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### Authors

Scherrer, Jeffery

Whooley, Mary

Hajagos, Janos

et al.

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## The Association of Post-Traumatic Stress Disorder with Glomerular Filtration Rate Decline

Farrukh M. Koraiшы, MD, PhD<sup>1,2</sup>, Beth E. Cohen, MD, MAS<sup>3,4</sup>, Jeffery F. Scherrer, PhD<sup>5</sup>, Mary Whooley, MD<sup>3,4</sup>, Janos Hajagos, PhD<sup>6</sup>, Cassianne Robinson-Cohen, PhD<sup>7</sup>, Wei Hou, PhD<sup>8</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, Stony Brook University, NY

<sup>2</sup>Northport VA Medical Center, Northport, NY

<sup>3</sup>Department of Medicine, University of California, San Francisco

<sup>4</sup>San Francisco VA Health Care System, San Francisco

<sup>5</sup>Department of Family and Community Medicine, Saint Louis University, MO

<sup>6</sup>Department of Medical Bioinformatics, Stony Brook University, NY

<sup>7</sup>Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, TN

<sup>8</sup>Department of Family, Population, and Preventive Medicine, Program in Public Health, Stony Brook University

### Abstract


While major depression is known to be associated with glomerular filtration rate (GFR) decline, there is a lack of data on the association of other mental illnesses like posttraumatic stress disorder (PTSD) with kidney disease. In 640 adult participants of the Heart and Soul Study (mean baseline age of 66.2 years) with a high prevalence cardiovascular disease, hypertension and diabetes, we examined the association of PTSD with GFR decline over a 5 year follow-up. We observed a significantly greater estimated (e) GFR decline over time in those with PTSD compared to those without (2.97 versus 2.11 ml/min/1.73m<sup>2</sup> per year; p = 0.022). PTSD was associated with 91% (95% CI 12%– 225%) higher odds of ‘rapid’ versus ‘mild’ (>3.0 vs < 3.0 ml/min/1.73m<sup>2</sup> per year) eGFR decline. These associations remained consistent despite controlling for demographics, medical comorbidities, other mental disorders and psychiatric medications. In conclusion, our study provides evidence that PTSD is independently associated with GFR decline in middle aged adults with a high comorbidity burden. This association needs to be examined in larger cohorts with longer follow-ups.

### Graphical Abstract

**To whom correspondence should be addressed:** Dr. Farrukh M. Koraiшы, Department of Medicine/Nephrology, Stony Brook University, 100 Nicolls Road, HSCT16-080E, Stony Brook, NY, USA. Tel: 631-638-2164, Fax: 631-444-6174, Farrukh.Koraiшы@stonybrookmedicine.edu.

Conflicts of Interest

The authors have nothing to disclose.

The Association of Post-Traumatic Stress Disorder with Glomerular Filtration Rate Decline		NEPHROLOGY
Aim: / Background:	Methods:	Outcomes: / Results:
<p><b>Background:</b> Major depression is known to be associated with glomerular filtration rate (GFR) decline.</p> <p><b>Hypothesis/Aim:</b> To test whether a closely related mental illnesses: posttraumatic stress disorder (PTSD) is also associated with GFR decline?</p>	<p>In 640 adult participants of the Heart and Soul Study (mean baseline age of 66.2 years) with a high prevalence cardiovascular disease, hypertension and diabetes, we examined the association of PTSD with GFR decline over a 5 year follow-up.</p>	<ul style="list-style-type: none"> <li>A significantly greater estimated (e) GFR decline over time was observed in those with PTSD compared to those without (2.97 versus 2.11 ml/min/1.73m<sup>2</sup> per year; p = 0.022).</li> <li>PTSD was associated with 91% [95% CI 12%–225%] higher odds of 'rapid' versus 'mild' (&gt;3.0 vs &lt; 3.0 ml/min/1.73m<sup>2</sup> per year) eGFR decline.</li> <li>These associations remained consistent despite controlling for demographics, medical comorbidities, other mental disorders and psychiatric medications.</li> </ul>
<p><b>CONCLUSION:</b> PTSD is independently associated with GFR decline in middle aged adults with a high comorbidity burden. This association needs to be examined in larger cohorts with longer follow-ups.</p>		
Farrukh M. Koraishy et al., 2022		

## Introduction:

Chronic kidney disease (CKD) is a common condition associated with high morbidity, mortality and health-care costs<sup>1</sup>. While numerous risk factors for CKD progression are known<sup>2</sup>, emerging evidence indicates that mental health disorders are highly comorbid with CKD<sup>3</sup>. Major depression is known to be associated with CKD progression<sup>4</sup> and with estimated glomerular filtration rate (eGFR) decline in the general population<sup>5</sup>. A recent study found that receiving a 'stress-related disorder (SRD)' diagnosis was associated with a 23% higher risk of CKD progression<sup>6</sup>.

We recently reported that post-traumatic stress disorder (PTSD) was associated with decline in eGFR among World Trade Center (WTC) responders<sup>7</sup>. This cohort consisted of relatively young participants (mean age 53.1 years), mostly Caucasians, with low prevalence of diseases associated with CKD like diabetes mellitus (DM), hypertension (HTN) and cardiovascular disease (CVD)<sup>7</sup>. Whether PTSD is also an independent risk factor for GFR decline in older people, with diverse racial backgrounds and a greater comorbidity burden is not known. To address this gap in the field, we estimated the association of PTSD with eGFR decline in the Heart and Soul Study. This is a well-characterized cohort of older adults with coronary heart disease and a high prevalence of HTN and DM, where data on renal measures, mental health disorders and psychiatric medications was collected as part of the study protocol.

## Methods:

### Heart and Soul (H&S) Study Cohort:

This prospective cohort study enrolled 1024 participants with coronary heart disease from multiple medical centers in San Francisco, USA, between September 01, 2000 and December 31, 2002<sup>8</sup>. The study was approved by the institutional review board (IRB) of the University of California, San Francisco and all participants provided written informed consent. The 640 participants who completed a second in-person visit approximately 5 years after their baseline visit and with complete data on all variables were included in this study. No participant in the study had end-stage kidney disease (EKSD). Use of existing H&S data for the present study was approved by the Stony Brook University IRB (#2019–00732).

**PTSD measures:**

PTSD was assessed with the Computerized Diagnostic Interview Schedule (CDIS) for DSM-IV<sup>9</sup>.

**Covariates:**

All baseline (indexed at the individual's first eGFR observation) covariates known to be associated with CKD<sup>2</sup> were included in models: demographic factors (age, race, gender) and co-morbidities (DM, HTN, body mass index [BMI] and CVD [left ventricular hypertrophy [LVH], angina and stroke]). Psychiatric diseases associated with PTSD<sup>10</sup> (major depressive disorder [MDD] and generalized anxiety disorder [GAD]); psychiatric medications (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs] and 'others' [not classified]), substance abuse (smoking [pack year] and alcohol intake [alcohol score]) were also included. MDD was defined by a 9-item Patient Health Questionnaire (PHQ9) score  $\geq 10$ <sup>11</sup> and GAD was determined by the CDIS using DSM-IV criteria<sup>9</sup>.

**Outcome measures (eGFR decline):**

Serum creatinine (SCr) was measured at baseline (year 1) and 5-year follow-up visits (year 6). eGFR was calculated using the 2021 CKD-EPI equation<sup>12</sup>. We reported the mean rate of eGFR decline (ml/min/1.73m<sup>2</sup> per year) defined as the total change in eGFR (from baseline to follow-up) divided by the years of follow-up. We further sub-divided the cohort into subjects with 'rapid' versus 'mild' ( $>3.0$  vs  $< 3.0$  ml/min/1.73m<sup>2</sup> per year) eGFR decline<sup>13</sup>.

**Statistical Analysis:**

Baseline characteristics were described using means and standard deviations (SD) or frequencies (percentages) in each category, as appropriate. The baseline characteristics and renal profile were compared between 'PTSD' vs 'no PTSD' and between 'rapid' versus 'mild' eGFR decline using  $\chi^2$ -tests for categorical variables and t-tests for continuous variables. We used generalized estimating equations to estimate the association of PTSD diagnosis with slope of eGFR decline using the following six sequential adjustment models: unadjusted [Model 1] followed by sequential adjustment for demographics (age, gender, race) [Model 2], medical comorbidities (BMI, HTN, DM, CHF, LVH, stroke and angina) [Model 3], other psychiatric diagnoses (MDD and GAD) [Model 4], psychiatric medication use [Model 5], and finally alcohol intake and smoking [Model 6]. We used logistic regression to estimate the association between PTSD and odds of 'rapid' versus 'mild' eGFR decline with the six sequential adjustment models. Unadjusted and multivariable-adjusted  $\beta$  statistics & odds ratio (OR), 95% confidence intervals, and p-values were reported. All analyses were performed using SAS v9.4 (the SAS Institute, Cary, NC).

**Results:**

Baseline cohort characteristics overall and by PTSD status are shown in Table 1. Of a total of 640 individuals, the mean age was 66.18 (SD 10.13) years, and those with PTSD were significantly younger. 83.1% were males, 59.1% were Whites participants, mean BMI was 28.50 (5.09). 69.4% had HTN and 23.6% DM. These characteristics were similar between

those with or without PTSD. Those with PTSD had a higher prevalence of CHF and angina but a lower prevalence of LVH. Subjects with PTSD were more likely to be smokers, have comorbid MDD and GAD and be on anti-depressants compared to those without PTSD (Table 1).

No differences were noted in the mean baseline (Y1) and final (Y6) SCr between the 2 groups, however those with PTSD had a higher mean eGFR at baseline than those without PTSD (82.72 versus 76.43 ml/min/1.73m<sup>2</sup>). The overall decline in eGFR over time was significantly greater in those with PTSD compared to those without (2.97 versus 2.11 ml/min/1.73m<sup>2</sup> per year; p = 0.022).

#### **Association of PTSD with the trajectory of GFR decline:**

As shown in Figure 1, PTSD was associated with a significantly greater GFR decline over time ( $\beta$  statistic  $-0.855$  [95% CI  $-1.567$  to  $-0.143$ ]; p= 0.018) and this association remained significant after sequential adjustment for demographics followed by medical comorbidities followed by MDD and GAD and then psychiatric medications and substance abuse ( $-0.918$  [ $-1.734$  to  $-0.101$ ], p = 0.027).

#### **Comparison of eGFR decline categories and association of PTSD with 'rapid' GFR decline:**

The baseline characteristics and renal profile of subjects with 'mild' versus 'rapid' eGFR decline ( $< 3.0$  versus  $>3.0$  ml/min/1.73m<sup>2</sup>) per year are shown in Table 2. Subjects with 'rapid' eGFR decline were more likely to be hypertensive and diabetic and be on TCAs. As shown in Figure 2, PTSD was significantly associated with 91% (95% CI 12%– 225%) higher odds of 'rapid' versus 'mild' eGFR decline (p=0.018). This association remained statistically significant after adjustment for demographics, comorbidities, mental disorders and psychiatric medications (OR = 1.98 [1.00–3.77]), p<0.05). The significance was borderline after further adjustment for alcohol abuse and smoking even though the odds ratio was similar (OR = 1.94 [1.00–3.77]), p=0.05).

#### **Discussion:**

A major increase in PTSD has been noted since the start of the COVID-19 pandemic<sup>14</sup> and the clinicians need to be cognizant of the potential impact of PTSD on the kidney. In a cohort of middle aged and elderly subjects we observed that PTSD was significantly associated with greater decline in eGFR over time after sequential adjustment for traditional CKD risk factors including demographics and medical comorbidities and further adjustment for other mental disorders, psychiatric medications and finally smoking and alcohol use.

PTSD was also significantly associated with higher odds of 'rapid' versus 'mild' ( $> 3.0$  versus  $<3.0$  ml/min/1.73m<sup>2</sup>) eGFR decline. This association also remained statistically significant after adjusting for all covariates except became borderline significant at the final step of adjustment for smoking and alcohol use. This could potentially be related to our limitations of the small sample and lower proportion (34.4%) of patients with rapid eGFR decline.

Our results are consistent with our previous report of the association of PTSD with GFR decline in WTC responders<sup>7</sup> that were young and relatively healthy. Compared to the WTC cohort<sup>7</sup>, the H&S cohort participants were older (mean baseline age 66.2 vs. 53.1 years), more likely to be non-White (40.9 vs. 10.9%) and with greater prevalence of HTN (69.4% vs 29.7%) and DM (23.6% vs. 8.6%) and lower baseline renal function (77.02 *versus* 90.42 ml/min/1.73m<sup>2</sup>). The mean rate of GFR decline over time was greater in this study compared to the WTC cohort: 2.19 vs. 1.51 ml/min/1.73m<sup>2</sup> per year. Moreover, compared to the large portion (25%) of subjects in the WTC cohort who had a significant rise in GFR overtime (> 1.0 ml/min/1.73m<sup>2</sup> per year) this proportion was much smaller (8.5%) in the present cohort. Finally, this study had a longer follow-up time of 5 years compared to 2 years<sup>7</sup>. Therefore the current study extends the evidence of the association of PTSD with eGFR decline to an older, more racially diverse population with additional comorbidities.

Mechanisms for the association between PTSD and increased rates of GFR decline remain uncertain. In this study the participants with PTSD were younger, had a higher baseline eGFR and a similar prevalence of the major risk factors of CKD i.e. HTN and DM compared to those without PTSD diagnosis. PTSD could potentially cause kidney damage via systemic pathophysiological mechanisms like inflammation<sup>15</sup>, altered hypothalamic-pituitary axis<sup>16</sup>, endothelial dysfunction<sup>17</sup> or premature aging<sup>18</sup>. Depression has been postulated to accelerate CKD progression through similar mechanisms and PTSD and depression share pathophysiology.<sup>19</sup> However our findings remained significant even after controlling for MDD and anti-depressant medications suggesting an independent association of PTSD with CKD. Besides the potential of direct kidney damage as a result of systemic pathophysiology in patients with PTSD, an alternate hypothesis is that patients with mental health disorders like PTSD have medical non-compliance<sup>20</sup> that has been associated with adverse outcomes including CKD progression<sup>21</sup>. However this hypothesis was not tested in this study.

Limitations: This is an observational study that did not test for causality. The study was limited to a small sample size and relatively small numbers of subjects with PTSD compared to those without. We did not have data on proteinuria and other nephrotoxic drugs on all patients. We also did not have complete data on medications associated with renal protection like blood pressure and diabetic medications. eGFR progression was based only on two time points, which is suboptimal to describe trajectories. Due to relatively short follow-up and normal baseline GFR of our subjects, we could not test for the association of PTSD with advanced renal outcomes like incident CKD, doubling of serum creatinine or ESKD. Finally, the low proportion of females and limited geographic region of the H&S cohort limits generalizability.

In conclusion, our study provides further evidence that PTSD is a potential risk factor for GFR decline. This association needs to be tested in larger cohorts with longer follow-ups for advanced renal outcomes.

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### List of Abbreviations:

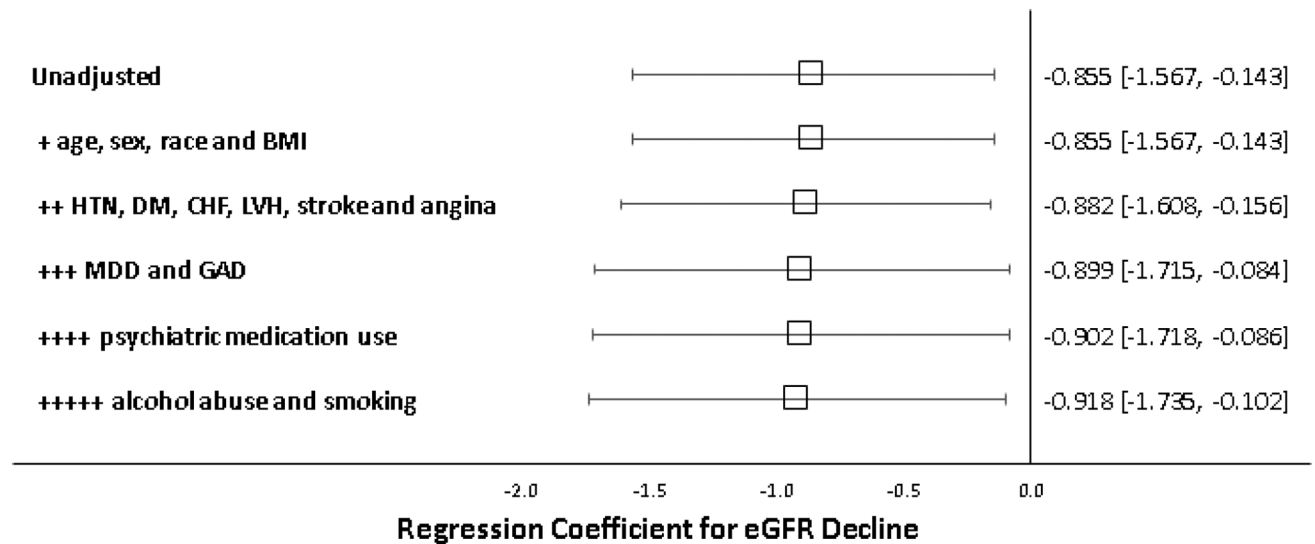
<b>BMI</b>	Body Mass Index
<b>CKD</b>	Chronic Kidney Disease
<b>CVD</b>	Cardiovascular Disease
<b>DM</b>	Diabetes Mellitus
<b>eGFR</b>	Estimated Glomerular Filtration Rate
<b>ESKD</b>	End Stage Kidney Disease
<b>GFR</b>	Glomerular Filtration Rate
<b>HTN</b>	Hypertension
<b>PCL</b>	PTSD 17-item symptom checklist
<b>PTSD</b>	Post Traumatic Stress Disorder
<b>WTC</b>	World Trade Center
<b>PHQ9</b>	9-item Patient Health Questionnaire
<b>MDD</b>	major depressive disorder
<b>GAD</b>	generalized anxiety disorder
<b>SSRIs</b>	selective serotonin reuptake inhibitors
<b>TCA</b> s	tricyclic antidepressants

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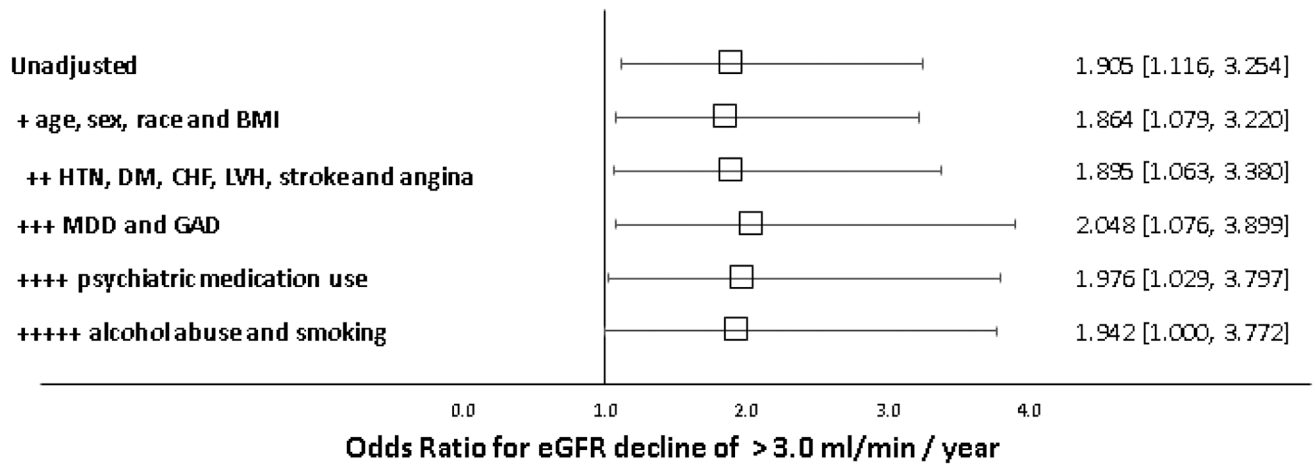




**Figure 1: Association of PTSD with the slope of eGFR Decline**

Forest Plot to display to association between PTSD and slope/trajectory of eGFR decline unadjusted [Model 1]. In addition, after sequential adjustment for demographics (age, gender, race) [Model 2], medical comorbidities (BMI, HTN, DM, CHF, LVH, stroke and angina) [Model 3], psychiatric diagnoses (MDD and GAD) [Model 4], psychiatric medication use [Model 5], and finally alcohol abuse and smoking [Model 6]. Regression coefficient ( $\beta$  statistic) and 95% confidence interval (CI) is shown for each model.

Abbreviations: BMI (body mass index), HTN (hypertension), DM (diabetes mellitus), CHF (congestive heart failure), LVH (left ventricular hypertrophy), MDD (major depressive disorder), GAD (generalized anxiety disorder).



**Figure 2: Association of PTSD with 'rapid' (> 3.0 ml/min/1.73m<sup>2</sup> per year) versus 'mild' (< 3.0 ml/min/1.73m<sup>2</sup> per year) eGFR decline**

Forest Plot to display to association between PTSD with 'rapid' compared to 'mild' eGFR decline unadjusted [Model 1]. In addition, after sequential adjustment for demographics (age, gender, race) [Model 2], medical comorbidities (BMI, HTN, DM, CHF, LVH, stroke and angina) [Model 3], psychiatric diagnoses (MDD and GAD) [Model 4], psychiatric medication use [Model 5], and finally alcohol abuse and smoking [Model 6]. Odds Ratios (OR) and 95% confidence interval (CI) is shown for each model.

Abbreviations: BMI (body mass index), HTN (hypertension), DM (diabetes mellitus), CHF (congestive heart failure), LVH (left ventricular hypertrophy), MDD (major depressive disorder), GAD (generalized anxiety disorder).

**Table 1**

Mean (standard deviation) and N (%) are presented for continuous and categorical variables respectively.

	All subjects N=640	No PTSD N=580	PTSD N=60	P value
<b>Demographics</b>				
Baseline Age	66.18 (10.13)	66.63 (10.06)	61.82 (9.83)	<b>0.0006</b>
Male	532 (83.1%)	487 (84.0%)	45 (75.0%)	0.078
White	378 (59.1%)	345 (59.5%)	33 (55.0%)	0.501
married	288 (45.1%)	267 (46.2%)	21 (35.0%)	0.097
<b>Co-morbidities</b>				
BMI	28.50 (5.09)	28.58 (5.12)	27.69 (4.83)	0.180
HTN	444 (69.4%)	400 (69.0%)	44 (73.3%)	0.485
DM	151 (23.6%)	134 (23.1%)	17 (28.3%)	0.364
Stroke	78 (12.2%)	69 (11.9%)	9 (15.0%)	0.487
CHF	94 (14.8%)	77 (13.3%)	17 (28.8%)	<b>0.001</b>
Angina	231 (36.1%)	199 (34.3%)	32 (53.3%)	<b>0.003</b>
LVH	342 (53.9%)	318 (55.2%)	24 (40.7%)	<b>0.033</b>
<b>Renal measures</b>				
Y1SCr	1.09 (0.55)	1.10 (0.56)	1.03 (0.48)	0.274
Y6SCr	1.24 (0.62)	1.24 (0.61)	1.23 (0.71)	0.912
Y1eGFR (ml/min/1.73m2) (Cr - CKD EPI 2021)	77.02 (18.92)	76.43 (18.88)	82.72 (18.52)	<b>0.015</b>
Y6eGFR (ml/min/1.73m2) (Cr - CKD EPI 2021)	66.06 (18.85)	65.87 (18.90)	67.88 (18.35)	0.423
eGFR decline (ml/min/1.73m2 per year)	2.19 (2.71)	2.11 (2.70)	2.97 (2.70)	<b>0.022</b>
<b>Psychosocial</b>				
Alcohol abuse (score)	2.35 (2.43)	2.39 (2.44)	1.98 (2.40)	0.218
Smoking (Pack Years)	18.22 (20.44)	17.27 (20.01)	27.29 (22.37)	<b>0.001</b>
<b>Mental health disorders</b>				
MDD	112 (17.5%)	90 (15.5%)	22 (36.7%)	<b>&lt;0.0001</b>
GAD	62 (10.2%)	44 (7.9%)	18 (34.6%)	<b>&lt;0.0001</b>
<b>Psychiatric Medication use</b>				
SSRIs	51 (8.0%)	41 (7.1%)	10 (16.7%)	<b>0.01</b>
TCAAs	18 (2.8%)	16 (2.8%)	2 (3.3%)	0.807
other antidepressants	42 (6.6%)	30 (5.2%)	12 (20.0%)	<b>&lt;0.0001</b>
any antidepressant	97 (15.3%)	79 (13.7%)	18 (30.0%)	<b>0.0009</b>

PTSD (post-traumatic stress disorder), BMI (body mass index), HTN (hypertension), DM (diabetes mellitus), CHF (congestive heart failure), LVH (left ventricular hypertrophy), Y1 (year 1, baseline), Y6 (year 6, follow-up), SCr (serum creatinine), eGFR (estimated glomerular filtration rate), CKD-EPI 2021 (Chronic Kidney Disease Epidemiology Collaboration 2021 equation), MDD (major depressive disorder), GAD (generalized anxiety disorder), SSRIs (selective serotonin reuptake inhibitors), TCAs (tricyclic antidepressants)

**Table 2**

Mean (standard deviation) and N (%) are presented for continuous and categorical variables respectively.

	'Mild' eGFR decline ( $< 3.0$ ml/min/1.73m <sup>2</sup> per year) N=420	'Rapid' eGFR decline ( $> 3.0$ ml/min/1.73m <sup>2</sup> per year) N=220	P value
<b>Demographics</b>			
Baseline age	66.66 (10.20)	65.25 (9.95)	0.093
Male	350 (83.3%)	182 (82.7%)	0.846
White	261 (62.1%)	117 (53.2%)	<b>0.029</b>
married	198 (47.3%)	90 (41.1%)	0.138
<b>Co-morbidities</b>			
BMI	28.30 (4.89)	28.88 (5.46)	0.190
HTN	273 (65.0%)	171 (77.7%)	<b>0.0009</b>
DM	81 (19.3%)	70 (31.8%)	<b>0.0004</b>
stroke	43 (10.3%)	35 (15.9%)	<b>0.038</b>
CHF	55 (13.1%)	39 (17.9%)	0.108
angina	158 (37.6%)	73 (33.2%)	0.267
LVH	219 (52.3%)	123 (56.9%)	0.263
<b>Renal measures</b>			
Y1 SCr (mg/dL)	1.16 (0.66)	0.98 (0.20)	<b>&lt;0.0001</b>
Y6 SCr (mg/dL)	1.18 (0.65)	1.36 (0.55)	<b>0.0002</b>
Y1 eGFR (Cr - CKD EPI 2021)	73.59 (19.58)	83.59 (15.67)	<b>&lt;0.0001</b>
Y6 eGFR (Cr - CKD EPI 2021)	69.95 (18.88)	58.63 (16.43)	<b>&lt;0.0001</b>
eGFR decline (ml/min/1.73m <sup>2</sup> per year)	0.73 (1.76)	4.99 (1.86)	<b>&lt;0.0001</b>
<b>Psychosocial</b>			
Alcohol abuse (score)	2.35 (2.46)	2.35 (2.40)	0.991
Smoking (Pack Years)	17.47 (19.99)	19.65 (21.24)	0.211
<b>Mental Health disorders</b>			
MDD	68 (16.2%)	44 (20.0%)	0.228
Anxiety disorder	42 (10.5%)	20 (9.7%)	0.739
PTSD	31 (7.4%)	29 (13.2%)	<b>0.017</b>
<b>Psychiatric medication use</b>			
SSRIs	28 (6.7%)	23 (10.5%)	0.096
TCA's	7 (1.7%)	11 (5.0%)	<b>0.016</b>
other antidepressants	25 (6.0%)	17 (7.8%)	0.398
any antidepressant	54 (13.0%)	43 (19.6%)	<b>0.027</b>

PTSD (post-traumatic stress disorder), BMI (body mass index), HTN (hypertension), DM (diabetes mellitus), CHF (congestive heart failure), LVH (left ventricular hypertrophy), Y1 (year 1, baseline), Y6 (year 6, follow-up), SCr (serum creatinine), eGFR (estimated glomerular filtration rate), CKD-EPI 2021 (Chronic Kidney Disease Epidemiology Collaboration 2021 equation), MDD (major depressive disorder), GAD (generalized anxiety disorder), SSRIs (selective serotonin reuptake inhibitors), TCAs (tricyclic antidepressants)