Study Title: Social Stress, Inflammation, and Chronic Kidney Disease among African Americans

Short Study Title: Stress and CKD among African Americans

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Abstract

Chronic kidney disease (CKD) is a global public health problem. African Americans have a higher prevalence of late stage CKD than Whites and progress from early stage to late stage at a much more rapid rate. Biomedical explanations for African Americans' faster CKD progression prevail, with virtually no research attention paid to the role of social factors. Stress related to discrimination is a particularly compelling area of study in light of strong evidence demonstrating its linkages to CKD risk factors such as hypertension, diabetes, and obesity. The proposed proof of concept study will recruit 100 African American patients (both with and without diagnosed CKD) to determine whether discriminatory stressors are an important risk factor for CKD-related physiological processes and kidney functioning.

The _long-term goal_ of this research program is to understand the impact of and pathways through which discriminatory stress contributes to CKD progression. The _overall objective_ of this R21 application, which is the first step towards attainment of this long-term goal, is to obtain effect sizes for a larger prospective R01 and explore two hypothesized pathways (i.e., blood pressure reactivity and pathophysiological mechanisms) using a multi-method research design. This study will carry out the following _specific aims_:

1. **To examine associations between chronic stressors (i.e., discriminatory versus general), pathophysiological mechanisms (i.e., elevated inflammation and nocturnal blood pressure), and <u>poor kidney functioning</u> among 100 African American patients.**
   a. Based on a cross-sectional research design, we hypothesize that chronic discriminatory stressors will be associated with poor kidney functioning independent of other chronic stressors as mediated by CKD-related inflammatory biomarkers and autonomic arousal.

2. **To examine the impact of acute stressors (i.e., discriminatory versus general) on short-term changes in <u>CKD-related physiological processes</u> (i.e., increases in inflammatory markers and blood pressure reactivity) in patients from aim 1.**
   a. Based on an experimental research design, we hypothesize that discriminatory stressors will be more physiologically impactful than general stressors. Outcomes include several critical CKD-related inflammatory biomarkers and blood pressure reactivity assessed at three time points during the experimental manipulation.

Collectively, these outcomes are expected to support the advancement of science-based information about CKD that can be disseminated in order to improve health and quality of life.

I. Background and significance

The Problem of Chronic Kidney Disease among African Americans
Chronic kidney disease is a global public health problem that continues to increase in both incidence and prevalence, affecting more than 30 million adults in the United States.[1] The prevalence of CKD significantly increases with age[2] and is most commonly caused by diabetes, hypertension, and glomerulonephritis.[3] The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation established a classification system for determining CKD severity by using glomerular filtration rate as the determinant for the level of disease[4] (see Appendix 1). Based on this staging system, national prevalence data indicate dramatic increases in end stage renal disease (ESRD) from 1996 to 2013.[5] Moreover there is clear and compelling evidence of racial disparities in ESRD: African Americans have an ESRD prevalence that is almost four times that of Whites (5,671 vs. 1,432 per million population) and progress from early stage to late stage at a much more rapid rate.[5-7]

The Project Will Improve Scientific Knowledge of the Role of Social Stress in CKD
Scientific research to date has focused on genetic and biological explanations for African Americans' greater prevalence of ESRD than Whites. For example, African Americans have higher rates of diagnoses for the two leading causes of CKD (type II diabetes[8] and hypertension[9]) as well as other dietary and lifestyle factors that contribute to the progression of CKD.[10] Late referral to a nephrologist and socio-economic factors (including income and access to care) also explain part of the racial disparities in CKD progression.[11-13] However, even after controlling for all of these factors, racial disparities in ESRD remain.[12,14,15] Indeed, the growing literature on socioeconomic status (SES) is a platform to launch a conversation of the role of the social determinants of CKD progression,[16] but it cannot be where the conversation ends in light of evidence that race moderates this relationship. The relationship between SES and CKD is stronger for African Americans than Whites. [15,17]

The Need to Study Stress in Relation to CKD Rests on a Strong Scientific Premise
Several empirically-based conceptual models that consider how socio-cultural factors may contribute to racial disparities in CKD have been published in the peer-reviewed literature over the past decade.[10,14,18,19] For example, a conceptual model adapted by Norris and Agodoa[10] suggests the need to consider factors such as marginalization and discrimination, chronic stress, distrust, and neighborhood conditions to understand CKD outcomes. A recent heuristic model developed by Bruce et al.[19] seeks to integrate the socio-cultural factors hypothesized by Norris and Agodoa[10] and Norris and Nissenson[14] (e.g., stress, the social environment) with genetic, behavioral, and psychological factors and pathophysiological mechanisms to explain kidney outcomes. The Bruce et al.[19] model focuses on stress. It argues for strong influences of social environment and psychological factors on stress, which in turn relates to behavioral factors and pathophysiological mechanisms (such as inflammatory cytokines[20]), which then contribute to CKD risk factors (hypertension, diabetes, and obesity), and ultimately kidney outcomes. (Note that whereas the original Bruce et al. model includes blood pressure as a CKD risk factor, because blood pressure is reactive to stress we study it as a pathophysiological mechanism and leave diabetes and obesity as the key risk factors.) A strength of this model is that there is a large body of knowledge using rigorous research designs establishing certain critical pathways in other populations (e.g., research linking discriminatory stress to hypertension and obesity in healthy cohorts). [21-24] However, a major weakness is that the field has yet to embark upon empirical testing of other key pathways (e.g., research linking stress to kidney outcomes via the pathophysiological mechanisms proposed in this project) with few exceptions.[25]

The Project Will Improve Preventative Interventions to Delay CKD Progression
The ultimate goal of the proposed study is not to reduce the experience of social stress at the population level *per se*, but to understand whether these types of experiences have a deleterious impact on CKD outcomes and/or physiological processes and design psychological interventions with these stressors in mind. In this respect, experiences of racism and other social stressors are comparable to other forms of chronic (job strain, caregiving) or uncontrollable (breast cancer, loss, trauma) stress for which psychosocial treatments have been established. Current interventions to delay progression of CKD focus primarily on nutrition, lifestyle, and medical management of blood pressure and glucose and albuminuria. The proposed project establishes the need to determine whether stress reduction might also be an important target for future intervention.

II.   Goals/Aims:

This proof of concept study will recruit a sample of 100 African American patients, 80 with diagnosed CKD with equal numbers across stages 2, 3A, 3B, and 4 and 20 with no CKD diagnosis, to determine whether discriminatory stressors are an important risk factor for CKD-related physiological processes and kidney functioning in this understudied population (see Table 1).

Table 1. Stages of CKD

Stage	Description	Estimated GFR (mL per minute per 1.73 m^2)
1	Kidney damage with normal or increased GFR	$\geq$ 90
2	**Mild CKD**	**60 - 89**
3A	**Moderate CKD**	**45 - 59**
3B	**Moderate CKD**	**30 - 44**
4	**Severe CKD**	**15 - 29**
5	Kidney failure	<15 (or dialysis)

Drawing from a recent heuristic model by Bruce et al.,[19] it is theorized that the relationship between stress related to discrimination and kidney outcomes is mediated by inflammatory cytokines and blood pressure dysregulation. Further, because discriminatory stressors often co-occur with other chronic stressors (e.g., financial stress, occupational stress, relationship stress, and parental stress) in African Americans, we will also determine whether discriminatory stressors are independent of these other types of stress. The *long-term goal* of this research program is to understand the impact of and pathways through which discriminatory stress contributes to CKD progression. The *overall objective* of this R21 research project, which is the first step towards attainment of this long-term goal, is to obtain effect sizes for a larger prospective R01 and explore two of the pathways hypothesized by Bruce et al. (i.e., blood pressure reactivity and pathophysiological mechanisms) using a *multi-method* research design (i.e., both observational and experimental research methods). The *central hypothesis* of this study is that discriminatory stress is associated with poor kidney functioning and two potential mechanisms leading to poor kidney functioning -- increased inflammation and blood pressure dysregulation-- among African Americans with CKD. Using a multi-method design, we plan to objectively test our central hypothesis by pursuing the following *specific aims*:

Objective 1. To examine associations between chronic stressors (i.e., discriminatory versus general), pathophysiological mechanisms (i.e., elevated inflammation and nocturnal blood

pressure), and **poor kidney functioning** (as measured by eGFR and proteinuria) among 100 African American patients (80 with a CKD diagnosis and estimated glomerular filtration rate [eGFR] $\geq$15 or <90; 20 without a CKD diagnosis).

❖ Based on a cross-sectional research design, we hypothesize that chronic discriminatory stressors will be associated with poor kidney functioning independent of other chronic stressors as mediated by CKD-related inflammatory biomarkers and autonomic arousal.

Objective 2. To examine the impact of acute stressors (i.e., discriminatory versus general) on short-term changes in **CKD-related physiological processes** (i.e., increases in traditional and novel inflammatory markers and blood pressure reactivity) in patients from aim 1.

❖ Utilizing an experimental research design will allow us to explore causal mechanisms through which discriminatory stress may contribute to CKD-related physiological processes. We hypothesize that discriminatory stressors will be more physiologically impactful than general stressors. Outcomes include several critical CKD-related inflammatory biomarkers (i.e., Monocyte Chemoattractant Protein-1 [MCP-1],, Interleukin-6 [IL-6], and the novel soluble urokinase-type plasminogen activator receptor [suPAR][26]) and blood pressure reactivity assessed at multiple time points during the experimental manipulation.

It is anticipated that these aims will yield _outcomes_ with great clinical and public health impact. First, we will refine methods to experimentally manipulate exposure to general and discriminatory stressors and assess their relationship to clinically important outcomes. Second, we will use novel inflammatory markers alongside the more standard ones to determine whether they mediate these relationships. Collectively, these outcomes are expected to have an important _positive impact_ on the field of public health and the mission of NIDDK through the advancement of science-based information about CKD that can be disseminated for the purpose of improving health and quality of life.

III.   Study Design

Figure 1. Study Design

This multi-method study will collect data from 100 African American patients (80 patients in stages 2, 3A, 3B, and 4 of CKD and 20 with no CKD diagnosis) utilizing both cross-sectional (aim 1) and experimental (aim 2) research designs (see Figure 1). The proposed methods were designed to maximize the robustness of the data while minimizing bias in study design, methodology, analysis, interpretation, and reporting. The use of validated

instruments enhances the study's scientific rigor for aim 1. Random assignment to condition (for aim 2) eliminates selection bias as one potential threat to internal validity among others.[27] Additionally treating the two groups equivalently in terms of data collection methods and instrumentation improve internal validity by minimizing testing and instrumentation effects.[27] Detailed recruitment and data collection protocols further enhance the scientific rigor of the study because they ensure equal treatment of participants regardless of study condition. Finally, by intentionally studying patients along the continuum of CKD, we can explore whether there are "critical periods" in CKD progression where the relationships with stress are strongest.
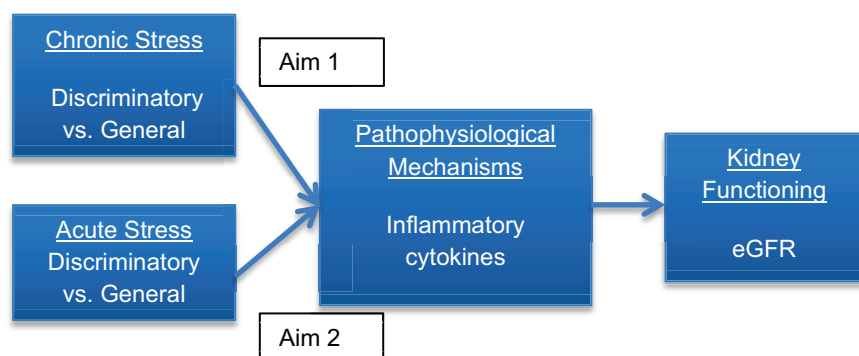
A. Organizational Structure

This study is funded by the National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and was developed by faculty in the Rollins School of Public Health. An internal medicine clinic within Emory University Hospital Midtown (at which Co-Investigator Dr. Janice Lea currently serves as a practicing nephrologist) and the Georgia Clinical and Translational Science Alliance (GCTSA) (for which Dr. Thomas R. Ziegler serves as Co-Director) will serve as study sites. Additionally, study participants' bio-specimens will be analyzed at the Molecular Neuroimmunology Laboratory in the Department of Epidemiology at Emory. Bradley Pearce, PhD, who also serves as a Co-Investigator on this project, will oversee analyses of select blood samples. Outside laboratory resources will be used for processing and analyses of the remaining biospecimens.

B. Setting and location

This study will take place in Atlanta, GA, within a region characterized by high rates of CKD.[28] We will recruit patients seen at a single clinic located at Emory University Hospital Midtown where Dr. Janice Lea (Co-investigator) practices. This clinic serves patients along the CKD continuum as well as those with no CKD diagnosis. The five physicians in this clinic see approximately 150 African American patients per week demonstrating the feasibility of recruiting 100 patients in eight months. Our prior experience conducting clinical studies suggests the importance of educating clinic staff about the study so that they can assuage patient concerns about participation. However, their involvement in the recruitment process is minimal, is not coercive, and does not undermine the voluntary nature of study participation.

C. Population to be studied
Inclusion criteria are as follows:
- Patient at Emory University Hospital Midtown
- Self-identify as African American or Black
- Age 25 to 65
- eGFR ≥ 15, or <90

Exclusion criteria are as follows:
- Mental disorder that prevents the completion of the Computer Assisted Personal Interview (CAPI) and the stressful recall manipulation
- Currently on maintenance dialysis
- Unable or unwilling to undergo intravenous catheterization

D. Recruitment
Study participants will be 100 African American adult aged 25 to 65 receiving services at Emory University Hospital, Midtown. Of these, 80 will have a CKD diagnosis and 20 will not. We will rely heavily on recruitment strategies that have been successful at recruiting African American patients into other clinical studies.[29,30] Initially, clinic staff will identify potential participants through the clinic appointment system, including those who meet the inclusion criteria through a preliminary review. The clinic staff will share this list with the study project coordinator, who will mail potential participants a letter inviting them to participate (see attached for sample letter). The letter will outline information about the study (including purpose and participant requirements), and interested participants will be instructed to contact the project coordinator to

learn more about the study. If he/she is interested in participating, he/she will have the opportunity to review specific participation requirements at their next appointment, or upon next visit to the clinic. Participants will provide consent and be enrolled in person. The second tier of participant recruitment will consist of the project coordinator using the potential participant list to call individuals who are patients in the clinic and potentially eligible for the study, and inform them about the opportunity to participate in the study. Those individuals who are interested in participating will have an opportunity to review specific participation requirements at their next appointment, or upon visiting the clinic, and will provide consent and be enrolled in person. Next, the project coordinator will provide clinic staff with a recruitment postcard (see attached example) which will be included in potential participant's exit material after their doctor's visit. The postcard provides study information, and instructs patients to contact study staff through email or phone calls if they are interested in the study. Finally, study recruitment flyers will be placed throughout the clinic (see attached for flyer example) and remain in the clinic until the conclusion of the study. The flyer provides preliminary information about the study, and instructs patients who may be interested in participating to call or email the project coordinator for more information. The project coordinator will provide further information about the study; those individuals who are interested in participating will have an opportunity to provide consent and be enrolled in person at their next appointment time. We will continue this quota sampling and recruitment process until we have enrolled 20 participants in each of the five categories: no CKD diagnosis and CKD diagnosis stage 2, 3A, 3B, and 4.

Study enrollment will occur in person within the clinic. The previously mailed letter, phone call and posted flyers will serve as an initial introduction to the study. Upon study enrollment, we will work with clinic staff to verify stage of CKD diagnosis (where applicable) to ensure that we are achieving the desired quotas. We will continue recruitment until the desired sample is achieved.

E. Field Methods

Data Collection Overview
Study participation entails completion of a computer administered personal interview (CAPI) that assesses experiences of general and discriminatory stress, behavioral and socio-economic variables, and other psychological characteristics. Upon completion of the CAPI, participants would be scheduled to attend a second session. During this session the experimental manipulation entails them being asked to recall a general or discriminatory stressor (the participant is randomized to one of the two groups), while changes in blood pressure and inflammatory processes are monitored. Finally, participants provide blood pressure assessments over a 24-hour period using an ambulatory blood pressure monitor (ABPM). These methods are described below.

Data Collection Procedures

Day 1: Consent, CAPI and 24-hour Ambulatory Blood Pressure Monitor (ABPM)
Day 1 of data collection will occur at the Nephrology clinic within the Emory University Hospital, Midtown location. Those who consent to participate in the study will first complete a CAPI in a small private room at the clinic immediately following their appointment. This is a self-administered survey in which responses are directly entered into an iPad at the time of administration, thereby eliminating the need for subsequent data entry. REDCap software will be used to securely collect and manage CAPI-questionnaire data. The key advantages of this method include allowing the interviewer to answer respondent questions, probe for adequate

answers, and accurately follow complex instructions or skip patterns.[31] The survey will assess participants' experiences of general and discriminatory stress, behavioral and socio-economic variables, and other psychological characteristics. Participants will be paid a portion of the monetary incentive ($50) at the conclusion of the survey interview. The proposed CAPI-questionnaire is attached.

Prior to leaving the study site, the project coordinator will fit each participant with an ABPM, and provide detailed instructions on how to use and care for the device, (including removing the device for showering). Participants will also receive a handout of these instructions for reference at home (see attached). Participants will be asked to wear the ABPM for 24-hours, beginning the time they leave the clinic. Participants will return the ABPM the following morning between 9:00AM and 12:00 PM, or when their second day of participation is scheduled. Dr. Lewis (Co-Investigator) has used this approach in a recently completed pilot study with African American patients. Her prior experience demonstrates good compliance with adequate data readings and the return of the equipment. Blood pressure readings will be taken at 30 minute intervals, except between the hours of 10:00PM and 8:00AM when they are taken at 60 minute intervals. All blood pressure readings between 10:00PM and 8:00AM will be considered nocturnal blood pressure. In addition, participants will be asked to record an anticipated time they fell asleep, and the time they were awake the following morning using a diary (see attached). These data will be used for further analyses of daytime and nocturnal blood pressure readings. Participants will be expected to return the ABPM on Day 2 of data collection, which will be scheduled for 1-2 days from Day 1 of data collection using the CR-Assist appointment program.

Blood pressure readings captured during participants' 24-hour ABPM wear period will be reviewed once participants return the device. We anticipate these blood pressure readings to be beneficial knowledge to participants and their overall health plan, and as a result will retrospectively provide these readings to participants and their physician, as appropriate. The project coordinator will review all blood pressure readings upon return of the device, and relay all readings to Dr. Lea (Co-Investigator and nephrologist) for review. Potentially concerning readings (>170/110 mm Hg) will be flagged for immediate review, and Dr. Lea will contact participants with alarming readings by phone, as determined by her review. Participants with healthy / normal blood pressure readings may also benefit from this information, and as a result, will be notified of these numbers via mail from Dr. Lea along with information about what the readings mean for their health. All participants will have the 24-hour blood pressure readings incorporated into their personal health records; nephrology clinic staff will be responsible for integrating these numbers into participants' electronic health records within the nephrology clinic. Practices for reporting blood pressure readings will be outlined in the participant consent form (see attached).

Day 2: Experimental manipulation & ABPM return
Day 2 of data collection will take place at the Georgia Clinical and Translational Science Alliance (Georgia CTSA), Emory University Hospital Clinical Research site at the Atlanta Midtown location within a room with a door (see attached). All Day 2 data collection appointments will be scheduled between the hours of 9:00 AM and 11:00 AM to account for diurnal changes in inflammatory markers. First, participants will return the ABPM and the ABPM diary to the project coordinator.

Prior to initiating data collection on Day 2, study staff will retrieve a History & Physical (H&P) form from the participant's Emory physician. The H&P form is an official record of a physical from a physician, and must have been obtained within the past 30 days to confirm that patients are fit to participate in the study. Study staff will upload the H&P form into the CR-assist appointment system for easy retrieval at the participant's next visit. Participants will be

instructed to bring a list of current medications and to indicate any medical conditions on a patient history form (see attached). We will document these medications and any reported medical conditions (in addition to any reported conditions on participants' medical charts), and control for them in analyses.

Participants will first provide height and weight measurements, a urine sample, and baseline blood pressure testing. A research nurse will insert an intravenous catheter, and take an initial blood draw (up to 4 mL to measure A1C and up to 4 mL to measure creatinine) and allow for a 30-minute habituation period so that the participant adapts to the indwelling catheter. Once the participant has adapted, participants will be asked to rate their level of distress using the Subjective Units of Distress Scale[32] (SUDS). Participants will be asked to rate their level of distress on a linear scale of 0 to 100, with 100 being the highest. The nurse will take a blood draw (up to 6mL to measure inflammatory biomarkers and up to 4mL to measure eGFR).

Figure 2. Day 2 Data Collection, Experimental Manipulation

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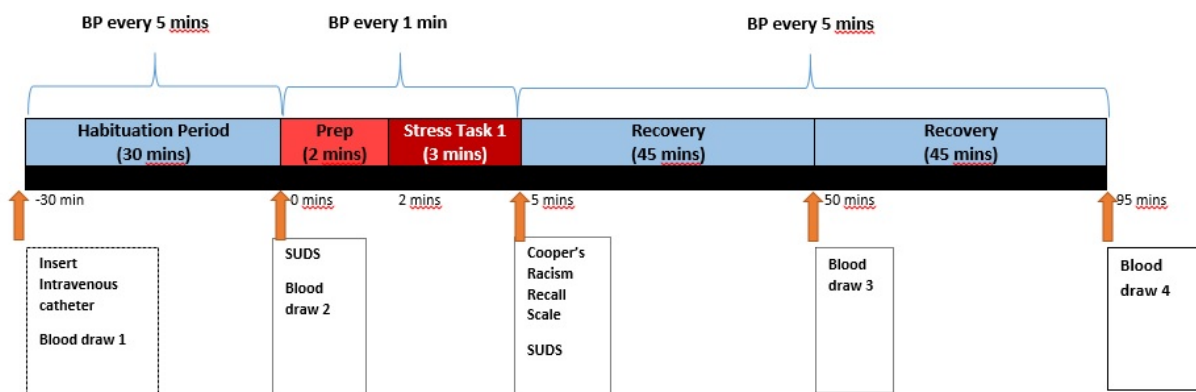
Next, participants will undergo a moderate psychological stress adapted from the commonly used Trier Social Stress Test (TSST)[33]. The TSST protocol has been adapted for use in recalling race-related experiences[34] underscoring its appropriateness for our protocol. Dr. Vaccarino (Co-Investigator) and colleagues, have also used a similar experimental protocol and will provide related expertise for this project.[35,36] Participants will be asked to recount one real-life stressful situations; one event will be a stressful race-related event and one event will be a stressful event that is not race-related. We will randomize participants such that half will recall the racial experience and half will recall the non-racialized stressful event. Each participant will have an equal chance of being placed in the racialized or non-racialized experience group. The Project Coordinator will provide instructions using a script. Participants will be given two minutes to prepare their statement, and three minutes to deliver the statement. There will be an 'audience' present at each participant's speaking task. Aligning with previously conducted involving audiences[33,35-38], each audience will include two observers who are of same race as the participant (African American), to heighten stress responses. Observers will wear white coats, and will be trained on the study protocol such that their behaviors are identical for each

manipulation task. The audience will be trained to remain neutral during the task, told to not show empathy and not to smile at any time during the test. Observers have not yet been identified, however once determined, the individuals serving as observers will obtain a CITI certification, and study staff will submit observer credentialing as amendment modification to the protocol. The project coordinator will also remain in the room while participants recall each designated stressful experience. Blood pressure readings will be taken every 1 minute during the participant's preparation time and the actual recall task. The participant will be expected to use the entire three minutes for recall in each exercise; the project coordinator will cue the participant to continue until the 3-minute mark via standardized prompts from a script. Participants will be asked to rate their level of distress caused by the stressful event using an adapted version of Cooper's racism recall scale.[34] and again rate their level of distress on a linear scale (0 to 100) using the SUDS[32]. Participants will undergo a 45-minute recovery period after the first recall task; blood pressure readings will be taken every 5 minutes during this period. Immediately following the first 45-minutes of recovery, participants will provide a third blood draw (6 mL). Participants will undergo another 45-minutes of recovery, and provide and one final blood draw (6 mL) at the conclusion of the recovery period.

Over the course of the study, participants will provide 3, 4 mL samples of blood and 3, 6mL samples of blood. A total of up to 30 mL may be taken over the course of the study. The project coordinator will debrief participants on the purpose of the experimental manipulation and common reactions to it. Participants will also be debriefed on the entire experimental manipulation experience, including the audience's purpose. Participants will be paid $150 at the conclusion of Day 2 ($50 for return of ABPM and $100 for completion of experimental manipulation). The experimental protocol along with data time points are outlined in Figure 2.

Data Sources
Participants will be asked to provide data from the following sources:

- **Cross-sectional survey data** that are provided by completing the CAPI (see attached)
- **Medical chart data**, used only to verify their last eGFR in order to achieve equal numbers of participants by study stage/CKD diagnosis
- **Biological data** in the form of blood and urine in order to assess kidney functioning and inflammation
- **Biological data** in the form of height, weight, and blood pressure to assess standard control variables (i.e., Body Mass Index) and blood pressure reactivity

Table 2 below lists the key constructs that will be measured, how they will be assessed, and the data source.

Table 2: Key constructs, measures, and data sources

Construct*	Measure	Data Source
Study Aim 1 (Chronic General and Discriminatory Stress)		
Chronic General Stress	Perceived Stress Scale, Financial stress, Neighborhood stress scales	Cross-sectional survey (CAPI)
Chronic Discriminatory Stress	Everyday discrimination, Major experiences of discrimination, Vicarious exposure to discrimination scales	Cross-sectional survey (CAPI)
Inflammation	MCP-1,, IL-6, suPAR[26,39]	Baseline blood draw
Autonomic arousal	Nocturnal blood pressure	ABPM
Kidney functioning	eGFR based on the abbreviated Modification of Diet in Renal Disease study equation[40,41]	Baseline blood draw

Kidney functioning	Proteinuria based on the albumin-creatinine ratio[42]	Baseline urine sample
Study Aim 2 (Acute General and Discriminatory Stress)		
Subjective ratings of distress	Subjective Units of Distress Scale (SUDS)[32]	Cross-sectional survey (SUDS)
Subjective ratings of recall distress	Cooper's Racism Recall Scale[34]	Cross-sectional survey
Inflammation	MCP-1, IL-6, suPAR[26,39]	Blood draw at 2 time points
Autonomic reactivity	Blood pressure	Blood pressure reading

Research Instruments and Assessment

i. **Chronic General Stress**. The *Perceived Stress Scale (PSS)* assesses different areas of life stress (e.g., overall stress, financial stress, occupational stress, significant other stress, parental stress, and stress within friendships). Moreover, the PSS has documented validity and reliability, and is short (14 items) and easy to administer.[43] A total score is derived by summing responses to all items, with higher scores indicating greater perceived stress. The *Financial Adjustments* and *Can't Make Ends Meet* scales by Conger and Elder [44-46] will be used to measure financial strain and stressful financial events. [45-47] The *Can't Make Ends Meet* scale assesses the overall feeling that financial resources are insufficient (e.g. "During the last 12 months, how much difficulty have you had paying your bills?"); while the other scale captures adjustments made due to inadequate finances (e.g. "postponed medical or dental care to save money"). Ongoing stressful life events were measured using the *Chronic Burden* scale by Bromberger[48].

ii. **Chronic Discriminatory Stress**. Based on recent recommendations,[49] we plan to assess discrimination comprehensively, via multiple measures. Exposure to "everyday" forms of discrimination will be assessed with the Detroit Area Study (DAS) *Everyday Discrimination Scale* [50], adapted by Dr. Lewis and colleagues. This scale asks participants to indicate the frequency with which they experienced various forms of interpersonal mistreatment in their day-to-day lives over the previous 12 months. A single attribution item assesses the main reason for these experiences.[51] The *Major Experiences of Discrimination* scale and *Vicarious Exposure to Discrimination* using modifications made in prior studies [52,53] measures experiences of unfair treatment over the lifespan in domains such as employment, police interactions, housing, and healthcare. Additional attribution items assess the reasons for these experiences (e.g., race/ethnicity, gender, education).[51]

iii. **Inflammatory Markers.** The inflammatory markers were selected based on our own pilot studies, their sensitivity to acute stress induction [54,55] and strong associations with CKD. [26,56] The initial measure of inflammation will be based on the baseline blood draw. Plasma samples will be stored in -80ºC until used for analysis in duplicate. To quantitate levels of IL-6 and MCP-1, we will employ the MesoScale system (MSD Rockville, Maryland) according to the protocols supplied by the manufacturer, which includes generation of a 6-7 point standard curve with standards validated by the company. The MSD system uses electrochemiluminescence for high sensitivity with a dynamic range of 0.06–488 pg/mL for IL-6, and 0.09–375 pg/mL for MCP-1. For suPAR we will use the Virogates (CEDARLANE Laboratories, Burlington, NC) suPARnostic® ELISA according

to the protocols supplied by the manufacturer. This assay has a high sensitivity (0.1 ng/mL) giving consistently quantitative results in plasma samples.

iv. **Autonomic Arousal.** Ambulatory Blood Pressure (ABP) will be assessed over 24 hours, using the SpaceLabs model 90217 (Issaquah, WA), a small, noninvasive device.[57] Patients will be fit with the monitor and trained on proper application and removal techniques. They will wear the monitor for up to 24 hours, removing it only to shower or bathe. Prior to fitting the monitors, patients will be asked about their regular sleep and wake times, and monitors will be programmed to record systolic (SBP) and diastolic blood pressure (DBP) every 30 minutes during the day and every 60 minutes during the night. Patients will be provided with a bedside diary, to record actual sleep and wake times, and any medications taken. Following the ABP assessments, BP readings will be screened, and values that are ±3 standard deviations from the participant's individual mean will be deleted. Remaining valid values will be used to compute average daytime and nighttime SBP and DBP for each patient. *Note:* Because nocturnal BP is believed to be the most deleterious for later outcomes,[58] our aims do not include BP dipping as a primary outcome; however, BP dipping will be assessed and analyzed in exploratory analyses, as detailed in Gallo et al.[59]

v. **Kidney Functioning**. We will use eGFR to measure kidney function using the abbreviated Modification of Diet in Renal Disease study equation as is recommended.[41,42] Thus, we will measure serum creatinine from a baseline blood draw. Along with age, gender, and race, this information will be used in an online GFR calculator that is made available by the National Kidney Disease Education Program. At baseline, participants will provide a urine specimen so that we can determine the protein/creatinine ratio.[42]

vi. **Covariates**. Covariates to be assessed include behavioral factors (e.g., smoking, alcohol use, unhealthy diet, physical activity), socio-economic factors (e.g., health insurance status, income, and education), psychosocial factors (e.g., depression, quality of life), comorbidities (e.g., health conditions, medications, blood glucose control measured via HbA1C, and ApoL1 status), and demographics such as age, sex, and body mass index. Depressive symptoms will be assessed with the Beck Depression Inventory (BDI),[60] which is a self-administered 21-item scale that has acceptable sensitivity and specificity with regards to a clinical diagnosis of depression, and also provides a continuous measure of depressive symptoms. We will also assess previous self-reported diagnosis of major depression and previous use of antidepressant medications in addition to kidney disease quality of life.[61]

vii. **Acute vs. Discriminatory Stress Experimental Manipulation.** At the end of the rest period, patients will asked to recall a personally relevant stressor, involving a general or racism-related stressful experience. Participants will be randomized into one of the two recall groups.. In the general stress protocol, participants will be asked to give a detailed account of a stressful experience (non-racial in nature) in which they felt so upset, angry, or annoyed at the time that talking about it during the clinic visit might still be upsetting to them. In the racism recall protocol, patients will be asked to provide a detailed account of a stressful experience involving *racism*-- one where they were so upset/angry/annoyed at the time that talking about it during their visit might still be upsetting to them. In both scenarios, patients will be asked to visualize the situation and recall the details of what happened, including: 1) where they were; 2) who else was there; 3) what was said and done (by the participant and by any other individuals present

at that time; 4) how they felt at the time and 5) the most stressful/upsetting aspect of the experience. Patients will be given 2 minutes to prepare and 3 minutes to recount their experience for either the racial and non-racial stressful experience. This protocol has been used in other studies of African Americans [34] and is adapted from a widely used mental stress protocol used in studies of anger.[62,63]

Subjective Ratings of Distress. In order to enhance the scientific rigor of this study, we will conduct a manipulation check to determine whether the experimental manipulation had its intended effect on study participants. Thus, subjective levels of distress will be measured immediately before and after the recall task. Using the Subjective Units of Distress Scale[32] patients will be asked to rate their level of distress on a linear scale of 0 to 100, with 100 being the highest. Participants will also be asked to assess their level of stress directly related to reliving the stressful experience using an adapted version of Cooper's Racism Recall scale[34].Patients will rate their level of distress at the time of the event, and currently while thinking about the event on a linear scale of 0 to 10, with 10 being the highest.

viii.   **Inflammatory and Blood Pressure Reactivity.** Levels of inflammation will be measured at three time points during the experimental manipulation (immediately before the experimental manipulation, 45 minutes after the manipulation and 90 minutes after the manipulation) as shown in Figure 2. A description of the inflammatory markers is provided above under "Aim 1 Assessments". Systolic and Diastolic blood pressure will be assessed every 5 minutes during the rest and instruction period, every minute during the preparation and recall task, and every 5 minutes during recovery, as shown in Figure 2. Mean scores for rest, recall task, and recovery will be calculated by averaging the readings taken during each period. Blood pressure reactivity will be a change (or delta) score, calculated as the mean of the scores during the recall task minus the mean of the scores during rest, designed to represent the change in blood pressure induced by the recall task.

Overall Time Burden

Study participation occurs over the course of 2 days (Day 1=consent, CAPI and 24-hour Ambulatory Blood Pressure Monitor (ABPM); Day 2= experimental manipulation and ABPM return). Those who agree to participate in the study will be consented at the clinic and asked to complete the self-administered survey with responses entered into an iPad (approximately 1 hour). At the conclusion of Day 1, participants will be fitted to wear ABPM assessing their blood pressure over 24-hours and asked to return the device to the study site upon return for Day 2 of data collection. In the second session, participants will provide a urine sample and undergo baseline blood pressure testing. A research nurse will insert an intravenous catheter (allowing for a 30-minute habituation period so that the participant adapts to the indwelling catheter) and take a baseline blood draw. Participants will also be asked to recall a racial or non-racialized upsetting experience (approximately 3 hours). In total, participant time burden is approximately 4.5 hours, plus the 24-hours wearing the ABPM.

Storage of Biological Samples

Biological samples will be analyzed for blood biomarkers relevant to psychosocial stress and kidney disease in the laboratory of Dr. Pearce. In order to protect privacy, all samples will be assigned an identification number that does not include personal information. After samples have been centrifuged, the plasma, serum and buffy coat will be aliquoted and stored at -80°C. The sample ID will be barcoded and this barcode and sample ID will be used to label stored

aliquots.   If any samples remain after analysis, they may be stored under the control of the Kimberly Arriola, PhD (PI) and Brad Pearce, PhD (Co-Investigator).

The samples will be stored for as long as they are useful, unless the participant asks us to destroy their sample sooner. If a participant chooses to have his/her sample material destroyed, he/she can do so by contacting Dr. Kimberly Jacob Arriola, who will provide Dr. Pearce with the required study and subject numbers. Any remaining blood samples will be located and destroyed. The PI will provide written confirmation that the sample was destroyed to the participant. The samples will not be distributed to anyone outside the immediate study team without express approval from IRB.

F. Informed Consent Process

The consent process will be conducted in-person by the study staff, in a private location near the waiting room in order to maximize convenience and privacy for the participant. An IRB-approved written informed consent will be obtained from each participant at entry into the study; elements of informed consent will include: (a) participant reviews the study consent form; (b) investigator(s) or study staff review the consent with participants to confirm understanding and answer any pending questions; and (c) participant signs the consent form once the investigator(s) or study staff are convinced that the protocol is understood. Key elements of the consent form describe the voluntary nature of study participation, clarification that the decision to join or not join the research study will not affect the participant's status as a patient, and that participants are free to withdraw at any point in time. The consent form includes a standard HIPAA Authorization document as well. After signing the consent form, participants will be given a hard copy of the form for their own records. Please see the attached consent form for details.

IV.   Potential Risks/Discomforts to Study Participants and measures to prevent occurrence

Possible risks are related to:

1. CAPI: Being asked questions about the stress in participants' lives may cause them to have unpleasant and/or upsetting feelings.
2. Intravenous catheter: This can result in infection, bruising of the skin, or a blood clot in the vein. Participants may have some discomfort from the blood drawing. The risk from blood drawing is minimal, but may include bruising and infection.
3. Experimental manipulation: Recalling an upsetting experience may be unpleasant.
4. Blood pressure monitoring: Wearing the ABPM throughout the day and night may be inconvenient for participants, and some people may experience sleep disturbance while wearing the device at night. Some individuals might also experience some bruising where the cuff is located.

V.   Benefits

Participants may not derive personal benefit from their involvement in this study. However, participants may find some of the information they receive from this study helpful. For example, participants will receive a detailed report of their nocturnal blood pressure after wearing the ABPM device. Participants with healthy reports may use this information to continue healthy practices, and participants with concerning reports may use this information to seek professional

counsel on how to improve blood pressure readings. Additionally, what we (the research team) learn from this study will inform the development of a program of research that generates new understanding of the role of social stress on chronic kidney disease progression.

VI.   Compensation for time and effort:

Participants will be offered a $200 monetary incentive for completing the study all steps of the study. Study participation occurs over the course of 2 days. Participants will receive $50 for completing the CAPI; $50 for return of the ABPM and $100 for completing the experimental manipulation. If participants return on Day 2 without the ABPM, the $50 incentive for its return will be withheld until the equipment is returned. This methodology addresses concerns about participant fatigue by scheduling assessments over the course of several days.

VII.   Data Analysis: Data Management and Monitoring:

We will minimize the risk of loss of confidentiality by keeping all hard copy documents in a locked file cabinet; soft copy files will be on a password-protected secure network drive. The file that contains the crosswalk between participant identification codes and their names (allowing us to ensure that samples are properly matched with each other and with the questionnaire data) will be password protected, also on a password protected secure network drive, in order to prevent theft or loss of data. All survey data will be retrieved and stored using REDcap software, which is HIPAA-compliant.

VIII.   Plans for analysis, statistical and/or otherwise:

The study team will conduct data analyses within offices of the Department of Behavioral Sciences and Health education at Emory University. All data will remain de-identified during data analyses to protect participants' identities.

A. Exploratory Analyses
We will start by creating a data set that merges the survey data will all biometric data. Traditional data entry for the survey data will be unnecessary as data will be imported directly into SPSS from the REDCap software that houses the CAPI-questionnaire. Data will be cleaned, coded, and examined for any missing data or unlikely values. We will examine frequency distributions for all variables, with particular attention to variable ranges, missing values, and transforming variables as needed, depending on evidence of internal consistency within scales. Next, we will conduct exploratory analyses to determine whether participants with the different sequences (i.e. race-related recall first or second) differ on demographic, clinical, or behavioral variables. Specifically, we will use logistic models to regress recall sequence on all relevant variables. If significant differences are identified, we will conduct further analyses by stratifying by these particular variables and consider adjustment for these variables in our main analyses as described below.

B. Main Outcome Analyses
These analyses are driven by the two hypotheses stated above: (1) Chronic discriminatory stressors will be associated with poor kidney functioning independent of other chronic stressors

as mediated by CKD-related inflammatory biomarkers and autonomic arousal; (2) Discriminatory stressors will be more physiologically impactful than general stressors on critical CKD-related inflammatory biomarkers and blood pressure reactivity.

The first hypothesis is a meditational hypothesis. We recognize that Baron and Kenny[64] methods for testing mediation are among the most widely cited, but also acknowledge that there are convincing critiques of this approach such as the requirement that there be a significant direct effect of the independent variable on the outcome in order to proceed with meditational analyses.[65,66] Thus, we will use meditational methods proposed by Zhao et al[65] that entail first running the Preacher and Hayes[67] SPSS syntax commands to generate "bootstrap" results for the indirect effect of chronic discriminatory stress (controlling for general stress) on each of the two kidney outcomes (eGFR and proteinuria) through the inflammatory pathway as measured by each of the proposed biomarkers (MCP-1, IL-6, suPAR). Bootstrapping relaxes assumptions about the shape of the sampling distribution of the indirect effect over repeated sampling from the population.[68] These analyses will control for relevant covariates. Next we will classify the type of mediation using the Zhao et al typology (complementary, competitive, indirect only, direct only, or non-mediation), and proceed with interpreting the findings in light of our hypotheses. We will consider using structural equation modeling as another technique recommended to test mediation.[69,70]

The second hypothesis will entail use of a 2X3 ANOVA to simultaneously test the main effects of stress recall (race-related or not) (discriminatory stress vs. general stress) and data collection time point (rest, stress, and recovery) on each of the outcomes (i.e., each inflammatory biomarker and blood pressure), also controlling for the relevant covariates. This test provides a form of economy by examining multiple effects at a time, while also allowing us to study the interaction between study condition and time.[71]

C. Statistical Power

The proposed proof-of-concept study is designed to generate effect sizes to inform a future power analysis and thereby establish the legitimacy of studying this topic in a subsequent large-scale clinical trial. Thus, it is not intended to achieve the level of power to demonstrate statistical significance as is common in larger studies. Nevertheless, regarding study aim 1, if we were to perform a multiple regression with 8 predictors that explain just 15% of the variance in a given outcome, we would achieve 84% power at α=.05 (http://danielsoper.com/statcalc3/calc.aspx?id=9) at N=100. For aim 2, collecting data at multiple time points is one way to maximize power. If we just consider the two study groups (intervention and control) we would achieve power of .80 to detect a medium effect (.25) at α=.05 with a sample of just 64 participants.[72]

IX.   Training of study team

All research staff maintains a current CITI, (Group 3 Social/Behavioral) certification. Proof of certifications has been uploaded for further review. Corresponding study team members (including members of the Georgia CTSA team and nurses within the Emory University Healthcare Nephrology clinic) will undergo study-specific training.

X.   Plans for monitoring the study for safety

The Data and Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by Emory University. An IRB-approved written informed consent will be obtained from each participant at entry into the study; elements of informed consent will include: (a) having the participant review the study consent form; (b) having the investigator(s) or study staff meet with the participant to review the consent, confirm understanding, and answer any questions; and (c) once the investigator(s) or study staff are convinced that the protocol is understood and that there is agreement to participate, having the consent signed. The principal investigator (PI) will review all data collection documents weekly for completeness and accuracy of the data as well as protocol compliance. The PI will review this protocol on a continuing basis for participant safety and include the results of the review in annual progress reports submitted to the IRB and the NIH.

Patient Monitoring will be performed by the P.I., Co-Investigators, the Project Coordinator and medical staff present during the experimental manipulation. Also, H&P is required per the GCTSA protocol.

Stopping Rules for Stress-Inducing Experimental Manipulation

Absolute Indications for Termination

- Drop in systolic blood pressure >10 mm Hg (persistently below baseline).
- Technical difficulties monitoring blood pressure.

Relative Indications for Termination

- Increasing chest pain.
- Participant becomes excessively anxious, uncomfortable, or requests to stop.
- Fatigue, shortness of breath, wheezing, leg cramps, or claudication.
- Hypertensive response (systolic blood pressure >200 mm Hg and/or diastolic blood pressure >92 mm Hg).

Patient reporting rules for blood pressure
Dr. Lea (Co-Investigator and nephrologist) will review all participants' blood pressure readings from the 24-hour ABPM task. Participants with healthy / normal blood pressure readings (readings ≤ 170/110 mm Hg) will be notified of these numbers via mail from Dr. Lea along with information about what the readings mean for their health. The project coordinator will immediately alert Dr. Lea of participants with blood pressure readings that may be concerning (>170/110 mm Hg). Dr. Lea will review associated readings, and notify the participants via phone at her discretion. All participants will have the nocturnal blood pressure readings incorporated into their personal health records; nephrology clinic staff will be responsible for integrating these numbers into participants' electronic health records within the nephrology clinic.

Patient safety data examination, monitoring procedures/oversight. All adverse events (AEs) will be graded as to their attribution (unrelated to protocol, or possibly, probably, or definitely related to protocol). Any AE that is reported to either the PI or her designated research associates by a study participant or by medical staff caring for the participant and which meets the criteria will be documented as such. Potential ("expected") AEs are described above under "Potential Risks". Serious adverse events (SAEs) are predefined as: any experience that suggests a significant hazard, such as events which: a) are fatal, b) are life threatening, c) result in permanent disability, d) require inpatient hospitalization, or e) involve cancer, a congenital anomaly, or drug overdose. The standard Emory IRB reporting guidelines for AEs and SAEs will

also be followed. The investigators and staff will report all AEs according to Emory IRB protocols and evaluate the SAEs, in close coordination with the Emory IRB. The IRB annual report from the PI will be stored as a hard copy file.

Plans to minimize potential AEs are described above under "Adequacy of Protection Against Risks."

Plans for transmission of temporary or permanent suspension actions. Any actions that mandate temporary or permanent suspension of the study will be transmitted to the Emory IRB and, if appropriate, to the FDA and the National Institutes of Health.

Plans for protecting participant confidentiality. Participants will undergo CAPI interview in a private room adjacent to the clinic waiting room. They will undergo the experimental manipulation in one of six private research bays within the outpatient research suite of the Georgia CTSA. All data will be collected by IRB-approved personnel.   All information and materials obtained will be used for research purposes only, and the data will be kept in strict confidence. Confidentiality will be assured by the use of participant codes rather than personal identifiers in all data collection forms, datasets, and reports. The study database will be secured, and information will be entered using participant identifier codes rather than personal identifiers. Only group data will be presented and published. ⌊SEP⌋

Plans for assuring data accuracy and protocol human safety compliance. The above detailed plans should assure data accuracy and protocol human safety compliance for this study. These also include computerized database management and IRB oversight and communication. This plan, together with the monitoring by the IRB, should be sufficient without the addition of more faculty members to constitute a Data Safety and Monitoring Board. ⌊SEP⌋

XI.   Confidentiality

Privacy will be maintained while individuals are participating in the study. Participants will be provided with a private room to provide consent and complete the CAPI instrument on Day 1, and will be provided with a private room to provide specimens and participate in the experimental manipulation on Day 2. Study participants' names will remain confidential. Names will not appear in the data collection documentation. Informed consent documentation will be stored in a separate location from participant data. Thus, the data will not be linked to participant identifiers. When reporting study findings, identifiable information will not be used.

The samples will be stored for as long as they are useful, unless the participant asks us to destroy their sample sooner. If a participant chooses to have their sample material destroyed, he/she can do so by contacting the PI (Dr. Kimberly Jacob Arriola) or the project coordinator (Nakeva Redmond). Participants will be informed that their data will be used for the current study, but removed for any potential use on future studies.

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