Association between goal-striving stress and rapid kidney function decline among African Americans: the Jackson Heart Study

Loretta Cain-Shields, LáShauntá Glover, Bessie Young, Mario Sims

ABSTRACT
African Americans (AAs) are disproportionately affected by kidney disease and also report higher psychosocial stressors than other racial groups. Goal-striving stress (GSS) is an understudied psychosocial stressor related to attempting to accomplish one’s life goals. Given the numerous social determinants that contribute to health inequities among AAs, stress from goal striving may also disproportionately affect the health of AAs and in particular kidney disease outcomes. The objective of this study was to explore the association between GSS and rapid kidney function decline (RKFD) in an AA cohort. Using examination 1 (2000–2004) and examination 3 (2009–2013) data from the Jackson Heart Study (n=2630), we examined associations of baseline levels of GSS with RKFD among AAs using multivariable Poisson regression models, adjusting for sociodemographics, health behaviors, chronic disease and discrimination. We also explored baseline cortisol as a mediator. The incidence of RKFD in this sample was 7.34% (mean years of follow-up: 8.06±0.84 years). The mean GSS score was 3.80 (±4.88) and total GSS score ranged from 0 to 36. Those who reported high (vs low) GSS were 1.60 times more likely to experience RKFD after full adjustment (incidence rate ratio (IRR) 1.60; 95% CI 1.11 to 2.14, p=0.01). After confirming cortisol as a mediator and adding it to the model, those who reported high (vs low) GSS had 3.80 times the rate of RKFD (IRR 1.58; 95% CI 1.09 to 2.30, p=0.0153). Stress related to not achieving goals was associated with a greater risk of RKFD in this sample of AAs.

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INTRODUCTION
Kidney disease is a significant public health problem. The overall chronic kidney disease (CKD) prevalence in the US population is about 15% or (30 million people), and adults with diabetes and high blood pressure are at higher risk of developing CKD.1 Complications of CKD include end-stage renal disease (ESRD), heart disease, stroke, anemia, infections, low calcium levels, high phosphorus levels, high potassium levels, loss of appetite, excess fluids, depression and higher risk of mortality. The most recent estimate for Medicare expenditures for beneficiaries with CKD exceeded $84 billion in 2017 and for those with ESRD, an additional $36 billion, for a total of $120 billion.2

Racial and ethnic disparities in kidney disease are also a significant public health problem.3 African Americans (AAs) are 3 times more likely to progress to ESRD, and AAs develop albuminuria at higher rates when compared with their white counterparts.4 5 Studies have found that traditional risk factors (e.g., cardiovascular disease (CVD), hypertension (HTN) and diabetes) only partially explain the higher rates of kidney disease among AAs; therefore, psychosocial factors, such as stressors, should be explored as contributors to the racial disparities found in kidney disease trends.6 7

It is known that psychological stressors create demands that require an individual’s internal environment to maintain stability in response to the stress (i.e., allostatic) through changes

What is already known about this subject?
► Kidney disease is a public health problem.
► Ethnic and racial disparities in kidney disease are also a public health problem.
► Traditional modifiable risk factors only partly explain racial disparities in chronic kidney disease.
► Stressors disproportionately affect racial and ethnic minorities and are non-traditional risk factors that may lead to kidney disease.

What are the new findings?
► Goal-striving stress is associated with rapid kidney function decline in African Americans.
► Controlling for baseline cortisol only partially mediated this association.
► There was no effect modification by sociodemographics, health behaviors or chronic disease.

How might these results change the focus of research or clinical practice?
► Researchers and clinicians should continue to explore non-traditional risk factors in an effort to explain and prevent racial disparities in kidney disease.
in the autonomic nervous, immune, metabolic, cardiovascular, and endocrine systems.\textsuperscript{8,9} McEwen (1993) suggests that increased allostatic load (AL) occurs in 4 ways: (1) frequent stress, (2) inability to adapt to repeated stressors, (3) inability to shut off stress response, and (4) an unbalanced allostatic response.\textsuperscript{10} Increased AL may predispose individuals to disease, including HTN, CVD, and kidney disease.\textsuperscript{9} The relationship between psychosocial stress with HTN and CVD is well documented.\textsuperscript{11-14} However, research regarding psychosocial stressors and kidney disease is limited. Suggested mechanisms between psychosocial stressors and kidney disease include increased sympathetic nervous system activity, alternations in the hypothalamic-pituitary-adrenal axis, and changes in inflammatory cytokines and endothelin-A.\textsuperscript{15}

One psychosocial stressor that has not been adequately examined in relation to kidney disease is goal-striving stress (GSS). GSS is the discrepancy between aspiration and achievement, weighted by the level of disappointment experienced if goals are not reached.\textsuperscript{16} GSS captures negative emotions and challenges related to upward mobility and attaining life goals.\textsuperscript{17,18} Given the racial inequalities of wealth, wages, educational attainment, perceived job control and occupational stress, stress from goal striving may disproportionately affect AAs.\textsuperscript{19-21} Therefore, AAs may be more susceptible to increased AL through McEwen’s first mechanism, frequent stress.\textsuperscript{10} Because stress hormones are both metabolized and cleared by the kidneys, those with disproportionate amounts of stress may be more susceptible to kidney disease.\textsuperscript{7}

Cross-sectional research has established positive relationships between GSS and prevalent CKD in AAs, and longitudinal research has established positive relationships between GSS and incident CVD in AAs.\textsuperscript{22,23} However, the temporal association between GSS and kidney disease has not been explored. One temporal measure of kidney disease is rapid kidney function decline (RKFD), which averages the change in kidney function (i.e., estimated glomerular filtration rate, eGFR) across years. Assessing the association between GSS and RKFD would add temporality and possibly improve our understanding of psychosocial stress and kidney disease in AAs. Therefore, our study examined the associations of baseline GSS with RKFD among AAs in the Jackson Heart Study (JHS). We hypothesize that those who report high (vs low) baseline GSS will have a greater risk for RKFD over time. We also hypothesize that baseline plasma cortisol will partially mediate the association between GSS and RKFD.

METHODS

The JHS is a large, prospective cohort study of the etiology of CVD in AAs who reside in the tri-county area of the Jackson, Mississippi (MS) metropolitan area (Hinds, Madison, and Rankin counties). Of the 5306 JHS participants, 31% were recruited from the Atherosclerosis Risk in Communities study, 22% were family members, 17% were randomly selected, and 30% were community volunteers. Participants provided medical history, physical and biochemical measurements, diagnostic procedures, and DNA.\textsuperscript{24} Our study used data from examination 1 (2000–2004) and examination 3 (2009–2013). At baseline, there were 5306 participants 21–94 years of age enrolled, and at examination 3, 3819 participants (age 28–100 years) remained. Details on the study have been published elsewhere.\textsuperscript{25,26} Of the 3819 participants present at examination 3, we excluded those who had kidney disease at baseline (n=468), defined as <60 mL/min/1.73 m\textsuperscript{2}, a self-reported history of CKD, the use of dialysis, or the presence of albuminuria. We also excluded those with missing baseline GSS values (n=67), missing serum creatinine values at examination 3 (n=88), and missing covariate information (n=566), leaving a sample of 2630 participants.

Goal-striving stress

Baseline GSS was defined as the difference between aspiration and achievement, both using a 10-step ladder (1—worst possible way of life and 10—best possible way of life), weighted by disappointment experienced if the goal was not achieved by the following year (ranging from very disappointed to not at all disappointed using a 4-point ladder; the GSS score was derived using the following equation: aspiration−achievement × disappointment.\textsuperscript{15,17,27-30} GSS scores ranged from 0 to 36. A higher GSS score indicated greater stress from goal striving. GSS was analyzed both continuously and categorically (low (0–1), moderate (2–4), and high (≥5)) to explore both the continuous and threshold effects of GSS with RKFD.

Rapid kidney function decline

eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to measure kidney function based on the validated serum creatinine.\textsuperscript{31} Serum creatinine was measured with a multipeak enzymatic spectrophotometric assay at the baseline visit.\textsuperscript{32} An eGFR <60 mL/min/1.73 m\textsuperscript{2} was indicative of CKD. RKFD was determined based on measurement of eGFR from visit 1 to visit 3, divided by the number of years from visit 1 to visit 3.\textsuperscript{33,34} RKFD was defined as >4 mL/min/1.73 m\textsuperscript{2}/years as described in previous research regarding RKFD.\textsuperscript{33,34} Currently, there are no official clinical cut-points for RKFD.

Serum creatinine was measured using a multipoint enzymatic spectrophotometric assay at baseline entry into the study using the Vitros Ortho-Clinical Diagnostics Analyzer (Raritan, New Jersey).\textsuperscript{35} Serum creatinine was remeasured in 2006 for 206 participants using the enzymatic method on a Roche chemistry analyzer (Roche Diagnostics, Indianapolis, Indiana). In order to harmonize serum creatinine measurements across study examinations, we calibrated all examination 1 serum creatinine measurements to those at examination 3, using the isotope dilution mass spectrometry (IDMS)-traceable method.\textsuperscript{32} Because the CKD-EPI equation, used to determine kidney disease, is designed to be used with IDMS-calibrated serum creatinine values only,\textsuperscript{31} serum creatinine measurements at examination 1 were optimally calibrated using a Deming regression model, as described previously.\textsuperscript{32}

Covariates

Demographic, health behavior, risk factor and discrimination covariates were chosen based on their known relationships with kidney disease and stress. Baseline covariates included age (continuous), sex (men (referent)/women),...
education (less than high school graduate (referent), high school graduate, attended college), smoking status (current smoker, quit <12 months ago, and never smoked or quit ≥ months ago (referent)), alcohol use within the last year (yes/no (referent)), and physical activity based on the American Heart Association’s Life’s Simple Seven criteria poor (0 minute of moderate physical activity/week; and 0 minute of vigorous physical activity/week), intermediate health (0 < minutes of moderate physical activity/week <150 or 0 < minutes of vigorous physical activity/week <75 or 0 < minutes of combined moderate and vigorous physical activity/week <150) (referent).

Other baseline covariates included were body mass index (BMI) categories (obese, overweight, normal (referent)), HTN status (normal (referent): 0 < systolic blood pressure <120 and 0 < diastolic blood pressure <80, pre-HTN: 120 ≤ systolic blood pressure <140 or 80 ≤ diastolic blood pressure <90, HTN: systolic blood pressure ≥140 or diastolic blood pressure ≥90), diabetes status (non-diabetes (referent) fasting plasma glucose (FPG) <100 and HbA1c <5.7 and no diabetes medication use), pre-diabetic (100 ≤ FPG <126 or 5.7 ≤ HbA1c <6.5 and no diabetes medication use), diabetic (FPG ≥126 or HbA1c ≥6.5 and diabetes medication use), CVD history (defined as self-reported physician-diagnosed cardiovascular history (CVD/no CVD (referent))), and plasma cortisol (μg/dL).

The burden of perceived lifetime discrimination was also included (continuous score range 1–4) as a potential psychosocial confounder in the association between GSS and RKFD, since it is a common stressor reported among AAs.36–38 Burden of lifetime discrimination was measured using 3 questions (codes): ‘When you had experiences like these over your lifetime, have they been—very stressful (4), moderately stressful (2.5), or not stressful (1)?’, ‘Overall, how much has discrimination interfered with you having a full and productive life?— lot (4), some (3), a little (2), or not at all (1)?’, and ‘Overall, how much harder has your life been because of discrimination— lot (4), some (3), a little (2), or not at all (1)?’ Responses were averaged to create a mean score of discrimination burden, ranging from 1 to 4. Higher scores indicated greater burden of discrimination. Internal consistency for this scale was 0.63.36–38

Statistical analysis
Observations with missing covariates were compared with the analytical sample on age, sex, educational attainment, alcohol use, smoking status, HTN status, diabetes status, and CVD history and discrimination score. Missing observations were statistically different from the analytical sample by mean age (57.37 vs 53.28 years), college attendance (51.73% vs 71.25%), current alcohol use (42.10% vs 49.6%), current smoking (15.53% vs 11.06%), HTN (24.97% vs 17.19%), diabetes (27.08% vs 17.53) and CVD history (15.28% vs 6.20%), respectively. Therefore, those who were missing from this sample were older, less likely to attend college and use alcohol, more likely to smoke and more likely to have HTN, diabetes, and a history of CVD.

Unadjusted differences in baseline characteristics were assessed across tertiles of GSS using χ² test for categorical variables and Kruskal-Wallis test for non-normal continuous variables. There were no normal continuous variables. Multivariable Poisson regression analyses estimated the associations of baseline GSS levels and continuous GSS with RKFD, where incidence rate ratios (IRR, 95% CIs) estimated the relative rate of RKFD. Model 1 was adjusted for demographics: age, sex, and education. Model 2 was additionally adjusted for health behaviors: smoking status, alcohol use and physical activity. Model 3 was additionally adjusted for risk factors: HTN, BMI, diabetes mellitus, and history of CVD. Model 4 was additionally adjusted for an important psychosocial risk factor: perceived burden of lifetime discrimination. Model 5 additionally adjusted for plasma cortisol (μg/dL) after mediation was confirmed.

Because kidney disease is known to vary by sex and the above-mentioned risk factors, interaction tests for GSS with sex, HTN, BMI, diabetes mellitus, and history of CVD were conducted, and effect modification was explored. To test the theory that stress causes a disproportionate amount of stress to be filtered through kidneys, causing kidney disease, a mediation analysis was performed using the Baron and Kenny method,46 testing baseline plasma cortisol (μg/dL) as the mediator. To conclude mediation, Baron and Kenny proposed the following: (1) the dependent and independent variables are correlated, (2) the independent and mediator variables are correlated, and (3) controlling for the mediator attenuates the relationship between the independent and dependent variables.46 All analyses were performed using SAS 9.3 (SAS Institute). Statistical significance was inferred at two-sided p<0.05.

RESULTS
RKFD occurred in 7.34% (n=193) of the sample population (table 1). At baseline, participants who reported high (vs low) GSS had higher eGFR at visit 1 (102.96±18.22 vs 93.35±16.61), higher eGFR at visit 3 (93.20±21.97 vs 84.17±19.89), higher GSS score (9.96±5.55 vs 0.25±0.43), were more likely to be younger (48.21±11.23 vs 58.04±10.58), female (66.90% vs 62.61%), college attendees (72.28% vs 66.91%), current smokers (15.70% vs 8.48%), use alcohol (54.88% vs 44.94%), obese (55.87% vs 54.65%), and have a higher discrimination score (2.49 vs 2.26). They were less likely to have poor physical activity (40.59% vs 48.21%), hypertension (13.86% vs 20.33%), diabetes (15.56% vs 20.53%), and less likely to have a history of CVD (4.53% vs 8.38%) (table 1).

The mean follow-up time from visit 1 to visit 3 was 8.06±0.84 years. After adjustment for age, sex and education, participants who reported high (vs low) GSS had 1.73 times the rate of RKFD (IRR 1.73; 95% CI 1.12 to 2.48, p=0.0031) (table 2). This association slightly attenuated across models 2, 3 and 4, but remained significant (p=0.01) (table 2). Continuous GSS was significantly associated with RKFD in models 1 and 2 but not in models 3 and 4.

The interactions between GSS with sex, HTN, BMI, diabetes mellitus, and history of CVD were not significant. In addition, there was no effect modification by these variables. In the mediation analysis, controlling for all covariates, GSS was significantly associated with RKFD (p=0.0134), plasma cortisol (p=0.0476), and RKFD, when controlling for plasma cortisol (p=0.0173). The result of adding cortisol to the model is shown as model 5 in table 2. Adding plasma cortisol to the model resulted in a 2%
Table 1  Sample population demographics by goal-striving stress (GSS) levels, JHS (2000–2004)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire cohort (n=2630)</th>
<th>Low GSS (n=979)</th>
<th>Moderate GSS (n=944)</th>
<th>High GSS (n=707)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RKFD (%)</td>
<td>193 (7.34)</td>
<td>70 (7.15)</td>
<td>61 (6.46)</td>
<td>62 (8.77)</td>
<td>0.1972</td>
</tr>
<tr>
<td>eGFRvisit (mean±SD)</td>
<td>98.25±17.40</td>
<td>93.35±16.61</td>
<td>98.76±16.63</td>
<td>102.96±18.22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eGFRvisit (mean±SD)</td>
<td>88.40±21.06</td>
<td>84.17±19.89</td>
<td>89.19±20.70</td>
<td>93.20±21.97</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eGFRvisit-eGFRvisit (mean±SD)</td>
<td>-9.85±15.32</td>
<td>-10.17±15.11</td>
<td>-9.57±14.61</td>
<td>-9.76±16.48</td>
<td>0.6369</td>
</tr>
<tr>
<td>GSS (mean±SD)</td>
<td>3.80±4.88</td>
<td>0.25±0.43</td>
<td>2.89±0.89</td>
<td>9.96±5.55</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>53.28±11.53</td>
<td>50.04±10.58</td>
<td>52.15±10.79</td>
<td>48.21±11.23</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Females (%)</td>
<td>1646 (62.59)</td>
<td>613 (62.61)</td>
<td>560 (59.32)</td>
<td>473 (66.90)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Attended college (%)</td>
<td>1874 (71.25)</td>
<td>655 (66.91)</td>
<td>708 (75.00)</td>
<td>511 (72.28)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>291 (11.06)</td>
<td>83 (8.48)</td>
<td>97 (10.28)</td>
<td>111 (15.70)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Use alcohol (%)</td>
<td>1305 (49.62)</td>
<td>440 (44.94)</td>
<td>477 (50.53)</td>
<td>388 (54.88)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Poor physical activity health (%)</td>
<td>1152 (43.80)</td>
<td>472 (48.21)</td>
<td>393 (41.63)</td>
<td>287 (40.59)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Obese (%)</td>
<td>1422 (54.07)</td>
<td>535 (54.65)</td>
<td>492 (52.12)</td>
<td>395 (55.87)</td>
<td>0.1419</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>452 (17.19)</td>
<td>199 (20.33)</td>
<td>155 (16.42)</td>
<td>98 (13.86)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>461 (17.53)</td>
<td>201 (20.53)</td>
<td>150 (15.89)</td>
<td>110 (15.56)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cardiovascular disease history (%)</td>
<td>163 (6.20)</td>
<td>82 (8.38)</td>
<td>42 (4.45)</td>
<td>32 (4.53)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Discrimination (1–4) (mean±SD)</td>
<td>2.35±0.76</td>
<td>2.26±0.79</td>
<td>2.33±0.74</td>
<td>2.49±0.74</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

P values were calculated using χ² and Kruskal-Wallis tests as appropriate.
*Significant p values.
eGFR, estimated glomerular filtration rate; JHS, Jackson Heart Study; RKFD, rapid kidney function decline.

decrease in the relative rate of RKFD when compared with the previous model, indicating only partial mediation. In model 5, participants who reported high (vs low) GSS had 1.58 times the rate of RKFD (IRR 1.58; 95% CI 1.09 to 2.30, p=0.0153).

DISCUSSION
In our sample, GSS was associated with RKFD after adjusting for demographics, health behaviors, risk factors, and burden of discrimination. Psychological stress increases AL in the autonomic nervous, immune, metabolic, cardiovascular, and endocrine systems in an effort to maintain physiological stability.8,9 These extra physiological demands may cause internal systems to break down, predisposing individuals to chronic disease, including kidney disease.6 Because stress hormones are both metabolized and cleared by the kidneys, those with greater amounts of stress may be more susceptible to kidney disease.7 However, after testing for the mediating effects of cortisol, a common stress hormone, the relative rate was only attenuated by 2%, indicating partial mediation. Therefore, other stress hormones should be explored in an effort to explain the association between GSS and RKFD.

Previous work has found positive associations between GSS and outcomes related to RKFD. Sellers et al found that as GSS increased, prevalent HTN, a kidney disease risk factor, increased in 3570 AAs, 891 Whites, and 1621 Caribbean descent participants from the National Survey of American Life (NSAL).41 In contrast, we found a higher prevalence of HTN in the lowest category of GSS as shown in our demographics table. There are several explanations for the difference in findings between GSS and HTN among the 2 studies. One, our population demographics are different from that of the NSAL study. Also, in the NSAL study, HTN was self-reported. Last, our look at HTN and GSS was only descriptive and unadjusted for potential confounders, as this was not our outcome variable of interest. Glover et al27 found a significant positive association between GSS and incident CVD, a kidney disease risk factor, among AAs in the JHS (n=4648). Cain et al26 found a significant positive association between GSS and prevalent CKD among the AA participants of the JHS (n=4967). Like the previously mentioned studies, the current study found a significant association between GSS and increased risk of RKFD.

This study reports the association between an understudied psychosocial stressor that is particularly relevant to AAs and kidney function decline in a large prospective study of AAs, which adds to both the kidney disease and GSS literature. GSS has not been previously linked to incident CKD in any population, especially a population that may be more susceptible to stress and kidney disease. In addition, the associations reported adjusted for multiple risk factors including demographics, health behaviors, chronic disease and discrimination which may impact the relationship between GSS and RKFD. Despite these strengths, this study also has limitations. Although we used an AA sample, the findings may only be generalized to AAs in the Jackson, MS area. Additionally, there may have been other factors that could explain the association between GSS and RKFD that were not identified, such as family history or genetic susceptibility to kidney disease. Also, using a complete-case analysis approach may not accurately represent the original population from which the sample was taken. It is also important to note that there is currently no clinical cut-point for RKFD and that eGFR decline was not evaluated as a continuous variable.

GSS was associated with a greater risk of RKFD among AAs in the JHS. Minorities typically report greater stressors and have lower socioeconomic status than their white counterparts,42 which influences health disparities. It is well known that stress increases the risk of disease and...
that traditional modifiable risk factors only partly explain racial disparities in CKD health.4 6 However, the associations between psychosocial stressors and kidney disease are less known. Future research should consider examining stress related to goal striving with other chronic diseases, such as diabetes and HTN among AA, as this type of stress may explain racial health disparities in these and other morbidities.

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Contributors  All authors (LCS, LG, BY and MS) have each substantially contributed to the design of the work and interpretation of data for the work, drafted or revised the work critically for important intellectual content, contributed to the design of the work and interpretation of data for the work, approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Additionally, LCS acquired and analyzed the data for the work.

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Patient consent for publication  Not required.

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