Examining Racial and SocioEconomic Disparities (ERASED) in Chronic Low Back Pain Study

Study Protocol & Statistical Analysis Plan

NCT03338192

12/18/2024

Burel Goodin, Professor of Psychology, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Methods:

An overview of the study methodology is provided in **Figure 7**. Following a telephone screening to determine initial eligibility, an electronic medical record review will be completed for all potential participants to determine continued study eligibility. Each potential participant's health history and cLBP information will be discussed with the study physician to determine appropriateness for ongoing participation. Eligible participants will then complete two experimental study sessions for collection of clinical, biomarker, psychosocial, QST, and functional performance data. In between the two study sessions, participants will complete 7 nights of actigraphic sleep monitoring along with diaries. Following the second experimental study session, participants will complete weekly pain and symptoms diaries for 4 consecutive weeks over the telephone. This study will be conducted using laboratory space and resources provided by the UAB Clinical Research Unit (CRU), which is supported by the UAB Center for Clinical and Translational Science and an NIH Center for Translational Science Award (CTSA; UL1TR000165).

D.1.1. Participants: We will recruit a total of 268 adult participants with cLBP with the expectation of approximately 10% attrition based upon the preliminary work of Drs. Trost and Goodin. This will result in a final sample size of 240 (120 non-Hispanic Black, 120 non-Hispanic White) study completers. Participants between 19 and 85 years of age will be enrolled. Enrollment will begin almost immediately after funding is awarded because most of the study policies and procedures have already been established as part of the pilot work previously completed by the PI. The inclusion criteria for participants with cLBP are: 1) non-specific cLBP that has persisted for at least 3 months and has resulted in pain on at least half the days in the past 6 months; 2) age 19 – 85; the lower end of this age range was chosen in order to capture the growing prevalence of young adults with cLBP, and participants over 85 years are increasingly likely to meet one or more exclusion criteria; and 3) participants report ethnic group as non-Hispanic and racial group as either Black/African American or White/Caucasian. Participants with cLBP will be excluded if they have any concurrent medical conditions that could confound interpretation of outcome measures or coexisting disease that could preclude successful completion of the protocol (specific exclusion criteria are presented in the Protection of Human Subjects section).

Given that participants will be primarily recruited from a pain treatment clinic, it is reasonable to assume that many may be using daily opioid medications. We will not exclude participants using opioids daily as this could seriously hinder recruitment efforts or otherwise bias our sampling (e.g., only participants with low severity cLBP not receiving opioids). We are aware that both continued use and temporary withdrawal from these medications (should we ask participants to withhold) could affect pain perception. Therefore, participants will not be asked to withhold pain medications on the day of quantitative sensory testing. Rather, all medications currently being used for pain (e.g., opioids, NSAIDs, SSRIs, etc.) will be recorded and controlled in statistical analyses as needed.

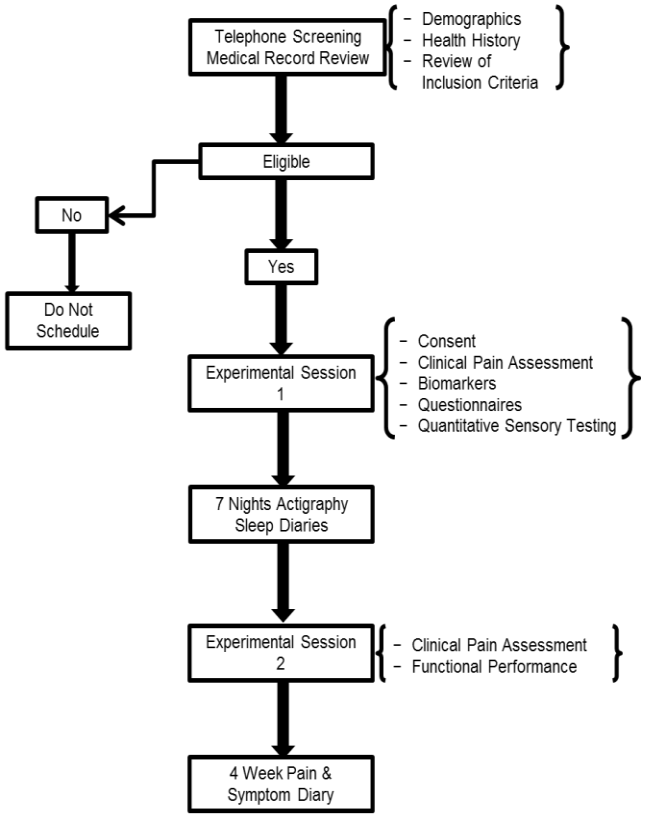

Figure 7: Flow diagram depicting matriculation through the study protocol.

D.1.2. Initial screening: All participants will undergo a cLBP screening interview using the recently developed research standards for defining cLBP proposed by the Research Task Force of the NIH Pain Consortium.[90] This will involve a review of each participant's UAB electronic medical record to confirm cLBP status and assess the reported duration of cLBP, current and past treatments for cLBP, comorbid conditions, and current medication use. Using the joint clinical practice guidelines from the American College of Physicians and the American Pain Society,[58] patients with cLBP will be placed into 1 of 3 broad categories: 1) nonspecific cLBP, 2) cLBP potentially associated with radiculopathy or spinal stenosis, or 3) cLBP potentially associated with another specific spinal cause. Patients placed into category 3 will be excluded if the cause of cLBP is determined to be ankylosing spondylitis, cancer or other malignancy, or in the context of autoimmune disease or other widespread pain condition (e.g., lupus, fibromyalgia). The screening will also assess demographic, SES, and health history information to ensure that no other exclusion criteria are

present. To ensure that a relatively equal number of Blacks and Whites with high and low SES are recruited, a stratified sampling approach will be incorporated for recruitment. This will be done by determining whether a participant falls above or below the poverty line (as a proxy for overall SES) based upon reported annual household income and number of occupants residing within the family/household using the 2015 HHS poverty guidelines.[101] In 2015 Alabama was the 6th poorest state in the Union, with 13% of Whites and 31% of Blacks living below the poverty line.[102] Therefore, we are confident in our ability to recruit individuals with high and low SES.

D.1.3. Demographic and SES measures: Ethnic and racial group will be determined by participant self-report using the standard Health and Human Services categories. We will recruit adults who report their ethnicity as non-Hispanic and their race as either Black/African American or White/Caucasian. Because racial groups often differ in socioeconomic status (SES),[103] and lower SES has been associated with increased risk of clinical pain[104] and increased prevalence of cLBP,[105] we will obtain a multidimensional battery of SES measures as part of this study. We will collect objective and subjective assessments of SES and social standing for individuals as well as the neighborhoods in which they live. The participant's self-reported educational attainment, annual household income, and occupational category will be used as an objective indicator of SES per the **Census Bureau Index of SES**.[106] The **Hollingshead Four-Factor Index of SES** will be used to assess four domains including educational attainment, retired/employed status, marital status, and occupational category/prestige.[107] The **MacArthur Scale of Subjective Social Status** will be used to measure participants' perceived social standing.[108] Research incorporating this measure has shown perceived social status to be determined by occupational position, education, household income, satisfaction with standard of living, and feelings of financial security regarding the future.[108,109] We will match U.S. Census tract data to participants' addresses **to define neighborhood SES**.[68] Lastly, participants will self-report whether they currently have health insurance as well as quantity and quality of ongoing cLBP management.

D.2. Experimental session 1

D.2.1. Clinical pain assessment: The **Patient-Reported Outcomes Measurement Information System (PROMIS)** pain intensity, pain interference, and pain behavior items will be used for this study.[110-112] For instance, patients will be asked to rate the intensity of their cLBP at its "worst" and "on average" over the past 7 days as well as the intensity "right now". The **Graded Chronic Pain Scale (GCPS)** is a reliable (Cronbach's alpha ≥ 0.80) and well-validated measure that evaluates global pain severity and pain-related interference over the past 6 months.[113] The GCPS yields a "Characteristic Pain Intensity" score and an overall "Disability" score. Taken together, the PROMIS pain intensity items and the GCPS will be our primary clinical outcome measures for data analytic purposes. The **Oswestry Low Back Pain Disability Inventory (ODI)** is a low back-specific instrument designed to address perceived disability in 10 areas: pain intensity, ability to lift objects, walking ability, sitting ability, standing ability, sleep, sex life, social life, traveling, and personal hygiene activities.[114]

D.2.2. Biomarker measures: All blood will be collected by research nurses at the UAB Clinical Research Unit prior to quantitative sensory testing. Vitamin D and CRP assays will be performed by the Physiology and Metabolism Core of the UAB University-Wide Interdisciplinary Research Centers (UWIRC) Program under the direction of Dr. Barbara Gower. Blood samples will be mailed to Dr. Sue Carter at Indiana University for assay of oxytocin. **Vitamin D assay:** Following blood collection and processing, serum will be stored in a -80 degree freezer. Serum 25(OH)D analysis will be completed by high performance liquid chromatography (total 25-hydroxyvitamin D = 25(OH)D2 plus 25(OH)D3) and enzyme immunoassay (Cayman Chemical) within six months of the date of collection. Clinical laboratory assessment of serum 25(OH)D best characterizes vitamin D status because it reflects vitamin D synthesized cutaneously as well as through dietary intake. Results of 25(OH)D testing will be shared with participants and if levels are found to be ≤ 30 ng/mL, they will be encouraged to discuss the result with a primary care provider. **Plasma oxytocin assay:** Plasma samples for the detection of oxytocin will also be collected, processed, and stored in a -80 degree freezer. Plasma oxytocin analysis will also be completed using high performance liquid chromatography with sample extraction and enzyme immunoassay (Cayman Chemical) within six months of the date of collection. It has been suggested that sample extraction and enzyme immunoassay may be the most appropriate way to accurately assess plasma oxytocin.[115] These assays are specific to oxytocin, but not vasopressin. **High sensitivity C-reactive protein (CRP):** Plasma samples for the detection of CRP will also be collected, processed, and stored in a -80 degree freezer. High sensitivity CRP was be quantified using Cayman Chemical CRP (human) ELISA Kits, which is an immunometric assay that can be used to measure CRP in plasma without prior sample purification.
The assay has a range from 46.9-3,000pg/ml and a limit of detection of approximately 46.9pg/ml.

D.2.3. Psychosocial questionnaires: The **Center for Epidemiological Studies – Depression Scale (CES-D)** measures symptoms of depression and is reliable and valid in both general and clinical populations.[116]

The CES-D items are relatively free of bias due to the pain and functional limitations associated with musculoskeletal disorders, and the CES-D is valid for use among low-income, minority persons as well as among middle class, white individuals.[117] The **Experiences of Discrimination (EOD)** measure will be administered to assess participants' self-reported experiences of racial discrimination across 9 different situations.[118] Participants indicate the frequency of each experience, how they responded to the situation, and their level of worry about discrimination. The EOD has shown good reliability and validity across multiple racial groups.[118] The **Injustice Experiences Questionnaire (IEQ)** will be used to assess perceptions of injustice.[82] The IEQ is a 12 item scale that asks participants to indicate the frequency with which they experience different thoughts concerning the sense of unfairness in relation to their injury. The IEQ yields two correlated factors that have been labeled severity/irreparability of loss and blame/unfairness. The IEQ has been shown to be internally reliable and to predict prolonged disability following musculoskeletal injury.[80] The **Multidimensional Scale of Perceived Social Support (MSPSS)** measures perceived support from three domains: family, friends, and a significant other.[119] Total and subscale scores range from 1 to 7, with higher scores suggesting greater levels of perceived social support. Adequate psychometric properties have been found with the MSPSS in several studies with young adults and adults in the United States and in Europe.[120] The **Pain Resilience Scale (PRS)** was developed as a pain-specific measure of resilience. In a recent study, this measure was shown to possess good psychometric properties, and its predictive validity of experimental pain outcomes was superior to general resilience measures.[121]

D.2.4. Endogenous pain modulation: All participants will undergo quantitative sensory testing for assessment of endogenous pain modulation using painful heat, mechanical, and cold stimuli in a laboratory session lasting approximately 2 hours. **Heat Testing Procedures:** Thermal stimuli will be delivered to the lumber region (i.e., most affected pain site) and to the non-dominant forearm, in randomized order, using a Medoc Pathway Thermal Sensory Analyzer (Ramat Yishai, Israel). Temporal summation of heat pain will involve brief repetitive suprathreshold thermal stimuli. The stimulus parameters for the heat testing procedures will be based on extensive experience in our laboratory and our previously published work.[92,122,123] **Punctate Mechanical Pain:** Punctate mechanical pain will be assessed at the lumber region (e.g., over erector spinae muscles) and the dorsal aspect of the non-dominant hand using a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300g of pressure. As in our previous studies, participants will provide a pain rating following a single contact of the monofilament, after which they will provide another pain rating following a series of 10 contacts at a rate of one contact per second.[92,122,123] The percent change (increase) between pain ratings for the single versus multiple contacts reflects temporal summation of mechanical pain. **Conditioned Pain Modulation (CPM):** CPM will be used to assess pain inhibitory function. The conditioning stimulus will be the cold pressor task (Thermo Scientific) applied to the dominant hand, which will be tailored for each participant to achieve a stimulus that produces moderate pain (i.e. a rating of 40-60 on the 0-100 scale) and can be tolerated for a 60-second period. The test stimulus will be algometry (Algomed, Medoc, Ramat Yishai, Israel) to assess pressure pain applied to the lumbar region and opposite ventral forearm. The CPM protocol will be conducted according to previously established protocols.[56,124] First, baseline PPTs will be assessed, after which the participant will immerse their hand in the cold water bath for 60 seconds and immediately afterwards PPTs will again be assessed at the testing sites. In order to operationalize CPM, percent change in PPTs from baseline will be calculated according to the following formula: [(conditioned PPT – test PPT) / test PPT) *100].[29] Higher percentages will reflect greater pain inhibition.

D.3. Actigraphy and daily diaries (7 days between experimental session 1 and 2)

D.3.1. Actigraphy: Objective sleep data will be acquired using the Actiwatch2 (Respironics, Bend, OR), a wrist-worn, watch-like actigraph. The Actiwatch2 is a solid-state accelerometer, or movement detector, designed to measure ambulatory activity. It will be used to measure daily sleep-wake patterns and record body movement (omni-directional, piezoelectric accelerometer with a sensitivity of >0.01 g-force). The Actiwatch2 has good reliability and criterion validity.[125,126] Actigraphy has been shown to be comparable to polysomnography[99] and studies have demonstrated the validity of actigraphic measurement in persons with and without chronic pain.[127,128]

D.3.2. Daily diaries: Participants will monitor and report on their sleep between the two experimental sessions in real-time using a pencil-and-paper consensus sleep diary.[129] This will be done in conjunction with the actigraphic measurement of their sleep. Diaries will be completed twice per day, before going to bed at night, and then again the following morning, to provide a measure of participants' self-reported sleep patterns and quality. In addition to sleep and napping behavior, the daily diaries will also include questions related to pain and mood as well as alcohol, caffeine, and nicotine intake throughout the day, and medication use.

D.4. Experimental session 2

D.4.1. Clinical pain assessment: For experimental session 2, patients with cLBP will again be asked to complete the **(PROMIS)** pain intensity, pain interference, and pain behavior items in order to address any recent changes to the quality of their cLBP over the past 7 days since experimental session 1 as well as at the present moment (i.e., "right now").

D.4.2. Functional performance measures: All cLBP patients will be asked to perform a series of functional performance measures consistent with those previously incorporated in Dr. Trost's pilot work (see **section C.3.2**), including transitioning from a seated to standing position, and then sitting again. Additionally, a Short Physical Performance Battery and Timed Up and Go Test will also be completed. The **Short Physical Performance Battery (SPPB)** consists of three measures of lower-extremity function: standing balance, 4-meter walking speed, and ability to rise from a chair.[97] These measures have been standardized and are widely used in older populations as measures of lower extremity function.[130] We have experience with the SPPB and have successfully incorporated it in a prior project examining a painful musculoskeletal condition.[131] The **Timed Up and Go test (TUG)** is a simple test used to assess a person's mobility and requires both static and dynamic balance. It measures the time that it takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down.[96] During the test, participants will be expected to wear their regular footwear and use any mobility aids that they would normally require. The TUG is used frequently in older populations, as it is easy to administer and can generally be completed by older adults.[132] The TUG has previously been shown to be related to chronic pain-related disability.[133] Any pain experienced during completion of the functional performance measures will be assessed using the 0-100 numeric rating scale.

D.5. Follow up data collection

D.5.1. Follow-up component – predicting pain in daily life: As a component of Specific Aim 3 and to translate the laboratory findings to participants' daily environment, all participants will be contacted by phone once per week for four weeks following completion of study session 2. Participants will be asked to report on symptoms of pain (average and worst intensity), mood, sleep, disability, and interference of pain with daily activities over the preceding week using appropriate PROMIS items banks.[111] We have successfully used a similar approach in a previous project to collect weekly follow up data.[92] Given that racial group differences in follow up data could be attributed to differences in treatments received or in comorbidities since completion of the experimental sessions, we will collect this information and control for these factors statistically, if needed.

D.6. Statistical methods

D.6.1. Statistical power: The power analysis for this study was completed with primary focus on the three hypotheses that comprise Specific Aim 1. We assumed the following race by SES interaction effect sizes for clinical pain severity (Cohen's f = .24), perceived disability (Cohen's f = .19), and functional performance difficulty (Cohen's f = .21) derived from out pilot data. Effect size conventions are .10 (small), .25 (medium), and .40 (large). Probability value was set at .05 and the desired power was set at .85. According to these parameters and effect sizes, a total sample size of 240 participants is required to detect all of the race by SES interaction effects hypothesized for Specific Aim 1 **(Table 5)**. These 240 participants will be allocated to four groups, such that there will be 60 low SES Blacks, 60 high SES Blacks, 60 low SES Whites, and 60 high SES Whites. Group sizes of 60 will provide greater than 95% power for detecting pair-wise differences while probing interaction effects based upon alpha level set as two-tailed .05/6 contrasts = .008 and Cohen's d ranging from 0.83 to 1.90 (see C.2.1. above). We plan to over-enroll by 10% to accommodate for participant attrition. Therefore, 268 participants will be recruited with the expectation that at least 240 will complete.

D.6.2. Data analysis: Data analysis will begin with calculating and comparing measures of central tendency (sample mean, sample median) and dispersion (sample variance, interquartile range) for all cLBP outcomes (e.g., PROMIS pain intensity, GCPS, ODI) as well as other study variables (CPM and TS, oxytocin, vitamin D, CRP levels, sleep, Perceived Injustice, Experiences of Discrimination, CES-D, etc.) according to race by SES groups. Confounding variables may include age, sex, pain medication use, engagement in treatments during the 4 week follow up period, and others as appropriate and will be considered as statistical controls.

Specific Aim 1: General Linear Models incorporating a 2x2 factorial design for Analysis of Covariance (ANCOVA) will be used to examine race by SES differences in cLBP outcomes including pain severity, disability, and functional performance. Race will include Blacks and Whites, while the Hollingshead Index will comprise the primary SES measure with participants split into high versus low SES according to previously published work.[134,135] Significant interaction effects will be probed using pair-wise contrasts with Bonferroni-adjusted alpha levels to examine differences across racial and SES groups, with emphasis on low SES Blacks compared to high SES Whites. Additional

Table 5: Sample sizes needed to detect hypothesized race by SES differences in cLBP severity, perceived disability, and functional performance with $p < .05$ and power = to .85.

	Effect size (f)	Sample size needed
Clinical pain severity	.24	158
Perceived disability	.19	240
Functional performance	.21	206

analyses will be completed considering other indicators of high and low SES including subjective social status (MacArthur) and neighborhood SES. This will be done to determine which aspects of SES are most relevant to consider when addressing cLBP outcomes.

Specific Aim 2: The hypotheses that comprise this aim suggest that pain-relevant biopsychosocial factors including endogenous pain modulation, biomarkers, sleep, and psychosocial functioning will also differ according to racial and SES groups. These hypotheses will be tested using 2x2 ANCOVAs in the same manner indicated in Specific Aim 1. Significant race by SES interactions will be probed using pair-wise contrasts adjusted for multiple comparisons.

Specific Aim 3: The analytic strategy is designed to test the hypothesis that the biopsychosocial factors included in this study will differentially predict cLBP outcomes in Blacks compared to Whites, and furthermore that the strength of prediction will vary according to high versus low SES. We will use a multiple regression framework to build separate models for Blacks and Whites. Within these models, SES will be included as an effect moderator when examining the associations of biopsychosocial predictors (independent variables) with cLBP outcomes (dependent variables). To illustrate how models will be built and data used, we offer examples. Separate models will be built for Blacks and Whites to determine whether endogenous pain modulatory processes (e.g., CPM and TS) predict functional performance (e.g., SPPB and TUG). Within each model the SES variables will be added to examine interaction effects (i.e., moderation), such that the strength of prediction between endogenous pain modulation and functional performance will be greatest for those with low SES. The same process will be used to examine whether aggregated actigraphic sleep and diary data differentially predicts pain in everyday life (e.g., average ratings of pain intensity collected across 4 weeks of follow up) according to race and SES.