following the CPT.

Hypothesis 2. Basal cortisol levels and/or cortisol release following the CPT will partially mediate ethnic differences in pain unpleasantness ratings and pain tolerance levels during the CPT.

Aim 3: Determine if perceived racial discrimination is related to lower basal cortisol levels and/or lower cortisol release following the CPT separately for AAs and NHWs, which are in turn related to greater pain sensitivity during the CPT.

Hypothesis 3: Perceived racial discrimination will be associated with greater pain unpleasantness ratings and lower pain tolerance levels during the CPT in AA participants, but not NHW participants.

Hypothesis 4: Among AA participants, basal cortisol levels and/or cortisol release following the CPT will partially mediate the relationship between perceived racial discrimination and pain unpleasantness ratings as well as pain tolerance levels. These relationships will not be found among NHW participants.

Aim 4: Determine if SES moderates the relationship between perceived racial discrimination and pain sensitivity during the CPT among AA participants of relatively low and high SES.

Hypothesis 5: The positive relationship between perceived racial discrimination and pain sensitivity during the CPT will be more pronounced in AA participants of relatively low SES compared to those of relatively high SES.

BACKGROUND AND SIGNIFICANCE

Ethnic Differences in Pain

Past research has consistently reported significant differences between AAs and NHWs in the experience of pain. Among healthy adults, AAs demonstrate greater pain sensitivity during exposure to a number of noxious stimuli compared to their NHW counterparts (1). Among persons with knee OA, AAs report greater clinical pain severity, physical disability, and psychological disability than NHWs (2, 3). A growing number of researchers are using a biopsychosocial model consistent with the revised gate control theory to explain ethnic differences in the experience of pain (12). This model posits that the experience of pain results from a complex interaction of biological and psychosocial factors (13). The majority of the literature has focused on the contribution of psychosocial variables to the relationship between ethnicity and pain, while less emphasis has been devoted to biological factors.

Recently, Mechlin and colleagues (5) showed that in response to the TSST, AAs exhibited lower pre- and post-stressor cortisol concentrations compared to NHWs. After stressor exposure, all participants underwent laboratory pain testing, including the

assessment of pain threshold and tolerance levels during thermal heat application, the submaximal effort tourniquet procedure, and the CPT. Post-TSST concentrations of cortisol were correlated with higher pain tolerances during the submaximal effort tourniquet test and CPT in NHWs, while no significant relationships were detected in AAs. These authors hypothesized that greater exposure to chronic stressors among AAs, such as perceived racial discrimination, may alter endogenous stress systems, which may in turn contribute to the enhanced pain sensitivity commonly observed in AAs. To the best of our knowledge, no one has specifically examined this hypothesis.

Below, I first discuss perceived racial discrimination, a psychosocial variable that is associated with enhanced pain sensitivity and exposure to chronic stressors among AAs. I then discuss the HPA axis and cortisol, a biological factor important in the study of stressor exposure and pain, followed by a literature review on differences in cortisol regulation between AAs and NHWs. Finally, I discuss the relationship between perceived racial discrimination and SES and why the relationship between perceived racial discrimination and pain sensitivity may differ as a function of SES.

Perceived Racial Discrimination and Pain

AAs differ from NHWs on a number of psychosocial variables that are related to the experience of pain, including pain coping (14), hypervigilance (15), and depression (16). A psychosocial variable that has received less attention in studies of ethnic differences in pain is perceived discrimination. This variable refers to the differential treatment of group members at the individual or institutional level (6). Perceived racial discrimination may be especially important in the relationship between ethnicity and pain

sensitivity because it occurs more frequently in AAs compared to NHWs (17, 18) and is associated with exposure to chronic stressors (6, 11).

Three studies have examined the relationship between perceived racial discrimination and pain in AAs. Edwards (8) showed that perceived discrimination was a strong predictor of back pain among AAs, but not their NHW counterparts. In a second study, perceived racial discrimination was associated with greater bodily pain among older AA U.S. veterans (7). Recently in our laboratory, Goodin and colleagues (4) found that perceived racial discrimination was a significant predictor of lower heat pain tolerance in AAs with symptomatic knee OA, but not in their NHW counterparts. It was hypothesized that the stressors associated with perceived racial discrimination among AAs may have led to physiological alterations in endogenous stress response systems (e.g., HPA axis) and subsequent reduced pain tolerance. However, no one has assessed the relationship between perceived racial discrimination, physiological markers of stress, and pain sensitivity.

Perceived Racial Discrimination as a Stressor

It has been shown that perceived racial discrimination elicits stress responses among AA individuals in the laboratory. For example, among AA women, discussing controversial, racist topics elicited greater cardiovascular responses (i.e., augmented blood pressure and heart rate) and emotional distress than discussing nonracist, controversial topics (19). Among AA men, watching racist film clips evoked greater increases in diastolic blood pressure compared to watching a neutral film (20). Several observational studies have shown that perceived racial discrimination among healthy

AAs is positively associated with anxiety (21), anger (22), and hostility (23), as well as higher ambulatory blood pressure (24). Furthermore, reporting racial discrimination at work has been associated with greater blood pressure and increased likelihood of hypertension in AAs (25). These studies demonstrate that racial discrimination, whether manipulated in the laboratory or self-reported, is typically perceived as stressful for AAs.

The HPA Axis and Allostatic Load

Exposure to prolonged stressors is believed to diminish endogenous stress regulatory systems that subsequently predispose individuals to a number of physical and mental health conditions (26). A framework that is helpful for conceptualizing the negative effects of exposure to prolonged stressors is the construct of allostatic load. This construct suggests that the body is in a constant, active process of responding to environmental stressors in order to maintain homeostasis (i.e., "allostasis") (27). To accomplish this, a number of biological systems are constantly being adjusted to promote adaptation and survival. Although the behavioral and physiological responses to a perceived stressor are adaptive when acutely activated and deactivated, prolonged activation of these systems leads to "wear-and-tear" of the body (i.e., allostatic load). The HPA axis is an allostatic system to which investigators have devoted much attention. This hormonal response system can be activated by a broad range of physiological and psychological stressors and has a direct influence on the secretion and release of cortisol. Cortisol plays a powerful role in the stress response because of its widespread influence on a number of systems. This includes the (a) central nervous system, where it influences learning, memory, and emotion through limbic structures; (b) metabolic system, where it

regulates glucose storage, regulation and utilization; and (c) immune system where it initiates and regulates a number of inflammatory responses (28). A sustained level of elevated cortisol elicited by chronic stressors is thought to break down muscle, bone, and neural tissue that predispose the dysregulation of biological systems (28, 29).

Chronic Stressors and Chronic Pain

Researchers have posited that exposure to perceived chronic stressors precedes the development of painful conditions, such as fibromyalgia, chronic low back pain, and chronic pelvic pain (30-32). This hypothesis is supported by strong evidence showing reports of exposure to work-related stressors prospectively predict the development of chronic pain diagnoses, such as fibromyalgia, generalized widespread pain, and knee pain (33-35). For example, workplace bullying, high workload, and low decision latitude predict the development of fibromyalgia at 2-year follow-up (34). Interestingly, in this study, the strongest predictor of fibromyalgia onset was workplace bullying, a form of "subordinate stress" which is associated with hypocortisolism in animal models (36) and shares features with perceived racial discrimination (i.e., social isolation/exclusion). In addition, Jones et al. (33) reported that work-related psychological distress prospectively predicted the development of new-onset knee pain over a 2-year follow-up period.

Exposure to stressors also exacerbates the pain associated with chronic pain conditions. Among patients with fibromyalgia, those who report a traumatic event preceded the onset of fibromyalgia symptoms are more likely to report greater pain, disability, life interference and affective distress compared to patients reporting an idiopathic onset (37). Among patients with rheumatoid arthritis, symptoms of pain,

stiffness, and functional impairments are significantly associated with reported levels of psychological distress (38). Lastly, Harris and colleagues (39) showed that perceived exposure to stressors prospectively predicted the onset of arthritis (defined as being treated for "arthritis/rheumatism") three years later. In this study, higher levels of stressor exposure were associated with greater probability of developing arthritis.

Hypocortisolism and Chronic Pain

It is believed that tonic activation of feedback pathways produced by sustained levels of cortisol leads to down regulation of cortisol activity, referred to as hypocortisolism. Hypocortisolism has been demonstrated in a number of chronic pain conditions, including fibromyalgia, rheumatoid arthritis, chronic headache, and chronic pelvic pain (40-43).

The majority of literature on the relationship between hypocortisolism and chronic pain centers on persons with fibromyalgia because this disorder is highly associated with perceived exposure to chronic stressors (44-46). Additionally, HPA axis abnormalities are highly reliable across fibromyalgia studies (47). Compared to healthy controls, patients with fibromyalgia exhibit lower 24-hour urinary free cortisol, but normal peak and plasma cortisol levels (40). Patients with fibromyalgia also demonstrate blunted cortisol reactivity after exposure to the TSST (48) and greater suppression of cortisol following the low-dose dexamethasone suppression test compared to controls (49).

Cortisol and Responses to Controlled Noxious Stimuli

To date, no one has assessed the relationship between pain sensitivity during exposure to controlled, noxious stimuli in the laboratory and cortisol responses in patients with fibromyalgia or in individuals with other painful conditions such as knee OA. Indeed, knee OA may be an ideal disorder for studies of stressor exposure and pain because, unlike fibromyalgia, the source of knee pain is relatively well understood, although additional endogenous and exogenous factors may alter the relationship between pain and measurable disease activity.

It is important to note that assessing experimentally induced pain in individuals living with painful conditions such as knee OA has relevance to the experience of clinical pain. Among persons with knee OA, experimental heat pain and clinical knee pain both activate similar brain regions involved in the perception of pain, including areas involved in the affective-emotional aspects of pain (e.g., cingulate cortex, amygdala) and the sensory-discriminative aspects of pain (e.g., somatosensory cortex) (50). While clinical knee pain was associated with higher levels of increased activity in a number of areas relative to those evoked by experimental heat pain, this investigation provides rationale that studying the cortical responses of persons with knee OA to noxious stimulation may be a valid analogue of cortical responses produced during clinical knee pain (50). Therefore, we believe the procedures used in the present study represent a valid model for examining the relationships among ethnicity, pain responses and cortisol among persons with knee OA.

Among healthy persons, basal cortisol concentrations are related to the pain experienced during exposure to noxious stimuli in the laboratory. For example, during the

CPT, in which participants submerge their hand in very cold water (i.e., 1˚ – 4˚ centigrade [C]), lower pre-task cortisol concentrations predicted greater pain ratings in men, suggesting pain perception is influenced by basal cortisol levels (51). These same findings were not reproduced in female participants, although it should be noted that all female participants in this study were pre-menopausal, and the fluctuation of sex-specific hormones may have influenced pain ratings (51). In contrast, all women in the present investigation were post-menopausal.

The CPT also elicits cortisol reactivity. Dixon and colleagues have shown that, compared to baseline levels, cortisol concentrations were significantly elevated when assessed 15-mins post-CPT (9). Additionally, lower post-CPT cortisol levels were significantly associated with lower pain tolerance levels (9).

Ethnic Differences in Cortisol

Although the interpretation of cortisol patterns is a subject of debate, there is a general consensus that abnormally high or an absence of a cortisol awakening response (CAR), and a flatter diurnal cortisol slope are associated with negative health outcomes (52). While ethnic differences in cortisol regulation have been demonstrated, the results have been inconsistent. Bennett, Merritt, and Wolin (53) showed no differences in the CAR between healthy AA and NHW adults. On the other hand, investigators have shown that healthy AAs, compared to NHWs, have a flatter diurnal slope (54) and higher evening cortisol levels (55). To our knowledge, only one study has assessed ethnic differences in cortisol levels obtained after exposure to a laboratory stressor. As previously discussed, Mechlin et al. (5) showed that, compared to NHWs, healthy AAs

demonstrate lower basal cortisol levels and lower cortisol levels following exposure to the TSST.

We noted earlier that we are unaware of any studies that have examined changes in cortisol and ethnic differences in pain responses among healthy persons or individuals with knee OA. Figure 1 shows pilot data produced by 28 adults with symptomatic knee OA (16 AA and 12 NHW) who completed the same CPT used in this investigation. The CPT involved hand immersion in cold water for a maximum of 60 seconds at temperatures of 16, 12, and 8˚ C with 5-minutes separating each trial. Blood was drawn at 4 time points: 1) immediately prior to the CPT; 2) immediately after the CPT; 3) approximately 20 minutes post-CPT; and 4) approximately 40 minutes post-CPT. As can be seen in Figure 1, both ethnic groups show decreases in cortisol immediately following the CPT with NHW participants producing a sharper reduction relative to those of AAs. At 20 minutes post-CPT, NHW participants produce large increases in cortisol whereas AA participants show further reductions in cortisol. At 40 minutes post-CPT, AA participants show further reductions in cortisol while NHWs show maintenance of their cortisol levels. Although no significant ethnic differences were found in univariate or multivariate analyses, this is likely due to the small sample size, as there are clear group differences in cortisol regulation across time.

One investigation has specifically examined the relationship between perceived discrimination and cortisol. This study found that perceived discrimination was associated with a steeper diurnal slope among AAs, and a flatter diurnal slope among NHWs (54). However, the relationship between perceived discrimination and cortisol responses to noxious stimulation among AA and NHW has not been explored.

Perceived Racial Discrimination and SES

SES is an important variable to consider when assessing outcomes associated with perceived racial discrimination. First, individuals of lower SES are more likely to experience racist and nonracist discrimination compared to individuals of higher SES (10). Second, AAs of low SES may have fewer resources and healthy coping mechanisms, which may in turn exacerbate the psychological and physiological distress associated with perceived racial discrimination (11). Therefore, any relationship between perceived racial discrimination and pain sensitivity may be more pronounced among persons of low SES.

Conversely, other reports suggest the opposite relationship between perceived racial discrimination and SES. For example, among rural, older AA adults with type 2 diabetes, reporting an annual household income of $15,000 or greater was associated with greater lifetime exposure to racism compared to those reporting lower household income (56). However, this study also showed that low income was associated with passive coping responses to racism (e.g., accepting, ignoring, avoiding, etc.). This may be especially relevant in regard to pain, because passive coping is related to greater pain and distress among persons living with conditions characterized my recurrent or persistent pain (57).

Summary

It has been consistently shown that healthy AA persons, compared to their NHW counterparts, demonstrate greater pain sensitivity in the laboratory. Additionally, AAs report greater clinical pain intensity and disability associated with knee OA than do

NHWs. Although the relationship between ethnicity and pain sensitivity is likely multifactorial, perceived racial discrimination may be an especially important psychosocial variable to study because it occurs more frequently in AA persons compared to NHWs, and is associated with exposure to perceived chronic stressors. Indeed, investigators have posited that perceived racial discrimination leads to prolonged activation of endogenous stress regulatory systems that may underlie the number of physical and mental health disparities observed between AAs and NHWs. It is also important to consider the role of SES when assessing the negative consequences of perceived racial discrimination because the amount of exposure to perceived racial discrimination, as well as the emotional and behavioral responses to perceived racial discrimination may differ as a function of SES.

To our knowledge, the relationship between perceived racial discrimination, cortisol regulation, and pain sensitivity has never been specifically examined among healthy persons or those with a chronic disease such as knee OA. Therefore, the present investigation of persons with knee OA is the first to determine if the relationship between ethnicity and pain sensitivity can be explained in part by lower basal cortisol concentrations and/or cortisol release following the CPT. Additionally, it examines the role of basal cortisol levels and cortisol release after the CPT in the relationship between perceived racial discrimination and pain sensitivity separately for AAs and NHWs. Finally, it assesses whether the relationship between perceived racial discrimination and pain sensitivity is moderated by SES.

RESEARCH DESIGN AND METHODS

The proposed study is part of a larger ongoing project that aims to enhance the understanding of biopsychosocial factors contributing to pain and functional limitations among individuals with knee OA (Understanding Pain and Limitations in Osteoarthritic Disease, UPLOAD). The UPLOAD study is a multi-site investigation that recruits participants at the University of Alabama at Birmingham (UAB) and the University of Florida (UF).

Participants

Participants were 91 community-dwelling adults (44 AA; 47 NHW) between the ages of 45 and 85 with symptomatic knee OA recruited via posted fliers, radio and print media advertisements, orthopedic clinic recruitment, and word-of-mouth referral. The 28 participants that provided pilot data (see Figure 1) were not included in the present study. All procedures were reviewed and approved by the UAB and the UF Institutional Review Boards. Participants provided informed consent and were compensated for their participation.

Criteria for participant inclusion were as follows: 1) between 45 and 85 years of age; 2) unilateral or bilateral symptomatic knee osteoarthritis based upon the American College of Rheumatology clinical criteria (58); and, 3) availability to complete the two-session protocol. Individuals were excluded from participation if they met any of the following criteria: 1) prosthetic knee replacement or other clinically significant surgery to the affected knee; 2) uncontrolled hypertension, heart failure, or history of acute myocardial infarction; 3) peripheral neuropathy; 4) systemic rheumatic disorders

including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia; 5) daily opioid use; 6) cognitive impairment (Mini Mental Status Exam (MMSE) score ≤ 22); 7) excessive anxiety regarding protocol procedures (e.g., blood draws and controlled noxious stimulation procedures); and 8) hospitalization within the preceding year for psychiatric illness.

Identical screening procedures and laboratory pain testing were conducted at UAB and UF. Both study sites conducted the health assessment session (HAS) and quantitative sensory testing (QST) session (described below) in laboratory space provided in their respective Clinical Research Units (CRUs).

Initial Screening

All participants underwent an initial screening interview, via telephone or in person depending on the recruitment setting, as well as a knee OA screening interview that recently showed 87% specificity and 92% sensitivity for detecting knee OA (59). This interview includes four questions regarding knee pain, swelling, and previous diagnosis of knee OA. The screening tool also included questions regarding hip OA (93% sensitivity and 93% specificity). The initial screening also included questions regarding age, ethnic group, sex, and additional health history information to ensure that no exclusion criteria were present. Only individuals who were positive for knee OA on the screening tool and met all other eligibility criteria (e.g. age, ethnicity) were scheduled for the initial screening visit at the study site's CRU.

Determination of Ethnic Group

Ethnic group was determined by self-report of the participant using the standard Health and Human Services categories. Individuals who self-identified as Hispanic were not included. While the Hispanic population is an important minority group in the United States, we have chosen not to include them in this research project for several reasons: 1) while there is evidence of ethnic group differences in OA symptoms between Hispanic and non-Hispanic populations, there is more abundant evidence regarding differences between AAs and NHWs; 2) likewise, there is less information regarding group differences in experimental pain sensitivity between Hispanic and non-Hispanic populations; 3) while heterogeneity is present in all ethnic groups, the Hispanic population is arguably characterized by the greatest heterogeneity based on spoken language(s), country of origin, and biogeographical ancestry; and 4) at a more practical level, given the demographics of our two study sites, it would be difficult to recruit older Hispanic patients in sufficient numbers to address the proposed study aims, and adding an additional study site to this already resource-intensive project was not a legitimate option. Therefore, we only recruited older adults with OA who self-identified as non-Hispanic and either Black/AA or white/European.

Procedures

Anthropometric and Laboratory Tests

Height and weight were recorded for all participants and BMI was calculated. Weight-bearing radiographs of both knees were obtained for diagnostic purposes and for

determining OA severity (i.e., Kellgren-Lawrence score). The project radiologist at each site read the radiograph of each knee and provided a Kellgren-Lawrence Score, as well as information regarding which compartments are affected. The Kellgren-Lawrence Score categorizes the severity of knee OA into one of four grades based on narrowing of joint space, presence and size of osteophytes, and deformity of bone contour. Previous research has demonstrated the reliability of this scoring system (60).

Medical History Questionnaire

All patients completed a thorough medical history, which assessed the self-reported duration of OA, current and past treatments for OA, comorbid conditions, and current medication use. For women, menopausal status was obtained as well as whether they were using hormone replacement. This medical history information was reviewed with the patient by the project rheumatologist (or clinical research nurse) at each site to ensure all items were completed accurately.

Physical Examination

Each patient underwent a physical examination by the project rheumatologist in order to: 1) confirm the diagnosis of symptomatic OA according to ACR criteria; 2) rule out any exclusion criteria; and 3) identify the most symptomatic knee. After reviewing the health history, the project rheumatologist performed a manual examination of joint tenderness at the hands, hips and knees bilaterally. The project rheumatologist also evaluated the presence of sensory deficits that may suggest a neuropathy that would eliminate the participant from the study.

HAS Session (Session 1)

During the HAS, all participants completed an index of cognitive capacity, the mini mental status exam, to determine if cognitive or attentional deficits were present that would rule out participation in a study of pain responses. Additionally, all individuals underwent a bilateral knee joint evaluation by the project Rheumatologist. Lastly, x-rays were taken of both knees to determine the extent of radiographic knee OA.

QST Session (Session 2)

The QST was completed during a second visit scheduled between 1 and 4 weeks after the HAS session. On the day of the QST, participants indicated on a 0 to 100 scale the degree of clinical pain intensity in their index (i.e., most affected) knee, where 0 represents no pain and 100 represents the most intense pain imaginable (hereafter referred to as "OA pain intensity"). During the QST, a number of standard pain testing procedures were performed prior to the CPT (described below), including: heat pain threshold and tolerance levels assessed at the most affected knee and ipsilateral forearm; pain intensity ratings in response to repetitive 44, 46, and 48˚ C thermal heat pulses at the most affected knee and ipsilateral forearm; pressure pain thresholds at the most affected knee, as well as the ipsilateral forearm, trapezius, and quadriceps; and pain intensity ratings in response to single and repetitive punctate mechanical stimuli applied at the most affected knee and ipsilateral hand. For the purposes of this study, only the CPT was assessed in relation to cortisol and perceived racial discrimination because 1) the CPT reliably produces differences in pain among AAs and NHWs (1, 15) and 2) the CPT elicits significant cortisol reactivity (9, 51).

Cold Pressor Task (CPT). Each participant completed a series of hand immersions in a cold water bath (Neslab, RTE-111, Portsmouth, NH) at temperatures of 16, 12, and 8˚ C, with 5-minutes separating each cold water exposure. The water temperature was maintained at ± 0.1˚ C and the water was continuously recirculated to maintain a constant temperature throughout the water bath and to prevent local warming around the submerged hand. Participants were first instructed regarding the differences between pain intensity and pain unpleasantness (see Appendix A). Next, they placed their hand in the cold water bath up to their wrist for as long as possible up to 60 seconds. Participants were informed they could remove their hand from the cold water at any time if the pain becomes intolerable. Immediately after participants removed their hand, they rated the intensity and unpleasantness of any pain they were experiencing using 0 to 100 numeric rating scales with 0 indicating no pain and 100 indicating the worst pain they can imagine. In addition to ratings of pain intensity and unpleasantness, a measure of cold pain tolerance (CPTo) was captured. Specifically, CPTo was measured as the time at which participants removed their hand from the cold water. Thus, CPTo ranged from 0 to 60 seconds.

Questionnaires

Prior to the HAS, participants completed electronic study questionnaires either at home or at the laboratory. The following demographic and health data were obtained: self-reported sex, age, ethnicity, years of school completed, annual household income, smoking status, as well as health history that included information pertaining to whether individuals had any mental or physical health conditions that required hospitalization in the past year. In addition, participants completed several psychosocial questionnaires to assess pain

coping strategies, mood/affect, hypervigilance, mistrust of medical providers, ethnic identity and experiences of discrimination. For the proposed investigation, only responses on the Experiences of Discrimination scale were assessed in relation to pain sensitivity.

Experiences of Discrimination (EOD) scale

The EOD is a validated and reliable measure of lifetime occurrences of discrimination that was designed specifically for public health research (61). The EOD asks the question, "Have you ever experienced discrimination, been prevented from doing something, or been hassled or made to feel inferior in any of the following situations because of your race, ethnicity, or color?" This question is followed by 9 response options: at school; getting hired or getting a job; at work; getting housing; getting medical care; getting service in a store or restaurant; getting credit, bank loans, or a mortgage; on the street or in a public setting; from the police or in the courts. Respondents choose from the following responses, "never," "once," "two or three times," or "four or more time," which are assigned the value of 0, 1, 2.5, or 5, respectively. Thus, the EOD has a range from 0 to 45 with greater values indicating more frequent experiences of racial discrimination. Although there are additional ways to score the EOD (61), the frequency of experiences was chosen to be consistent with previous literature that has examined the relationship between perceived racial discrimination and pain sensitivity (4).

SES

SES is a multifaceted construct that has been operationalized in a variety of ways (e.g., education, income, median household income within a zip code, occupation, etc.). When examining SES, it has been suggested that multiple SES indicators be used when possible as different indicators may be capturing different aspects of SES (62). In the current study, years of school completed and annual household income were assessed separately as moderators in the relationship between perceived racial discrimination and pain sensitivity. For years of school completed, participants selected from one of the following choices: some school but did not complete high school, high school degree, two-year college degree, four-year college degree, master's degree, or doctoral degree. For income, participants indicated current annual household income by choosing one of the following: $0 - $10,000, $10,001 - $19,999, $20,000 - $29,999, $30,000 - $39,999, $40,000 - $49,999, $50,000 - $59,999, $60,000 - $79,999, $80,000 - $99,999, $100,000 - $149,999, or $150,000 or higher. Because we did not suspect any significant relationships between perceived racial discrimination and pain sensitivity among NHW participants, the moderating effect of SES was only assessed in AA participants.

Cortisol Measurement

At the beginning of the QST session, a CRU nurse placed an intravenous catheter in the arm opposite the arm used for sensory testing. Blood was drawn at five separate time points throughout the QST session (see Figure 2). For the purposes of this study, plasma cortisol was analyzed at three different time points: baseline (BS 1 in Figure 2), immediately after the CPT (BS 3 in Figure 2; hereafter referred to as "post-CPT") and

approximately 20 minutes after the CPT (BS 4 in Figure 2; hereafter referred to as "20 min post-CPT").

Plasma cortisol was quantified using enzyme immunoassay kits (Enzo Life Sciences), which provide accurate measures of cortisol within a range of 7.9-1,000 ng/mL. This assay was performed by the Metabolism and Translational Science Core of the Claude D. Pepper Older Americans Independence Center/Institute of Aging at the University of Florida.

Calibration across Study Sites

An important consideration in multi-site studies is consistency of data collection procedures across sites. Both Dr. Fillingim and Dr. Bradley, the co-PI's of UPLOAD, have experience as investigators in multi-center studies. Dr. Fillingim is an investigator in the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) study, and Dr. Bradley is an investigator in the MOST study (Multi-Center Osteoarthritis Study). Both of these studies involve collecting clinical and psychophysical data in large samples at multiple sites, and based on our experience with these projects, several steps have been made to ensure consistency across our two study sites. First, before commencing data collection, a calibration session was held at UF, which was attended by both PIs, both study rheumatologists, and the primary research staff. This calibration session was designed to ensure consistency in conducting the following procedures: 1) telephone screening; 2) taking weight-bearing radiographs; 3) assigning a diagnosis of symptomatic knee OA; and 4) experimental pain testing procedures. Standardized instructions for each study procedure were developed and audio-recorded for use at each site. Second, the PIs,

study rheumatologists, and research staff conduct biweekly conference calls to discuss recruitment progress and to address experimental issues. Based on our experience with multicenter studies, this frequent interaction across study sites is crucial to maintain consistency. Third, PI's and staff meet twice a year (once in Gainesville, once in Birmingham) to discuss the current state of UPLOAD, the development of research manuscripts, and the development of ancillary studies.

Data Analysis

There are a total of 3 outcome variables (ratings of pain intensity, ratings of pain unpleasantness, and CPTo) obtained during each cold water exposure for a total of 9 potential outcome variables. However, for the present project, we focus on pain ratings and CPTo obtained during the 8˚ C cold water immersion because 1) this temperature will likely lead to greater activation of the HPA axis compared to 12° and 16˚ C cold water immersions and 2) investigators using a single cold water exposure demonstrate significant cortisol reactivity approximately 15 minutes after the CPT (9, 51). Therefore, cortisol levels obtained after the CPT in the present investigation are most likely reflective of cortisol responses to the 8˚ C cold water immersion. In addition, pain unpleasantness ratings and CPTo serve as primary dependent variables because both are associated with the affective-emotional aspect of pain, whereas pain intensity ratings are associated with sensory-discriminative aspect of pain (63). This is important because in both healthy adults and persons living with chronic pain, differences between AAs and NHWs are more consistently shown in pain unpleasantness and pain tolerance levels verses pain intensity ratings (64, 65). Thus, there were two primary dependent variables

(pain unpleasantness ratings and CPTo during the 8˚ C cold water immersion) and one secondary dependent variable (pain intensity ratings during the 8˚ C cold water immersion) in the present investigation. We also assess pain intensity ratings, pain unpleasantness ratings, and CPTo at 12° C as exploratory outcomes because a recent investigation by Cruz-Almeida and colleagues (66) showed the strongest ethnic differences in pain sensitivity during the CPT at this temperature.

The following demographic variables were statistically controlled for: age, sex, education, and location of study site (0 = UAB, 1 = UF). Income was not used a covariate because 1) it was highly correlated with education (r = .52) and therefore would likely not help explain any additional variance in outcomes, and 2) education was more highly related to pain responses during the CPT compared to income (see Table 2). In regard to the assessment of cortisol, controlling for study site was particularly important because UAB typically began the QST session during the morning (approximately 9:30), while UF typically began in the afternoon (approximately 12:30). In addition, we controled for smoking status (0 = not a current smoker; 1 = current smoker), use of corticosteroid medications (0 = no corticosteroid medication use; 1 = current use of corticosteroid medications) and BMI, as these variables are known to interact with cortisol regulation (67, 68). Finally, OA pain intensity was added as a covariate to control for variations in clinical knee pain on the day of QST.

Relevant assumptions were inspected for perceived racial discrimination, cortisol, and pain responses. A small portion of missing data existed for pain intensity and pain unpleasantness ratings at 8° C. Rather than exclude from the analysis, a simple, well-validated imputation method was completed using the macro for Hot Deck imputation

(69). Z-scores were computed for perceived racial discrimination, cortisol, and pain responses to determine the presence of outliers. Two outliers (Z-scores greater than 3.3) were detected on the EOD. These cases were deleted prior to analyses using this variable. All cortisol values violated the assumption of normality (Shapiro Wilks < .001). After applying a logarithmic transformation, this assumption was no longer violated. Although pain intensity ratings, pain unpleasantness ratings, and CPTo at 8° and 12° C similarly violated the assumption of normality (Shapiro Wilks < .001), we decided to use non-transformed data because 1) transforming pain responses during the CPT did not result in non-significant Shapiro Wilks values, 2) pain ratings and CPTo did not violate normality when assessed by alternative methods (inspection of skewness and kurtosis values in SPSS EXPLORE), and 3) transforming pain responses during the CPT increases the difficulty of interpretation.

Partial eta squared (η_ρ^2) and Cohen's f^2 effect sizes are presented where appropriate following the conventions of Cohen (70) for tests of adjusted mean differences (ANCOVA) and linear relationships, respectively. Per Cohen's guidelines, $\eta_\rho^2 = 0.01$ is considered a small effect, $\eta_\rho^2 = 0.06$ a medium-sized effect and $\eta_\rho^2 = 0.14$ a large effect. Similarly, $f^2 = 0.02$ is considered a small effect, $f^2 = 0.15$ a medium-sized effect and $f^2 = 0.35$ a large effect. In addition, effect sizes for indirect effects (κ^2) were calculated for each mediation analysis as recommended by Preacher and Kelley (71). The size of each indirect effect is evaluated using the same criteria as Cohen's guidelines for η_ρ^2 (71). All data was analyzed using SPSS, version 20 (IBM; Chicago, IL).

All analyses were first inspected without adjusting for covariates followed by inspection of fully adjusted models. However, only adjusted analyses were used to test hypotheses.

Aim 1

Hypothesis 1. Separate one-way ANOVAs were performed to determine ethnic differences in pain intensity ratings, pain unpleasantness ratings and CPTo during the 12° C and 8˚ C cold water immersion, followed by separate one-way ANCOVAs to assess ethnic differences in cold pain sensitivity while controlling for covariates.

Aim 2

Hypothesis 2. The bootstrapping technique and macro created and described by Preacher and Hayes (72) was used to test whether ethnic differences in pain sensitivity during the CPT are partially mediated by basal cortisol levels, post-CPT cortisol levels, and/or 20 min post-CPT cortisol levels. Bootstrapping is a nonparametric resampling procedure that has been shown to be a viable alternative to other normal-theory tests of the intervening mediator between the independent and dependent variable (73). A 95% confidence interval was obtained to help minimize potential Type 1 error related to the test of mediation (74).

Aim 3

Hypothesis 3. Linear multiple regression models were used to determine the predictive utility of perceived racial discrimination for pain intensity ratings, pain unpleasantness

ratings, and CPTo during the 12° and 8˚ C cold water immersion, separately for AAs and NHWs.

Hypothesis 4. The same bootstrapping technique described above was used to determine if basal cortisol levels, post-CPT cortisol levels, and/or 20 min post-CPT cortisol levels mediate the relationship between perceived racial discrimination and pain sensitivity during the 12° C and 8˚ C cold water immersion, separately for AAs and NHWs.

Aim 4

Hypothesis 5. A total of 56.8% (*n* = 25) of AA participants reported a high school degree or less. Therefore, education was dichotomized as 0 = high school or less and 1 = some college or more. For income, 52.3% (*n* = 23) of AA participants reported an annual household income of $0 - $10,000 or $10,001 - $19,999. Therefore, income was dichotomized as 0 = less than $20,000 and 1 = $20,000 or greater. Perceived racial discrimination was centered prior to creating interaction terms with education and income. For all moderation analyses, a hierarchical linear regression was performed by entering covariates at step 1, perceived racial discrimination and education (or income) at step 2, and the respective interaction term at step 3. In the event that a significant interaction is revealed, simple slopes will be evaluated at both levels of the moderating variable using linear multiple regression.

RESULTS

Characteristics of the overall sample are shown in Table 1. Participants were primarily female (71.4%) with a mean age of 56.09 (±7.04). Compared to NHWs, AAs were younger in age, had lower education, reported lower annual household income, had a greater BMI, were less likely to use corticosteroid medications, and had greater perceived racial discrimination scores ($p < .05$). There were no ethnic differences in sex, smoking status, or OA pain intensity. Further, a greater number of participants were recruited at UF (75%) compared to UAB (25%); however, both study sites had roughly equal representation of AAs within their respective sample (47% at UF; 52% at UAB). The bivariate correlations of ethnicity and covariates with outcome variables are presented in Table 2.

Aim 1

In unadjusted analyses, AAs exhibited greater ratings of pain intensity at 12° C, greater ratings of pain unpleasantness at 8° and 12° C, and lower CPTo at 8° and 12° C. However, in fully adjusted models, only pain unpleasantness ratings at 12° C, as well as CPTo at 8° and 12° C remained statistically significant (see Table 3).

Aim 2

Table 4 shows mean (SD) cortisol levels at baseline, post-CPT, and 20 min post-CPT, as well as cortisol levels averaged across these three measurements. Compared to NHW, AA participants exhibited significantly lower cortisol levels at baseline and post-CPT, as well as lower average cortisol levels. However, after adjusting for covariates,

ethnic differences in cortisol were only observed at baseline (see Table 4). Table 5 shows correlations between cortisol and pain responses for the entire sample, while tables 6 and 7 show correlations between cortisol and pain responses separately for NHW and AA participants, respectively. Pain ratings were negatively associated with cortisol levels at all time points and positively associated with CPTo, but only basal cortisol levels and CPTo at 12° C were statistically significant. Baseline cortisol did not mediate the relationship between ethnicity and CPTo at 12° C in unadjusted or fully adjusted models (see Figure 3).

Aim 3

Table 8 shows the correlations between perceived racial discrimination and cortisol levels, whereas Table 9 shows the correlations between perceived racial discrimination and pain responses during the CPT for AA and NHW participants. Perceived racial discrimination was significantly correlated with pain intensity ratings at 8° C, but only in AA (see Table 9). After adjusting for covariates, regression analysis showed perceived racial discrimination was negatively associated with pain intensity ratings at 8° C (see Table 10). Cortisol did not mediate the relationship between perceived racial discrimination and pain intensity ratings, pain unpleasantness ratings, or CPTo at 8 or 12° C in unadjusted or fully adjusted models.

Aim 4

Because the only significant relationship between perceived racial discrimination and pain sensitivity during the CPT was found at pain intensity ratings at 8° C, this was

the only dependent variables inspected for aim 4. Education did not moderate the relationship between perceived racial discrimination and pain intensity ratings at 8° C (see Table 11). However, a significant interaction of perceived racial discrimination and income was detected at pain intensity ratings at 8° C (see Table 12). Analysis of simple slopes revealed that perceived racial discrimination was negatively associated with pain ratings among AA participants reporting an annual household income equal to or greater than $20,000 (see Table 13), but not among AA participants reporting an annual household income less than $20,000 (see Table 14). Figure 4 shows the graphical display of this interaction.

Supplemental Analyses

Supplemental analyses were completed at the request of dissertation committee members. First, a repeated measures ANOVA was employed to assess the relationship between ethnicity, cortisol, and the interaction between ethnicity and cortisol. Mauchly's test of sphericity was violated in both unadjusted and adjusted analyses; therefore, the Greenhouse-Geisser adjustment to degrees of freedom was used to assess statistical significance. In the unadjusted analysis, there was a significant between subjects effect of ethnicity [$F(1,89) = 6.03$, $p < .05$] and a within subjects effect of cortisol [$F(1.6,146.4) = 8.57$, $p < .05$]. However, there was not an ethnicity by cortisol interaction ($p > .05$). In the fully adjusted analysis, ethnicity and cortisol were no longer significant between and within subject effects, respectively ($p > .05$). The interaction between ethnicity and cortisol approached significance ($p = .06$). As can be seen in Figure 5, this marginally

significant finding was most likely driven by large ethnic group differences in baseline cortisol levels.

To further inspect differences in cortisol across time, a measure of area under the curve (AUC_I) was calculated using the trapezoid formula put forth by Pruessner and colleagues (75). AUC_I is a parameter that emphasizes the changes of a physiological marker over time. AUC_I was employed instead of AUC_G, because AUC_I uses the first observation (in this case, baseline cortisol) as the point of reference, as opposed to AUC_G, which uses a value of 0 as the point of reference (75). Thus, we report only findings in relation to AUC_I, as AUC_G is similar to the between subjects effect reported in the repeated measures ANOVA above. In the unadjusted analysis, there were no differences in AUC_I as a function of ethnicity ($p > .05$); however, in fully adjusted analyses, a significant effect of ethnicity was found, [$F(1,80) = 4.41$, $p < .05$]. Inspection of the means revealed that NHW participants exhibited a greater decrease in cortisol from baseline levels ($M = -18.76$, $SE = 5.03$) compared to AA participants ($M = -2.65$, $SE = 5.16$). AUC_I did not mediate the relationship between ethnicity and pain responses during the CPT in unadjusted or fully adjusted analyses.

DISCUSSION

The first aim of the present study was to assess ethnic differences in pain sensitivity during the CPT. Consistent with predictions, AAs exhibited lower CPTo at 8° C compared to NHWs. Further, in exploratory analyses, AAs exhibited lower CPTo and greater ratings of pain unpleasantness at 12 C° compared to NHWs. The second aim was to determine if ethnic differences in pain sensitivity could be partially explained by basal

cortisol levels and/or cortisol release following the CPT. Contrary to predictions, cortisol did not mediate this relationship. For the third aim, we first determined if perceived racial discrimination was related to greater pain sensitivity during the CPT, separately for NHWs and AAs. Opposite of predictions, perceived racial discrimination was related to lower pain intensity ratings at 8° C among AA participants. This relationship was not observed among NHW participants. Additionally, we assessed basal cortisol levels and cortisol release following the CPT as mediators in the relationship between perceived racial discrimination and cold pain sensitivity, separately for NHWs and AAs. However, cortisol did not mediate this relationship in either ethnic group. Finally, for the fourth aim, we assessed the moderating effect of two different SES indicators, educational attainment and annual household income, in the relationship between perceived racial discrimination and pain sensitivity during the CPT in AA participants. A significant interaction of perceived racial discrimination and income was detected for pain intensity ratings at 8° C. Analysis of simple slopes revealed that perceived racial discrimination was related to lower pain intensity ratings at 8° C only in AAs with relatively high incomes.

Aim 1

Compared to NHWs, AAs consistently demonstrate greater experimental pain sensitivity on a number of experimental pain tasks, including the CPT (1, 15). In the present study, AAs exhibited lower CPTo at 12° and 8° C, as well as greater pain unpleasantness ratings at 12° C compared to NHWs, but did not differ in pain intensity ratings. This finding is most likely related to the differences in the pain experience that

CPTo and pain unpleasantness ratings capture verses pain intensity ratings. For example, both pain unpleasantness and CPTo tend to be associated with the affective-emotional aspect of pain, whereas pain intensity ratings tend to be associated with the sensory-discriminative aspect of pain (63). The results of the present study corroborate existing literature because differences between AAs and NHWs are more consistently shown in pain tolerance and pain unpleasantness ratings than pain intensity ratings (64, 65).

Aim 2

In the present study, AAs had significantly lower basal cortisol levels compared to NHWs. This is consistent with other findings that have assessed basal cortisol levels in AAs and NHWs (5, 76), as well as studies showing AAs have lower waking levels of cortisol compared to NHWs (53, 54). Although it has been argued that these findings are indicative of HPA axis dysregulation associated with chronic stress exposure among AAs (54), no conclusive evidence exists to support this claim. Indeed, in the present study, there were no significant relationships observed between perceived racial discrimination, a marker of chronic stress exposure (11), and basal cortisol levels (see Table 8). It is possible there are allelic variations in the glucocorticoid receptor gene as a function of ethnicity, independent of exposure to chronic stressors (55).

This is the first study to investigate the role of basal cortisol and cortisol release following the CPT in the relationship between ethnicity and pain sensitivity among persons with knee OA. Contrary to predictions, basal cortisol levels and cortisol release following the CPT did not mediate this relationship. A potential explanation for this null finding is that AAs and NHWs differ in their endogenous responses to pain. For example,

among healthy young adults, stress-induced blood pressure, cortisol, and norepinephrine levels are positively associated with subsequent pain tolerances during the CPT among NHWs, but not their AA counterparts (5). Also in this study, baseline cortisol was marginally related to pain tolerance during the CPT in Caucasians ($p < .10$), but not AAs ($p > .90$). These findings are in line with the present study, because basal cortisol, post-CPT cortisol, and 20 min post-CPT cortisol levels were correlated with CPTo in NHWs (see Table 6), but not AAs (see Table 7). Because the associations between cortisol and pain responses during the CPT differ by ethnic group, it is not surprising that cortisol did not mediate the relationship between ethnicity and pain sensitivity during the CPT.

It should be noted that the relationship between post-CPT cortisol and 20 min post-CPT cortisol levels with CPTo at 12° C in NHWs became non-significant after controlling for basal cortisol level (results not shown), suggesting any relationship between cortisol and CPTo may be primarily associated with greater basal cortisol levels. This finding is important because Mechlin and colleagues (5) did not control for basal cortisol levels when assessing the correlation between post stress cortisol levels and CPTo.

Interestingly, cortisol was associated with pain intensity and unpleasantness ratings during the CPT, but only among AA participants (see Table 7). Specifically, greater post-CPT cortisol levels and 20 min post-CPT levels were negatively associated with pain intensity ratings at 8° C and pain unpleasantness ratings at 8° C, respectively. After controlling for baseline cortisol levels, the relationship between 20 min post-CPT cortisol levels and pain unpleasantness ratings at 8° C remained significant (partial correlation = -.31, $p < .05$), whereas the relationship between post-CPT cortisol levels

and pain intensity ratings at 8° C approached significance (partial correlation = -.30, p = .058) (results not shown). To our knowledge, we are the first investigators to show a significant relationship between pain intensity ratings during the CPT and cortisol levels obtained after the CPT in AAs with knee OA. This may be important, because previous investigations reporting a lack of association between HPA-axis measures and pain sensitivity in AAs have only assessed pain tolerance levels (a non-verbal report of pain sensitivity), not pain ratings (a verbal report of pain sensitivity) (5, 76). Our data suggest that AA participants' verbal reports of pain intensity are more closely associated with cortisol release following the CPT than non-verbal reports of pain sensitivity. Future research is needed to replicate this finding and to explore potential explanatory variables in this relationship.

Aim 3

Perceived discrimination is associated with a number of negative physical and mental health outcomes (77). To explain this relationship, investigators have posited that perceived discrimination leads to prolonged activation of endogenous stress regulatory systems that predispose a number of physical and mental health disparities observed between AAs and NHWs (77). This is the first study to investigate the role of basal cortisol and cortisol release following the CPT in the relationship between perceived racial discrimination and pain sensitivity in AAs with knee OA. Cortisol was not found to mediate this relationship; however, a notable, unexpected finding was found. Opposite to what was hypothesized, perceived racial discrimination was negatively associated with pain intensity ratings at 8° C, even after controlling for confounding variables, suggesting

greater reports of perceived racial discrimination are related to reductions in cold pain sensitivity.

Although most researchers have conceptualized perceived discrimination as a stressor, others have suggested perceiving negative experiences as discriminatory may serve a protective roll for stigmatized group members. For example, acknowledging the presence of racial discrimination may be necessary to effectively cope and adjust to discrimination (78), whereas underreporting perceived racial discrimination may be related to avoidance, denial, and suppression (54), which has been linked to several negative health outcomes (79). Further, in a recent fMRI study, attributing social exclusion to racial discrimination during a simulated, interactive laboratory game was associated with reduced activation in neural areas related to distress and increased activation in neural areas related to emotional regulation (80). Specifically, the more participants felt excluded because of their race, the less activation observed in the dorsal anterior cingulate cortex, a neural center involved in social threats, and the more activation observed in the rostral anterior cingulate cortex, a neural center involved in regulation of threat responses (80). This latter finding is particularly relevant for the present study because activity in the rostral anterior cingulate cortex is associated with reductions in pain perception (81). The results of the present study add to the existing literature suggesting that perceived racial discrimination may serve a protective role among AA persons (54, 82-83).

In the one other study investigating the relationship between perceived racial discrimination and experimental pain sensitivity in AAs with knee OA, greater reports of perceived racial discrimination were related to lower heat pain tolerances (4). Although

this finding seems to contradict the results of the present study, it is important to point out important differences. First, there are differences in the type of pain produced by heat pain and cold pain procedures in addition to differences of modality (i.e., heat verses cold), because cold pain stimulates deep tissues whereas heat pain stimulates superficial cutaneous nociceptors. Second, CPTo is a non-verbal measure of pain behavior, whereas a pain rating is a verbal measure of pain behavior. Thus, differences in modality (heat pain verses cold pain) and pain behavior (non-verbal verses verbal behavior) may partially explain the opposite findings between the present investigation and the findings by Goodin and colleagues (4). Future research is needed to better characterize the relationship between perceived racial discrimination and experimental pain modality.

Aim 4

There have been several studies that have addressed SES as a moderator between perceived racial discrimination and health outcomes among AAs, although none of these studies have assessed pain. These investigations have suggested that the negative emotional responses associated with reports of discrimination are greater among AAs of low SES (17), while others report no differences in emotional responses as a function of SES (12). In other studies, reports of perceived discrimination were found to be more beneficial for AAs of low SES compared to those of high SES (54). In the present study, the negative relationship between perceived racial discrimination and pain intensity ratings at 8° C was found only for AAs of relatively high SES. To further explain this finding, we employed post hoc analyses to inspect a number of culprit variables previously shown to differentiate the effects of perceived discrimination, including

coping style and depression (77, 84). Although reports of depressive symptomology (as characterized by the Center for Epidemiological Studies Depression Scale) did not differ by SES group, when participants were asked how they typically respond to unfair treatment on the EOD scale, AAs of relatively high income were less likely to "accept it as a fact of life" compared to AAs of relatively low income ($p < .05$; data not shown). This suggests a more active coping style to perceived racial discrimination in AAs with relatively high incomes. Although speculative, AA participants reporting high levels of perceived racial discrimination with relatively high incomes in our sample may have also used more active coping styles during exposure to noxious stimuli, which is associated with reductions in pain sensitivity (85). Further work is necessary to determine whether our findings are reliable across independent samples of AA persons with knee OA and to test the hypothesis that AA persons of relatively high SES use more effective pain coping techniques compared to AA persons of relatively low SES.

Unlike income, educational attainment did not moderate the relationship between perceived racial discrimination and pain intensity ratings at 8° C. Although income and education are related and have been used interchangeably (86), SES is a multifaceted construct and the relationship between SES and outcomes may vary based on the SES indicator used. For example, whereas education is the most important SES indicator when assessing environmental tobacco smoke exposure in non-smoking, healthy women (87), income is the strongest indicator in the relationship between SES and depression among AA women (88). The results of the present study corroborate these findings, suggesting that different SES indicators are likely capturing different aspects of the SES construct.

Limitations

The findings of the present study should be interpreted in light of its limitations. First, the cortisol findings need to be interpreted cautiously because there were differences between sites in how the blood samples were handled after being drawn from research participants. Specifically, a significant portion of blood (52%) was not iced immediately after being drawn from participants. Although there were no significant differences in cortisol as a function of placing the blood immediately vs. later on ice ($p > .05$), this difference may have influenced the present results. Second, we did not have cortisol levels obtained immediately prior to the CPT available, and therefore could not calculate a measure of cortisol reactivity in a meaningful way (9, 51). Future research will be needed to determine if cortisol reactivity helps explain ethnic differences in pain sensitivity during the CPT. Third, it should be emphasized that perceived racial discrimination is inherently a difficult construct to capture, as it measures participants' *willingness* to report past experiences that were potentially very distressing. It has been suggested that in depth interviews may more accurately reflect experiences of perceived racial discrimination (82). Fourth, although the EOD scale used in the present study captures the frequency of and responses to perceived racial discrimination, it does not measure the perceived severity of those experiences. This may be important because the appraisal of stressful events may be a better predictor of health outcomes associated with perceived racial discrimination than the frequency of those events (84). Fifth, as stated in the methods, all of our outcome variables violated the assumption of normality, even after performing transformations. Therefore, the results of the present investigation should be interpreted with this in mind.

Summary

The purpose of the present study was to 1) replicate previous findings showing AAs exhibit greater pain sensitivity during the CPT than their NHW counterparts, 2) determine if basal cortisol and/or cortisol release following the CPT partially explains the relationship between ethnicity and experimental pain sensitivity, 3) test the hypothesis that perceived racial discrimination is associated with greater dysregulation of cortisol, which is in turn related to greater pain sensitivity, and 4) determine if the relationship between perceived racial discrimination and experimental pain sensitivity in AAs differs as a function of SES. While we were able to show that AAs were more pain sensitive during the CPT compared to NHWs, cortisol did not help explain this relationship. Further, we found that reports of perceived racial discrimination were related to reductions in pain intensity ratings among AA participants, which was opposite of predictions. Cortisol similarly did not help us understand this relationship. Finally, the relationship between perceived racial discrimination and experimental pain sensitivity was only found in AA participants with relatively high incomes. Overall, the results of the present study add to the existing literature by showing that whereas cortisol levels are associated with CPTo in NHWs, cortisol levels are related to pain ratings in AAs. This is important because previous studies showing a lack of relationship between cortisol and pain in AAs have only assessed pain tolerance, a nonverbal measure of pain sensitivity (5). Additionally, we show that perceived racial discrimination is related to reductions in experimental pain sensitivity among AAs with knee OA, which is opposite of what others have reported (4). However, in line with the results from cortisol analyses, this relationship was found only with verbal ratings of pain, not non-verbal pain behavior

(i.e., tolerance). Taken together, the results of this investigation suggest that verbal reports of pain are important in understanding the relationship between cortisol and pain sensitivity, as well as perceived racial discrimination and pain sensitivity among AA persons with knee OA.

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Table 1

Sample Characteristics

Variable	Overall (N = 91)	African American (N = 44)	Non-Hispanic White (N = 47)	p value
Age	56.09 (7.04)	54.41 (5.40)	57.66 (8.03)	0.03
Sex (female)	71.4% (65)	70.1% (31)	72.3% (34)	0.84
Education (High school or less)	40.7% (37)	56.8% (25)	25.5% (12)	< 0.01
Annual Income ($20k or less)	29.7% (27)	52.3% (23)	8.5% (4)	< 0.001
BMI	32.17 (7.00)	33.76 (6.63)	30.69 (7.08)	0.04
Using Corticosteroid Medication (yes)	15% (14)	7% (3)	23% (11)	0.03
Current Smoker (yes)	21% (19)	32% (14)	11% (5)	0.13
OA Pain Intensity*	10.33 (19.00)	8.16 (16.84)	12.41 (20.83)	0.29
Perceived Discrimination Score	5.39 (7.61)	8.73 (8.83)	2.29 (4.51)	< 0.001

Note: Data presented as means (SD) or percentage (count); * Clinical pain intensity in the most affected knee rated on a 0 to 100 scale on the day of the QST

Table 2

Bivariate correlations among ethnicity and covariates with outcome variables

	Intensity 12°	Unpleasant 12°	CPTo 12°	Intensity 8°	Unpleasant 8°	CPTo 8°
Ethnicity	-.17	-.26*	.29**	-.21*	-.24*	.40**
Age	.04	.03	-.05	-.05	-.03	-.03
Sex	.12	.12	-.08	.15	.11	-.11
Education	-.23*	-.22*	.12	-.31**	-.28**	.24*
Income	-.13	-.14	.27*	-.20	-.14	.28*
Smoking Status	.07	.08	-.03	.02	.12	.09
BMI	.12	.16	-.14	.17	.18	-.05
Corticosteroid Medications	-.01	-.08	.13	-.01	-.05	.13
OA Pain Intensity	.08	.07	-.13	.02	.07	-.15
Site	-.20	-.13	.21*	-.19	-.12	.24*

* = p < .05; ** = p < .001

Note: CPTo = cold pain tolerance; Ethnicity: 0 = African American, 1 = non-Hispanic white; Sex: 0 = Male, 1 = Female; Education: 0 = High school or less, 1 = Some college or more; Income: 0 = less than $20k per year, 1 = $20k or more per year; Smoking: 0 = not a current smoker, 1 = current smoker; BMI = body mass index; Corticosteroid Medications: 0 = not using steroid medication, 1 = using steroid medication; OA Pain Intensity = Clinical pain intensity in the most affected knee rated on a 0 to 100 scale on the day of the QST; Site: 0 = UF; 1 = UAB

Table 3

Mean (SD) cold pressor responses as a function of ethnic group (N = 91)

Outcome Variable	African Americans	Non-Hispanic Whites	Unadjusted p value	Adjusted p value*	η_p^2
Intensity 12°	60.69 (30.90)	51.15 (28.7)	.14	.15	.03
Unpleasant 12°	69.17 (32.10)	53.36 (30.35)	.02	.04	.06
CPTo 12°	51.01 (13.70)	57.81 (9.72)	.01	.01	.08
Intensity 8°	77.21 (29.90)	65.43 (28.84)	.06	.27	.02
Unpleasant 8°	80.90 (28.76)	67.26 (28.89)	.03	.12	.03
CPTo 8°	40.02 (19.95)	54.20 (14.22)	<.001	<.001	.18

Note: * adjusted for age, sex, education, smoking status, clinical knee pain on the day of the QST, BMI, corticosteroid medications, and site; CPTo = cold pain tolerance

Table 4

Mean (SD) levels of cortisol (ng/mL) as a function of ethnic group (N = 91)

Cortisol	African Americans	Non-Hispanic White	Unadjusted p-value	Adjusted p-value*	η_ρ^2
Baseline	57.63 (34.71)	77.80 (36.85)	.004	.01	.08
Post CPT	50.22 (32.14)	61.61 (33.00)	.053	.35	.01
20 min post CPT	60.65 (37.35)	69.72 (34.29)	.14	.36	.01
Average Cortisol	56.17 (29.72)	69.40 (29.96)	.03	.08	.04

Note: * adjusted for age, sex, education, smoking status, OA pain intensity, BMI, corticosteroid medications, and site. CPT = cold pressor task

Table 5

Bivariate correlations between cortisol and cold pressor responses (N = 91)

Cortisol	Intensity 12°	Unpleasant 12°	CPTo 12°	Intensity 8°	Unpleasant 8°	CPTo 8°
Baseline	-.08	-.13	.24*	-.13	-.15	.16
Post-CPT	-.06	-.14	.19	-.14	-.15	.10
20 min Post-CPT	-.10	-.14	.16	-.04	-.18	.08

*p < .05

Note: CPT = cold pressor task; CPTo = cold pain tolerance

Table 6

Bivariate correlations between cortisol and cold pressor responses in non-Hispanic white participants (N = 47)

Cortisol	Intensity 12°	Unpleasant 12°	CPTo 12°	Intensity 8°	Unpleasant 8°	CPTo 8°
Baseline	-.01	-.01	.36*	.04	-.01	.28
Post-CPT	.09	.00	.30*	.14	.07	.08
20 min Post-CPT	.13	.13	.30*	.13	.13	.10

* $p < .05$

Note: CPT = cold pressor task; CPTo = cold pain tolerance

Table 7

Bivariate correlations between cortisol and cold pressor responses in African American participants (N = 44)

Cortisol	Intensity 12°	Unpleasant 12°	CPTo 12°	Intensity 8°	Unpleasant 8°	CPTo 8°
Baseline	-.05	-.10	.06	-.17	-.15	-.10
Post-CPT	-.12	-.19	.04	-.32*	-.28	-.02
20 min Post-CPT	-.14	-.27	.01	-.29	-.33*	-.04

* $p < .05$

Note: CPT = cold pressor task; CPTo = cold pain tolerance

Table 8

Bivariate correlations between perceived racial discrimination and cortisol as a function of ethnic group

Ethnic Group	Baseline	Post-CPT	20 min post-CPT
African American (N = 42)	.24	.18	.13
Non-Hispanic white (N = 46)	.09	-.14	-.02

Note: CPT = cold pressor task

Table 9

Bivariate correlations between perceived racial discrimination and pain sensitivity as a function of ethnic group

Ethnic Group	Intensity 12°	Unpleasant 12°	CPTo 12°	Intensity 8°	Unpleasant 8°	CPTo 8°
AA (N = 42)	-.27	-.26	.11	-.40*	-.14	.17
NHW (N = 46)	-.16	-.10	.08	-.12	-.10	.10

* $p < .05$

Note: AA = African American; NHW = non-Hispanic white; CPTo = cold pain tolerance

Table 10

Regression analysis assessing intensity ratings at 8° C as a function of perceived racial discrimination in African American participants (N = 42)

Variable	b (SE)	β	t score	p value	f^2
Perceived Discrimination	-1.29 (.57)	-.41	-2.27	.030	.17

Note: adjusted for age, sex, education, smoking status, OA pain intensity, BMI, corticosteroid medications, and site

Table 11

The moderating effect of education on the relationship between perceived racial discrimination and pain intensity ratings at 8° C in African American participants (N = 42)

	Variable	b (SE)	β	t score	p value
Step 1					
	Age	.05 (.85)	.01	.06	.95
	Sex	4.42 (10.92)	.08	.41	.69
	BMI	.52 (.78)	.12	.70	.51
	Corticosteroid Medications	-.44 (21.34)	-.00	-.02	.98
	Smoking Status	-6.76 (10.60)	-.12	-.64	.53
	OA Pain Intensity	-.14 (.29)	-.09	-.49	.63
	Site	-15.62 (10.81)	-.26	-.145	.16
Step 2					
	Education	-13.64 (11.50)	-.25	-1.19	.24
	Discrimination	-1.32 (.56)	-.42	-2.37	.02
Step 3					
	Edu*Disc	-.38 (.97)	-.08	-.38	.71

Note: Education: 0 = high school less, 1 = some college or more

Table 12

The moderating effect of income on the relationship between perceived racial discrimination and pain intensity ratings at 8° C in African American participants (N = 42)

	Variable	b (SE)	β	t score	p value
Step 1					
	Age	.05 (.85)	.01	.06	.95
	Sex	4.42 (10.92)	.08	.41	.69
	BMI	.52 (.78)	.12	.70	.51
	Corticosteroid Medications	-.44 (21.34)	-.00	-.02	.98
	Smoking Status	-6.76 (10.60)	-.12	-.64	.53
	OA Pain Intensity	-.14 (.29)	-.09	-.49	.63
	Site	-15.62 (10.81)	-.26	-.145	.16
Step 2					
	Income	-14.51 (9.71)	-.27	-1.50	.15
	Discrimination	-1.37 (.53)	-.43	-2.55	.02
Step 3					
	Income*Disc	-2.12 (.97)	-.55	-2.22	.03

Note: Income: 0 = less than 20k per year, 1 = 20k or greater per year

Table 13

The relationship between perceived racial discrimination and pain intensity ratings at 8° C in African American participants earning relatively high incomes (N = 19)

Variable	b (SE)	β	t score	p value	f^2
Perceived Discrimination	-2.49 (.86)	-.78	-2.88	.02	.80

Note: Adjusted for age, sex, smoking status, OA Pain Intensity, BMI, corticosteroid medications, and site

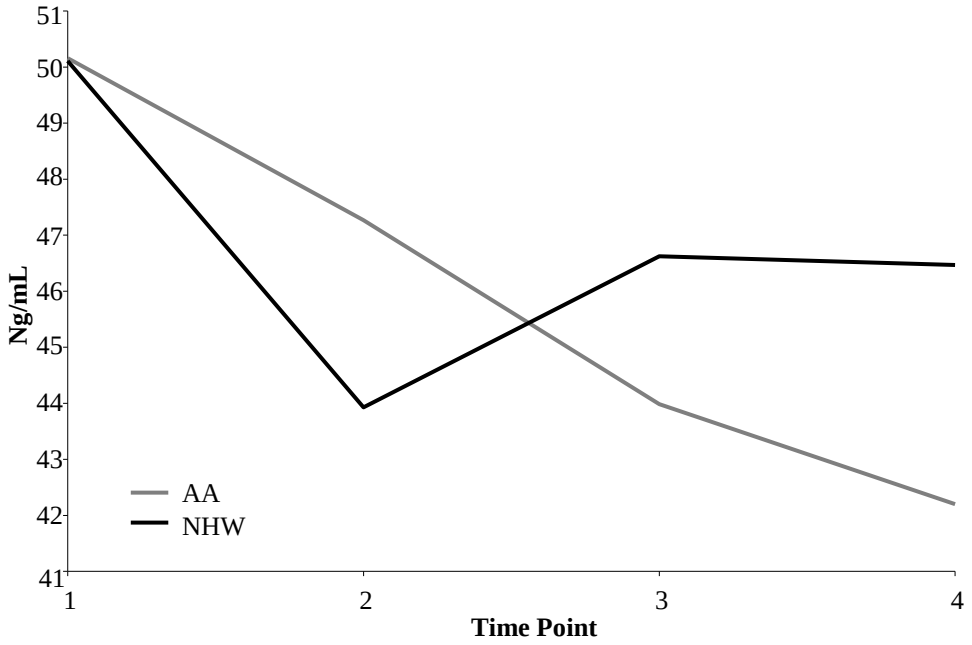
Table 14

The relationship between perceived discrimination and pain intensity ratings at 8° C in African American participants earning relatively low incomes (N = 21)

Variable	b (SE)	β	t score	p value	f^2
Perceived Discrimination	-.05 (.71)	-.02	-.07	.95	.04

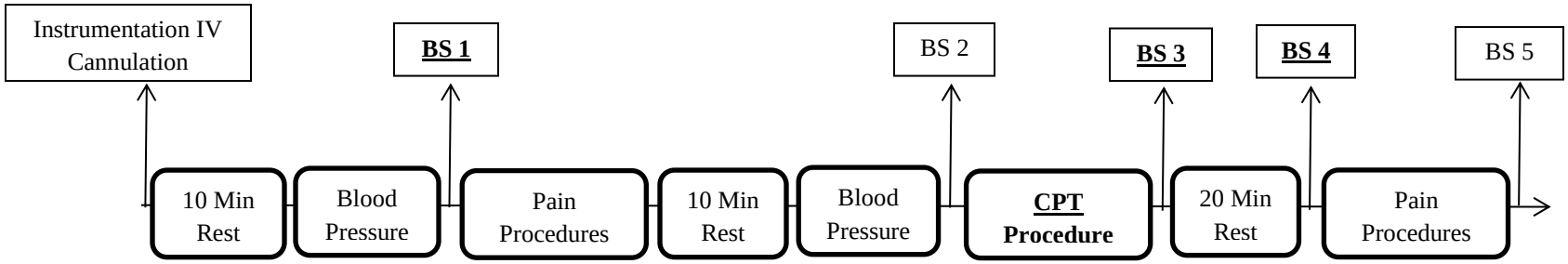
Note: Adjusted for age, sex, smoking status, OA Pain Intensity, BMI, hormone medications, and site

Figure 1. Mean cortisol levels as a function of time point and ethnic group



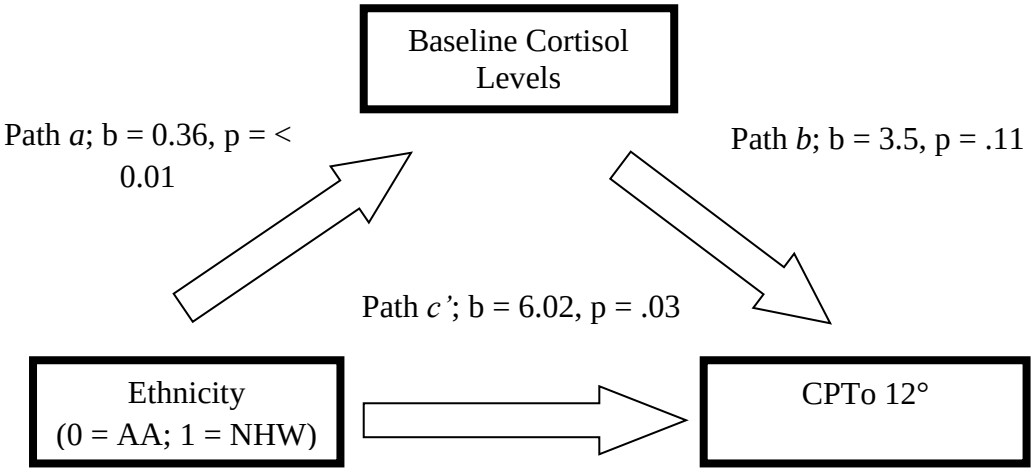
Note: N = 28; AA (*n* = 16; 4 males, 12 females); NHW (*n* = 12; 6 males, 6 females). Ng/mL = nanogram per milliliter; 1 = Plasma cortisol levels obtained immediately prior to the CPT; 2 = Plasma cortisol levels obtained immediately after the CPT; 3 = Plasma cortisol levels obtained approximately 20-min post-CPT; 4 = Plasma cortisol levels obtained approximately 40-min post-CPT

Figure 2. Timeline for QST session



Note: BS = Blood sample

Figure 3. Mediation analysis showing the indirect effect of baseline cortisol on the relationship between ethnicity and CPTo at 12° (N = 91)



Non-significant mediation: (*a x b* = 1.28 {95% CI -.50 to 4.32})

Note: Adjusting for covariates did not alter significance; AA = African American; NHW = non-Hispanic white; CPTo = cold pain tolerance

Figure 4. The relationship between perceived racial discrimination and pain intensity ratings at 8° C among African American participants with relatively low and high incomes

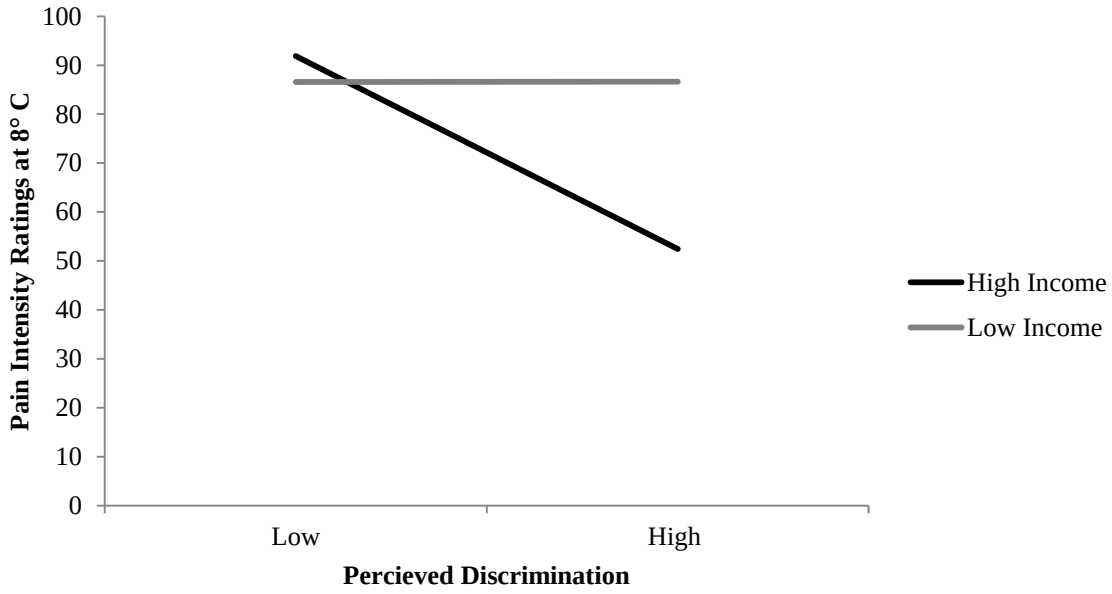
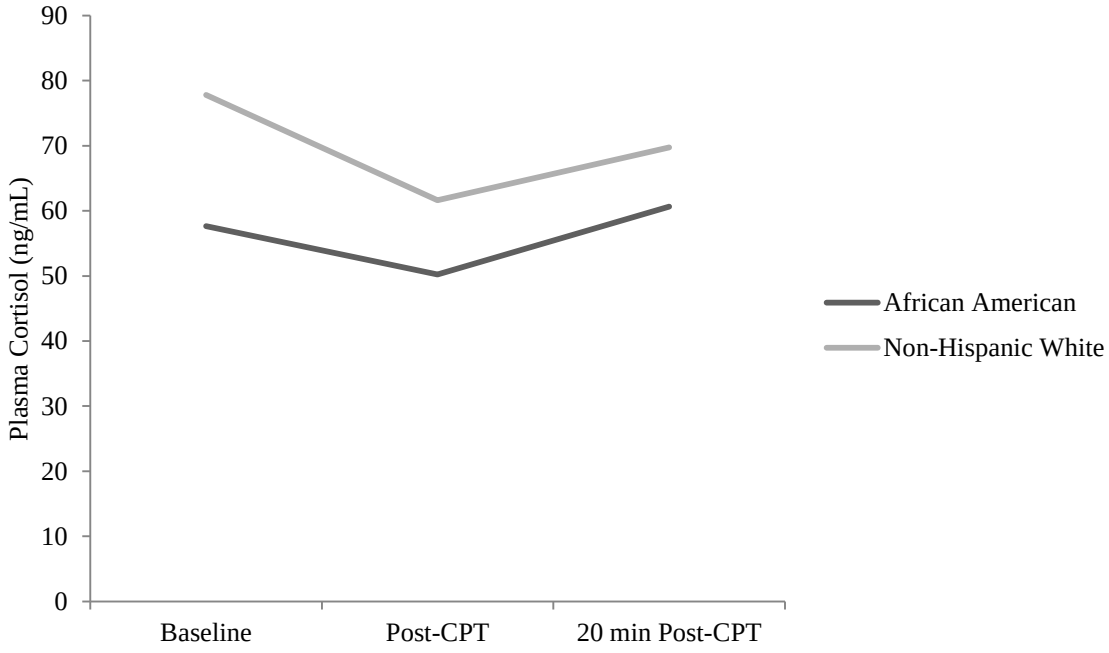


Figure 5. Mean cortisol levels obtained at baseline, post-CPT, and 20 min post-CPT in African American and non-Hispanic white participants



Note: ng/mL = nanogram per milliliter; CPT = cold pressor task

APPENDIX A

INSTRUCTIONS PROVIDED TO UPLOAD PARTICIPANTS PRIOR TO THE CPT

"There are two aspects of pain that we are interested in measuring for the next procedure: the *intensity* of the painful sensation, and how *unpleasant* or disturbing it is to have the pain. The distinction between these two aspects of pain might be clarified if you think of listening to a sound coming from a radio. As the volume of the sound increases, you can rate how loud it sounds or how unpleasant it is to hear. The intensity of painful sensation is like loudness while the unpleasantness of pain depends on its intensity and other things, such as its meaning, that may influence your estimation of unpleasantness. There are separate scales for measuring each of these two aspects of pain. Ratings of intensity and unpleasantness use the "0" to "100" scale where "0"indicates no pain or unpleasantness and "100" indicates the most intense or unpleasantness pain imaginable. Although some pains may be equally intense and unpleasant, we would like you to rate these two aspects of your pain separately. Do you have any questions about these scales?"

APPENDIX B

INSTITUTIONAL REVIEW BOARD APPROVAL

Project Revision/Amendment Form

Form version: October 28, 2010

In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck.

- Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for Investigators for additional information.
- Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.). See Item 4 for more examples.

1. Today's Date	June 15, 2011

2. Principal Investigator (PI)

Name (with degree)	Laurence A. Bradley, PhD	Blazer ID	Braddog
Department	Medicine	Division (if applicable)	Rheumatology
Office Address	177A Shelby	Office Phone	934-8550
E-mail	Braddog@uab.edu	Fax Number	934-1564

Contact person who should receive copies of IRB correspondence (Optional)

Name	Adriana Addison, MPH	E-Mail	Adriana@uab.edu
Phone	934-9614	Fax Number	934-1564
Office Address (if different from PI)	177C Shelby		

3. UAB IRB Protocol Identification

3.a. Protocol Number	F091231001
3.b. Protocol Title	Understanding Pain and Limitations in Osteoarthritic Disease (UPLOAD

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☐ Study has not yet begun — No participants, data, or specimens have been entered.
- ☒ In progress, open to accrual — Number of participants, data, or specimens entered: 32 persons
- ☐ Enrollment temporarily suspended by sponsor
- ☐ Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)
  - Date closed:
  - Number of participants receiving interventions:
  - Number of participants in long-term follow-up only:
- ☐ Closed to accrual, and only data analysis continues
  - Date closed:
  - Total number of participants entered:

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- ☐ **Protocol revision (change in the IRB-approved protocol)**
  In Item 5.c., if applicable, provide sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Protocol amendment (addition to the IRB-approved protocol)**
  In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☒ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c., (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).
- ☐ **Change in source of funding; change or add funding**
  In Item 5.c., describe the change or addition in detail, include the applicable OGCA tracking number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.
- ☐ **Add or remove performance sites**
  In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.

☐ **Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)**
To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789.

☐ **Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)**
In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.

☐ **Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)**
In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.

☐ **Revise or amend consent, assent form(s)**
Complete Item 5.d.

☐ **Addendum (new) consent form**
Complete Item 5.d.

☐ **Add or revise recruitment materials**
Complete Item 5.d.

☐ **Other (e.g., investigator brochure)**
Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable.
Include a copy of all affected documents, with revisions highlighted as applicable.

5. Description and Rationale

In Item 5.a. and 5.b, check Yes or No and see instructions for Yes responses.
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

☒ Yes ☐ No **5.a. Are any of the participants enrolled as normal, healthy controls?**
If yes, describe in detail in Item 5.c. how this change will affect those participants.

☐ Yes ☒ No **5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?**
If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c.
For more details on the UAB FAP, see www.uab.edu/cto.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

Personnel: Our post-doctoral fellow, Shelley Sanden PsyD, completed her fellowship on May 31, 2011, and is in Atlanta preparing for her State of Georgia licensure examination in psychology. We are currently recruiting a replacement for her. We will notify the IRB regarding the individual who fills her position.

Katie Byington, MA, will be leaving UAB on July 20, 2011 to begin her clinical psychology internship at Florida State University School of Medicine. She also will complete her oral doctoral examination in psychology at UAB later this summer. Ms. Byington will be working with us until July 15 and is training her replacement, Mr. Matthew Herbert MA, a second-year graduate student in the UAB doctoral training program in clinical psychology. Mr. Herbert will devote 20 hours per week to our project, as did Ms. Byington. Mr. Herbert has already completed his IRB human subjects training.

Protocol Amendment:

Knee Pain Questions: We request to add 3 questions regarding knee pain that our project rheumatologist, Barri Fessler MD, will ask all participants during the brief physical examination she performs in the first session of the 2-session protocol. These questions provide an opportunity to assess self-reports of consistency of knee pain, even among persons without knee OA. All participants will be asked:

How long have you been experiencing knee pain? _____Years _____Months
(If response indicates knee pain, go to next 2 questions)
Do you currently experience knee pain on most days? ____Yes ___No

For how long have you had knee pain on most days? ____Years _____Months

Prior Participation in Research Study: Given that we are recruiting older African-American and white participants from both urban and rural areas of Alabama, we wish to assess the extent to which our potential participants have previously been involved in research studies. We expect that our participants will vary with regard to prior research experience and this variation may be related to their willingness to engage in our research project, the pain responses they exhibit in our protocol, and perhaps in their responses to questionnaires or in biomarker findings. Therefore, during the initial screening of potential participants, we will ask the following question:

"Will your participation in UPLOAD be the first time that you have been involved in a research study?" (If clarification is needed, we will clarify: "a study which required signing an informed consent in order to participate.").

✓

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- a copy of the currently approved document (showing the IRB approval stamp, if applicable)
- a revised copy highlighting all proposed changes with "tracked" changes
- a revised copy for the IRB approval stamp.

Signature of Principal Investigator _____ Date June 15, 2011

FOR IRB USE ONLY

☐ Received & Noted ☑ Approved Expedited* ☐ To Convened IRB

_____ June 17, 2011
Signature (Chair, Vice-Chair, Designee) Date

DOLA 1-19-11

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111