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Journal

Psychosomatic Medicine, 83(9)

ISSN

0033-3174

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Publication Date

2021-11-01

DOI

10.1097/psy.0000000000000968

Peer reviewed

HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Psychosom Med. 2021 ; 83(9): 978–986. doi:10.1097/PSY.0000000000000968.

The Association of Post-Traumatic Stress Disorder with longitudinal change in Glomerular Filtration Rate in World Trade Center responders

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Abstract

Objective: High levels of psychological distress increase the risk of a wide range of medical diseases. We investigated the association between posttraumatic stress disorder (PTSD) and kidney disease in this study.

Methods: World Trade Center (WTC) responders were included if they had ≥ 2 measures of estimated glomerular filtration rate (eGFR). The PTSD checklist (PCL) was used to define no PTSD (PCL<40), 'mild' PTSD (40 ≤PCL <50) and 'severe' PTSD (PCL ≥50). Subtypes of PTSD by symptom clusters were analyzed.. Multinomial logistic regression was used to estimate the association of PTSD with two GFR change outcomes (decline or increase) compared to the stable GFR outcome.

Results: In 2,266 participants, the mean age was 53.1 years, 8.2% female, and 89.1% were White. Individuals with PTSD (N=373; 16.5%) did not differ in mean baseline GFR from individuals without PTSD (89.73 vs. 90.56 ml/min/1.73 m2); p=0.29). Over a 2.01 years mean follow-up,a mean GFR decline of −1.51 ml/min/1.73m^2 per year was noted. In multivariable-

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Conflicts of Interest and Source of Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

No conflicts of interest.

adjusted models, PTSD was associated with GFR decline (aRR = 1.74 [1.32-2.30], p<0.001) compared to stable GFR, with 'Hyperarousal' symptoms showing the strongest association aRR =2.11 [1.40-3.19]; p<0.001).. Dose-response effects were evident when comparing mild to severe PTSD and comparing PTSD with *versus* without depression. PTSD was also associated with GFR rise (aRR = 1.47 [1.10-1.97], p<0.009). The association between PTSD and GFR change was stronger in participants <50 years of age.

Conclusions: PTSD may be a novel risk factor for exaggerated longitudinal GFR change in young, healthy adults. These findings need to be validated in other cohorts.

Keywords

PTSD; GFR; depression; kidney disease

Introduction:

High levels of psychological distress in humans can lead to abnormal biological processes and behavioral changes that can eventually cause medical disease.[1, 2] Persistent intrusive memories and additional symptoms as a result of a traumatic life event are a major cause of chronic mental stress.[3] The dreadful September 11, 2001 terrorist attacks led to various stress reactions nationally[4]. Between 11 and 13 years after the World Trade Center (WTC) disaster, 9.7% of first responders met DSM-IV criteria for current 7.9% remitted, and 5.9% partial post-traumatic stress disorder (PTSD) [5].

Chronic kidney disease (CKD) is common and associated with significant morbidity, mortality and healthcare costs.[6] Established risk factors, including age, race/ethnicity, diabetes mellitus (DM), hypertension (HTN) and cardiovascular disease (CVD), explain only part of the CKD risk.[7] One promising area for risk factor identification efforts is in the area of mental health disorders[8]. It was recently reported that severity of mental illness is associated with CKD.[8] Evidence suggests that PTSD and depression are associated with socioeconomic and behavioral factors such as poverty, substance abuse, and medical non-adherence that increase the risk of adverse health outcomes, including kidney damage [9]. Depression has been associated with incident CKD, rapid glomerular filtration rate (GFR) decline, and (end-stage kidney disease) ESKD.[10-14] Depression is often seen closely associated with PTSD after traumatic events[15]. PTSD has been associated with increased risk of HTN[16, 17], CVD[18, 19] and DM.[20] However, there are no published data on whether PTSD is a correlate of GFR decline or CKD. It is also not known if the severity of PTSD or the presence of depression in patients with PTSD is also associated with renal outcomes.

GFR decline is the hallmark of progressive CKD. While advanced CKD is well known to be associated with adverse outcomes,[21] recent data associate even mild GFR reductions with increased morbidity and mortality[22, 23]. In healthy populations, where the incidence of CKD is very low, the degree and rate of GFR decline has been proposed as a better outcome measure than clinical diagnoses like 'incident CKD'.[24] Besides GFR decline, an abnormal rise in GFR that is sometimes noted early in pathogenesis of kidney disease (glomerular hyperfiltration), is also associated with CKD[25], CVD[26] and mortality[27].This makes

the interpretation of change in GFR over time difficult to interpret early in the course of CKD and highlights the need to separate fall and rise of GFR with time. Risk factors associated with GFR decline or rise in the 'normal' GFR range (estimated [e] GFR > 60 ml/min/1.73m^2), are not well defined.

In this study, we investigated the association of PTSD with longitudinal change in GFR in the WTC Responder study. The WTC cohort was selected for this study since it has longitudinal data on GFR, PTSD, PTSD severity, PTSD symptom clusters, depression and CKD risk factors collected as part of the study protocol. We tested the hypothesis that PTSD is associated with GFR decline. We also investigated whether severe PTSD is associated with a greater GFR decline compared to mild PTSD. In addition, we examined whether patients with PTSD and comorbid depression would be at a higher risk of GFR decline than those without depression. Finally, we explored the associations of specific PTSD symptom category clusters with GFR decline.

Methods:

Data sources:

WTC Cohort: The World Trade Center (WTC) responder study has been previously described [28]. Briefly, the Stony Brook WTC Health and Wellness Program is an academic health monitoring program set up to prospectively follow the entire population of individuals who responded to the WTC disaster. The subject enrollment and screening for PTSD started immediately after 9/11/2021. WTC responders were eligible for this study if they had the demographic information (age, race, sex) required to calculate eGFR and had at least two measures of serum creatinine to calculate change in GFR. Yearly measurement of serum creatinine started in 2013.

Measured variables:

GFR measures: Serum creatinine was reported from laboratory tests performed for responders during monitoring visits. All labs in the Stony Brook WTC responder study are collected during follow-up visits on site in a routine blood draw procedure. All labs are sent to Sunrise Medical Laboratory[29] for testing. Since the serum creatinine test for subjects in this study was done at the same lab, there is no concern of intra- and/or inter-assay variance of the creatinine assay[30]. eGFR was calculated using the CKD-EPI equation [31]. All individual eGFR measurements for each subject from the first assessment (in 2013) to the final assessment (in 2017) were used to calculate the yearly change in GFR. The mean follow-up time was 2.01 (SD 0.98) years. We reported the mean rate of GFR change (ml/min/1.73m^2 per year) defined as the total change (rise or fall) in eGFR (from baseline to final) divided by the years of follow-up. We divided the mean baseline eGFR into four categories: ≥120 ml/min/1.73m^2, 90-119 ml/min/1.73m^2, 60-89 ml/min/1.73m^2 and < 60 ml/min/1.73m^2. We also report the final mean eGFR, divided into two categories: ≥ 60 ml/min/1.73m2 (N, %) and < 60 ml/min/1.73m2 (N, %).

Outcomes measures (GFR categories):

Of 2,266 patients in the WTC cohort with ≥ 2 eGFR measures, we noted that a large proportion (>25%) had a rise in GFR over the follow-up period (compared to typical age related yearly GFR decline after age > 40 of around 0.8-1.0 ml/min/1.73 m^2 [32]). Due to concerns of a potentially pathologic increase in GFR (glomerular hyperfiltration), we categorized GFR into three longitudinal categories based on baseline and final GFR: 'Stable', 'Decline' and 'Rise'. We divided the total of 2,266 patients in the WTC cohort into four quartiles with the upper-most quartile categorized as 'GFR Rise' (N=575, mean rate of GFR rise of +4.89 [SD 3.79] ml/min/1.73m^2 per year), the lower-most quartile categorized 'GFR Decline,' (N=568, mean rate of eGFR decline of −8.00 [SD 3.92] ml/min/1.73m^2 per year) and the middle two quartiles categorized 'Stable GFR' (N=1,123, mean rate of eGFR decline of −1.50 [SD 1.45] ml/min/1.73m^2) used as a reference category for analysis

PTSD measures: PTSD symptoms were measured using the PTSD 17-item checklist (PCL) adapted to the WTC exposures[33]. For the PCL, Cronbach's Alpha met conventional standards for high reliability (a = 0.96), but some have argued that Cronbach's alpha is not a valid measure of internal consistency[34]. Alternatively, omega hierarchical (0.87) and omega total (0.97) indicate that approximately 3% of the total PCL score variance was due to unsystematic measurement error, 10% was explained by multidimensionality, and 87% was explained by a common depression factor, such that much of the reliable variance in PCL scores (90%) was attributed to a common depression factor. Taken together, these reliability statistics indicate that the PCL exhibited high internal consistency in the current study.

Because PTSD is a heterogeneous disorder, we categorized PTSD in multiple ways. We separated individuals into 'PTSD' (PCL ≥44) *versus (vs.)* 'no-PTSD' for most analysis. To test the association of severity of PTSD, we further categorized 'PTSD' into 'mild PTSD' (40 ≤PCL <50) and 'severe PTSD' (PCL ≥50) [35]. We used data on PTSD symptom clusters following the four-factor model of PTSD into 'Re-experiencing', 'Avoidance', 'Emotional numbing', and 'Hyperarousal'[36] where each symptom cluster score was normed so that 0 referenced no symptoms and 1 referenced maximal symptoms possible on the scale.

Depression: Depression was defined based on symptoms measured using the 9-item patient health questionnaire (PHQ9≥10) [37]. For the PHQ-9, Cronbach's Alpha met conventional standards for high reliability (a = 0.96). Omega hierarchical (0.90) and omega total (0.97) indicate that approximately 3% of the total PHQ-9 score variance was due to unsystematic measurement error, 7% was explained by multidimensionality, and 90% was explained by a common depression factor, such that much of the reliable variance in PHQ-9 scores (93%) was attributed to a common depression factor. Taken together, these reliability statistics indicate that the PHQ-9 exhibited high internal consistency in the current study.

Covariates: To evaluate the specific association of PTSD with GFR, we included all covariates (at baseline) known to be associated with CKD in the analysis. These included demographic factors including age [38], race [39], ethnicity[40], sex [41], and educational

level [42]. The co-morbidities included diabetes [43], hypertension [44], obesity (measured via mean body mass index [BMI]) [45], cardiovascular disease [46] and stroke [47]. In addition we also included psychosocial conditions like depression [14], smoking [48] and alcohol abuse [49]. Demographic variables including age, race (Black vs. White), ethnicity (Hispanic vs non-Hispanic), sex (female *vs* male) and educational attainment (less than high school or having a high school diploma) were self-reported. Comorbidities included mean body mass index (BMI) reported using kg/m^2 as measured by clinical staff, while self-reports were used to define diabetes, hypertension, heart attack, stroke, and heart failure. Smoking (categorized current, former and never smoker) and alcohol overuse (measured using the alcohol use disorders identification test [AUDIT≥10]) were self-reported.

Observations occurred from 1/1/2013-12/31/2017; covariates were indexed at the individual's first eGFR observation occasion.

Statistical Analysis:

Analyses began by describing the sample as a whole using means and standard deviations (SD) or percentages in each category when appropriate. Unadjusted p-values were derived either from χ^2-tests for categorical variables and from non-parametric trend tests for continuous variables. Next, we used multinomial logistic regression to estimate the risk of GFR decline and rise, as compared to stable GFR (the reference category). Multinomial logistic regression was used *in lieu* of ordinal regression because the proportional odds assumption was broken since GFR decline is believed to occur for a biologically different reasons as compared to GFR rise[50]. In these analyses, the reference category is labelled using the standard of 1.00. Multivariable-adjusted relative risks (aRR), 95% confidence intervals, and p-values were reported. All inferential analyses were performed using Stata V16/MP [StataCorp].

Results:

Baseline characteristics of individuals in the WTC cohort:

Table 1 shows the baseline characteristics and renal profile of all individuals. Of a total of 2,266 individuals in the WTC cohort had ≥ 2 eGFR measures. PTSD diagnostic criteria were met in 373 (16.5%) and depression criteria in 208 (9.2%). The mean age at baseline was 53.1 (SD 8.52) years, while 185 (8.2%) were female sex, 2019 (89.1%) were White and 185 (8.2%) were Hispanic. In total, 2169 (95.7 %) had at least high school level education. 154 individuals (6.8%) in the cohort were current smokers, 633 (27.9%) former smokers, while 1479 (65.3%) were never smokers. Alcohol abuse was reported in 382 (16.9%) individuals. The mean BMI was 31.21 kg/m^2 (SD 5.46). Hypertension was reported in 674 (29.7%), diabetes in 196 (8.6%), heart attack in 347 (15.3%), stroke in 27 (1.2%), and heart failure in 367 (16.2%).

The mean follow-up time was 2.01 (SD 0.98) years. The baseline eGFR was 90.42 (SD 13.85) $ml/min/1.73m^2$, the final eGFR was 87.45 (14.23) $ml/min/1.73m^2$ and the mean rate of eGFR change over time was −1.51 (SD 5.43) $ml/min/1.73m^2$. Among baseline GFR categories, 1262 (55.7%) individuals had a baseline eGFR of ≥90, 952 (42%) eGFR of

60-89 and only 52 (2.3%) had a baseline eGFR of < 60 ml/min/1.73m^2. A total of 2185 (96.4%) individuals had a final eGFR ≥ 60, while only 81 (3.6%) had a final eGFR < 60 ml/min/1.73m^2 (Table 1).

Comparison of individuals with and without PTSD:

Table 1 also compares the baseline characteristics and renal profile of all individuals with and without PTSD. Those with PTSD were more likely to be older, female, have depression and be smokers and have a history of alcohol abuse compared to those without PSTD. Those with PTSD also had a higher mean BMI and a higher prevalence of co-morbid hypertension, diabetes, heart attack and heart failure compared to individuals without PTSD.

The rate of GFR decline over time was greater (−1.80 [6.31] ml/min/1.73m^2 per year) in those with PTSD compared to those without (−1.45 [5.24] ml/min/1.73m^2 per year) but this difference was not statistically significant. Individuals with PTSD had a higher prevalence of baseline and final eGFR of < 60 ml/min/1.73m^2 (Table 1).

Comparison of GFR categories:

Table 2 compares the baseline characteristics and renal profile of individuals in the three GFR categories. Those in the ‘GFR Rise’ category (N=575) had a rate of GFR rise of +4.89 [SD 3.79] ml/min/1.73m^2 per year), while those in the ‘GFR Decline’ category (N=568) had a rate of eGFR decline of −8.00 [SD 3.92] ml/min/1.73m^2 per year. Those in the ‘Stable GFR’ category (N=1,123) had a rate of eGFR decline of −1.50 [SD 1.45] ml/min/1.73m^2 per year. Those with GFR decline (compared to stable GFR) were likely to have a history of stroke. Those with a GFR rise overtime were more likely to have younger age and stroke and less likely to have heart attack and heart failure history. Individuals with GFR decline were more likely to have PTSD (p= 0.005) and depression (p =0.034), however this association did not reach statistical significance in those with GFR rise.

Individuals with GFR decline had a higher (93.42 ml/min/1.73m^2) while those with GFR rise (84.31 ml/min/1.73m^2) had a lower baseline mean GFR compared to the stable GFR group (92.04 ml/min/1.73m^2). Individuals with a GFR decline had a lower (80.72 ml/min/1.73m^2), while those with a GFR rise had a higher final mean GFR (91.85 ml/min/1.73m^2) compared to those with stable GFR (88.6 ml/min/1.73m^2) (Table 2).

Associations of PTSD with change in GFR vs. stable GFR over time:

Because the biological factors involved in GFR increases may differ from those involved in GFR decreases, we conducted separate analyses for the association of PTSD with increases GFR vs. stable GFR and the association of PTSD with decreases vs. stable GFR (Table 3). PTSD was associated with GFR decline (RR = 1.67 [1.27–2.19], p <0.001). After adjusting for demographic features (age, sex, race and ethnicity), the association remained statistically significant (aRR = 1.68 [1.28–2.21], p <0.001). After subsequent adjustment for comorbid conditions (diabetes, hypertension, stroke, heart attack, chronic heart failure, and BMI) and further adjustment for psychosocial factors (educational attainment, smoking status, and alcohol abuse), the association of PTSD with GFR decline remained statistically significant:

aRR = 1.71 [1.30-2.26], p = <0.001 and aRR = 1.74 [1.32-2.30], p <0.001 respectively (Figure 1, Table 3).

Those with PTSD had a 1.39 times greater risk of GFR rise compared to stable GFR (p = 0.022) (Table 3). After adjusting for all key features, the association of PTSD with GFR rise remained statistically significant: aRR = 1.47 [1.10-1.97], p = 0.009 (Figure 2, Table 3).

Association of severity of PTSD with GFR decline:

The association of severity of PTSD with GFR decline and rise compared to stable GFR is shown in Table S1, Supplemental Digital Content. Those with mild PTSD had a 1.43 times greater association with GFR decline, while those with severe PTSD had a 1.68 times greater association with GFR decline compared with stable GFR (p = 0.05 and 0.001 respectively). After adjusting for all key features, the association of mild PTSD and severe PTSD with GFR decline remained statistically significant: aRR = 1.45 [1.01-2.07], p = 0.044; and aRR = 1.77 [1.28-2.24], p = <0.001 respectively (Figure 1). GFR rise was not associated with severity of PTSD (Figure 2, Table S1).

Association of GFR change with PTSD with and without co-morbid depression:

The association of PTSD and depression with GFR decline/rise is shown in Table S2, Supplemental Digital Content. Depression alone (in the absence of PTSD) was not associated with GFR decline (unadjusted RR = 0.99 [0.48-2.05). PTSD even in the absence of depression was associated with GFR decline (unadjusted RR = 1.64 [1.15-2.34], p = 0.007; fully adjusted RR = 1.67, [1.16-2.4], p = 0.006). However, when PTSD and depression were co-existent, the association with GFR decline was even stronger (unadjusted aRR = 1.71 [1.18-2.50], p = 0.005; fully adjusted RR = 1.83, [1.24-2.7], p= 0.002), (Figure 1, Table S2).

Depression alone (in the absence of PTSD) was also not associated with GFR rise (unadjusted RR = 0.77 [0.35-1.66) (Table S2). PTSD in the absence of depression was associated with GFR rise but the aRR did not reach statistical significance. However comorbid PTSD and depression, as compared to no PTSD and no depression, was significantly associated with GFR rise (unadjusted RR = 1.59 [1.09-2.32], p = 0.017; fully adjusted RR = 1.76, [1.19-2.6], p=0.005), (Figure 2, Table S2).

The interaction between PTSD and depression was not statistically significant for GFR decline (aRR = 1.04, 0.43-2.53, p=0.918) or GFR increase (aRR = 1.78, 0.69-4.53, p=0.231).

Association of specific PTSD symptom cluster categories with GFR change:

Table S3 (Supplemental Digital Content) shows the association of PTSD symptom categories with GFR change. The symptom categories of ‘Re-experiencing’ (unadjusted RR 1.82 [1.12-2.96], p = 0.016), ‘Avoidance’ (1.66 [1.17-2.35], p = 0.004), ‘Numbing’ (1.98 [1.26-3.12], p = 0.003) and ‘Hyperarousal’ (1.98 [1.33-2.95], p = 0.001) were all significantly associated with GFR decline. Even after adjustment for all covariates, the association of PTSD symptom categories with GFR decline remained statistically

significant: Re-experiencing: aRR =1.95 [1.18-3.24], p =0.010; Avoidance: 1.71 [1.18-2.46], p =0.003; Numbing: 2.10 [1.32-3.35], p =0.002; and Hyperarousal: 2.11 [1.40-3.19]; p<0.001 (Figure 1, Table S3).

Only the 'Hyperarousal' PTSD symptom category was significantly associated with GFR rise (unadjusted RR = 1.53 [1.02-2.29], p=0.040. and 1.55 [1.04-2.33], p= 0.033 after adjustment for all covariates), (Figure 2, Table S3).

Association of PTSD with change in GFR in young individuals:

In the WTC cohort, the mean age of the individuals was 53.1 (SD=8.52) years at baseline. We studied the association of PTSD with GFR in a sub-group of young individuals (mean baseline age =45.80 [SD 4.03] years). The association of PTSD with GFR decline in younger individuals was even stronger than in the overall cohort (Table S4, Supplemental Digital Content). PTSD was associated with 2.11-fold risk of GFR decline compared to stable GFR (aRR= 2.11 [1.38-3.22], p= 0.001) and there was an even lower probability of having observed this effect after adjustment for all covariates, if the null hypothesis (aRR = 1) were true (aRR= 2.21 [1.41-3.44], p= <0.001), (Figure 1, Table S4).

Similarly, the association of PTSD with GFR rise was stronger in the young than in the overall cohort (Table S4). PTSD was associated with 1.84 times increased risk of GFR decline compared to stable GFR (aRR= 1.84 [1.21-2.8], p= 0.004), which remained significant even after adjustment for all covariates (aRR= 1.97 [1.26-3.06], p= 0.003), (Figure 2, Table S4).

There was no interaction between PTSD and age in responders aged <50 years when looking at decline in GFR (aRR = 1.09, 0.97-1.21, p=0.148) or increase in GFR (aRR = 1.02, 0.91-1.13, p=0.781). This is also true for the entire population as a whole when looking at declines in GFR (aRR = 0.99, 0.96-1.03, p=0.599) or increases in GFR (aRR = 0.99, 0.95-1.02, p = 0 .473).

Discussion:

This study of patients from the World Trade Center cohort was conducted to determine whether PTSD was associated with changes in kidney function over time. We observed that PTSD, compared to no PTSD, was associated with GFR decline and this association increased with more severe PTSD. We observed that PTSD even in the absence of depression was associated with GFR decline. In the presence of comorbid depression, PTSD was more strongly associated with GFR decline than PTSD without depression. We also observed that each PTSD symptom category was associated with GFR decline. PTSD compared to no PTSD was significantly associated with GFR rise (compared to stable GFR) 'Hyperarousal' was associated with GFR rise and PTSD had an additive effect with depression in association with GFR rise. Finally, we noted that the association of PTSD with GFR decline and with GFR rise remained significant in younger individuals (baseline age < 50 years).

To our knowledge this is the first study to report the association of PTSD with GFR. While PTSD is known to be associated with CKD risk factors[16, 18, 20], our results indicate that PTSD is associated with greater GFR decline in patients without prevalent CKD. Those in the 'Stable GFR' category (used as the comparison outcome relative to those changing in GFR [either increasing or decreasing]) had a mean rate of eGFR decline of −1.50 [SD 1.45] ml/min/1.73m^2 per year similar to the age-related GFR observed in the general population after the fourth decade of life[32]. We observed a ≈ 1.7 times greater association of PTSD with GFR decline (compared to stable GFR) and that severe PTSD was more strongly associated with GFR decline than mild PTSD. Evidence of increased risk with more severe PTSD suggests a dose-response relationship and contributes to building evidence for a causal relationship between PTSD and GFR decline.[51] The prediction of change in GFR, as opposed to concurrent association with GFR at a single point in time, is also consistent with putative causality, as change in an outcome is a criterion of causality. Our observation that 'Re-experiencing', 'Avoidance', 'Numbing' and 'Hyperarousal' symptoms were individually associated with GFR decline suggests the association of GFR decline is present in all dimensions of PTSD symptomology, with 'Hyperarousal' being most strongly associated. This association of PTSD symptoms with kidney function has not been reported before. Finally, our finding that the association of PTSD with GFR decline was even stronger (≈ 2.2 times) in younger adults (baseline age < 50 years) is intriguing and opens the road to further studies of mental stress and associated kidney disease in young individuals. Taken together these findings suggest PTSD as a novel risk factor of GFR decline in young relatively healthy adults.

The association of PTSD with rise in GFR was unexpected. As mentioned previously, GFR rise could be physiologic but it is also seen in the pathologic setting of glomerular hyperfiltration that is often noted in the initial phase of some types of CKD, such as diabetic nephropathy[52]. We observed a ≈ 1.5 times greater association of PTSD with GFR rise (compared to stable GFR) and specifically with the 'Hyperarousal' symptom category. Our cohorts consisted of mostly overweight individuals (mean BMI was 31.21 kg/m^2 [SD 5.46]). However, even after adjustment for BMI and diabetes (conditions linked to glomerular hyperfiltration) the association of PTSD with GFR rise was significant. In addition, depression had an additive effect in the presence of PTSD similar to that noted with GFR decline. These data suggest some, albeit less robust, association of PTSD with rising GFR. But we did not observe a GFR rise association with PTSD severity as seen with GFR decline and only suggesting the association of PTSD with GFR rise might have a different implication and/or mechanism.

We found no overall association between PTSD and mean rate of GFR decline in the WTC cohort (Table 1).This appears to have emerged from the high variability in GFR in young, relatively healthy individuals suggesting that PTSD could be associated with GFR change in either direction at midlife in this cohort. Thus, while PTSD was associated with both increasing and decreasing GFR, this tendency towards high variance in this group were, on average, balanced. For this reason, and also because of the aforementioned differences in the biological processes involved in decreases vs. increases in GFR, we divided the sample into three categories for this analysis ("decline," "increase," and (for comparison purposes)

"stable"). Future studies are needed to determine whether early changes in GFR are truly pathologic for the development of advanced CKD in the setting of PTSD.

The potential mechanisms of how PTSD could affect GFR are not clear. Our findings remained significant even after adjustment for most known risk factors for CKD. One potential hypothesis is that inflammation-related processes associated with PTSD are a driving force for renal damage. This hypothesis is based on previous studies demonstrating inflammation to be strongly associated with PTSD [53, 54] and with CKD incidence [55] and progression [56]. Another possible hypothesis is the possible role of the hypothalamic-pituitary axis which is altered in PTSD[57] and has also been implicated in the genesis of kidney disease[58-60]. Hyper-arousal, the PTSD symptom cluster most strongly associated with GFR in this study, has been associated with blood pressure variability which is a hallmark of PTSD-associated autonomic dysfunction [61]. Interestingly BP variability has also been associated with adverse outcomes in patients with CKD[62]. In addition, there could be a potential role of premature biological aging which has been suggested as a potential mechanism involved in the pathogenesis of both CKD[63] and PTSD[64]. There has been some concern that WTC responders are aging more rapidly than expected, with notable results indicating associations between PTSD and increased c-reactive protein [65], changes to cognition [66], differences in markers of cerebral proteinopathy indicative of a neuroimmunologic response [67, 68], shortened leukocyte telomere length [69]. While we could not test these hypotheses in the current study, they should be a focus of future studies.

There is a strong association of PTSD and depression due to shared pathophysiology, overlapping symptoms and the association of depression with PTSD is also considered a separate subset of the PTSD phenotype.[70] Unlike previous studies, we did not observe an association of depression with GFR decline[10-14]. Possible reasons are the difference in the WTC cohort compared to previously studied cohorts which comprised of older, sicker individuals[10-14]. Also, previous studies did not separate PTSD from depression diagnosis to study the individual and combined effects like our study. We defined depression as a PHQ-9 score of > 10, which would capture cases of mild depression. It is possible that the effect of depression on GFR is noted only with more severe cases and this needs to be tested in future studies. Overall, our findings that depression increases the risk of GFR change in the presence ofPTSD supports the hypothesis that severity of mental stress is associated with GFR.

Strengths of the present study included the ability to measure PTSD diagnoses, severity and individual symptoms. The individuals in the WTC were relatively young and healthy at baseline compared to other cohorts that have been previously used to study kidney disease, providing a unique opportunity to test novel risk factors for GFR change in patients without existing CKD. Our study provides stimulus for further research on the effects/mechanisms of pathologic mental stress on the kidney. This study adds to the growing body of research demonstrating the long-term health consequences suffered by WTC first responders. Also our study is timely. In the recent changing world fighting with the COVID-19 pandemic, there is major increase in PTSD[71]. We recently reported the association of kidney disease with COVID-19[72]. It will be important to study the long-term effects of COVID-19-associated PTSD on the kidneys.

Our study also has significant limitations. This is an observational study and cannot establish causality, which can only be achieved in the context of a true experiment. We did not have data on proteinuria that is often associated with change in GFR over time. We did not have data on medications including drugs that influence GFR, that decrease PTSD severity and which are nephrotoxic. Because the individuals in this cohort were relatively young and healthy, the 'hard' kidney outcomes of incident CKD, doubling of serum creatinine or ESKD could not be analyzed in this study Also, due to the relatively young age and low prevalence of CKD, DM and CVD in our cohort, the expected association of these factors with GFR decline was not observed. Our study needs to be replicated in cohorts with older baseline age and a greater comorbidity burden, e.g. Claims (Medicare/Medicaid) databases, to test if the PTSD association with GFR is still present in sicker, older individuals. The co-morbid conditions were self-reported in the WTC database and were not defined on diagnostic codes. Finally, we had a very low proportion of females and African-Americans in our cohort, limiting the generalizability of our overall findings in these demographic sub-groups.

In conclusion, we report PTSD as a potential novel risk factor for early GFR change especially GFR decline in young, healthy individuals. The present findings need to be validated in more diverse cohorts with a higher risk of CKD and further studies are needed to investigate the possible mechanisms of chronic PTSD-related kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

List of Abbreviations:

BMI	Body Mass Index
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
ESKD	End Stage Kidney Disease
GFR	Glomerular Filtration Rate
HTN	Hypertension
PCL	PTSD 17-item symptom checklist
PTSD	Post Traumatic Stress Disorder
WTC	World Trade Center

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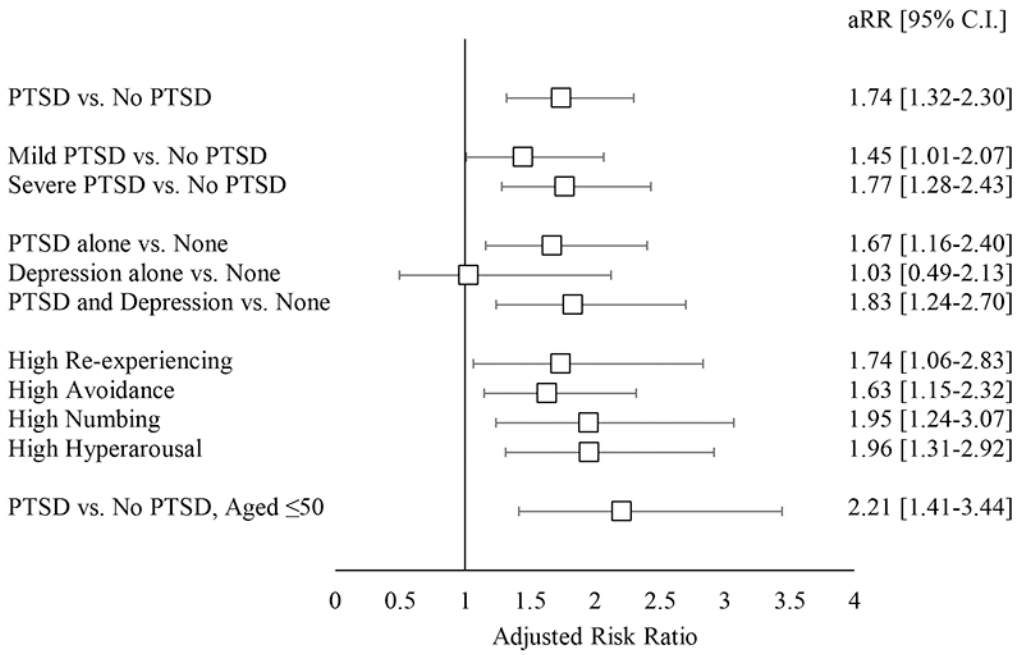

Figure 1: Association of PTSD with GFR Decline

Forest Plot to display to association between PTSD, severity of PTSD, co-morbid depression and symptom clusters of PTSD with GFR decline. The last bar displays the association of PTSD with GFR decline in individuals with a mean age < 50 at baseline. GFR = glomerular filtration rate, PTSD = post-traumatic stress disorder, aRR = adjusted risk ratio, CI= confidence interval

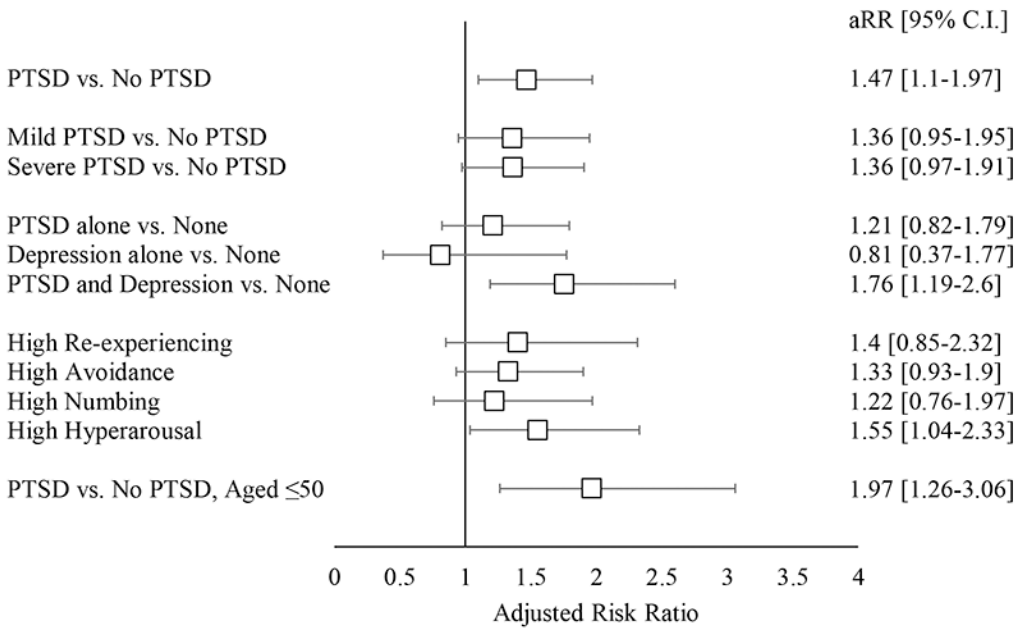

Figure 2: Association of PTSD with GFR Rise

Forest Plot to display to association between PTSD, severity of PTSD, co-morbid depression and symptom clusters of PTSD with GFR rise. The last bar displays the association of PTSD with GFR rise in individuals with a mean age < 50 at baseline. GFR = glomerular filtration rate, PTSD = post-traumatic stress disorder, aRR = adjusted risk ratio, CI= confidence interval

Table 1:

Characteristics of all individuals and those with PTSD vs no PTSD

Characteristics	All patients	No PTSD	PTSD	p-value
	N = 2,266	N=1,893 (83.5%)	N=373 (16.5%)	
Age (years, Mean, SD)	53.1 (8.52)	52.95 (8.61)	53.9 (7.99)	0.049
Sex (female, N, %)	185 (8.2)	145 (7.7)	40 (10.7)	0.048
Race/Ethnicity (N, %)				0.34
White	2019 (89.1)	1683 (88.9)	336 (90.1)	
Black	62 (2.7)	57 (3)	5 (1.3)	
Hispanic	185 (8.2)	153 (8.1)	32 (8.6)	
Education (high school degree) (N, %)	2169 (95.7)	1818 (96)	351 (94.1)	0.091
PTSD (N, %)	373 (16.5)	0 (0)	373 (100)	
Depression (N, %)	208 (9.2)	36 (1.9%)	172 (46.2)	<0.001
Smoking (N, %)				<0.001
Current Smoker	154 (6.8)	115 (6.1)	39 (10.5)	
Former Smoker	633 (27.9)	508 (26.8)	125 (33.5)	
Never Smoker	1479 (65.3)	1270 (67.1)	209 (56)	
Alcohol overuse (N, %)	382 (16.9)	270 (14.3)	112 (30)	<0.001
Hypertension (N, %)	674 (29.7)	538 (28.4)	136 (36.5)	0.002
Diabetes (N, %)	196 (8.6)	154 (8.1)	42 (11.3)	0.049
BMI (kg/m^2), Mean (SD)	31.21 (5.46)	31.08 (5.44)	31.85 (5.52)	0.012
Heart Attack (N, %)	347 (15.3)	267 (14.1)	80 (21.4)	<0.001
Stroke (N, %)	27 (1.2)	20 (1.1)	7 (1.9)	0.18
Heart Failure (N, %)	367 (16.2)	281 (14.8)	86 (23.1)	<0.001
Baseline GFR, Mean (SD) (ml/min/1.73m^2)	90.42 (13.85)	90.56 (13.76)	89.73 (14.34)	0.29
≥90 (N, %)	1262 (55.7)	1052 (55.6)	210 (56.2)	0.055
60-89 (N, %)	952 (42.0)	804 (42.5)	148 (39.8)	
< 60 (N, %)	52 (2.3)	37 (2.0)	15 (4.0)	
Rate of GFR decline, Mean (SD) (ml/min/1.73m^2/year)	−1.51 (5.43)	−1.45 (5.24)	−1.80 (6.31)	0.26
Final GFR, Mean (SD) (ml/min/1.73m^2)	87.45 (14.23)	87.65 (14.01)	86.43 (15.26)	0.13
≥ 60 (N, %)	2185 (96.4)	1832 (96.8)	353 (94.6)	0.042
< 60 (N, %)	81 (3.6)	61 (3.2)	20 (5.4)	

Note. Means are reported with standard deviations in parentheses for variables with interval/ratio scales. Frequencies and percentages are reported for nominal variables. p-values indicate the probability of the observed difference in subject characteristics in the current sample, if there is no difference in the population, unadjusted for multiple testing.

Table 2:

Characteristics of GFR categories

Characteristics	Stable GFR	GFR Decline	p-value	GFR Rise	p-value
	N=1123 (49.6%)	N=568 (25.1%)		N=575 (25.4%)	
Age (years, Mean, SD)	53.71 (8.26)	53.19 (9.19)	0.23	51.83 (8.2)	<0.001
Sex (female, N, %)	90 (8%)	45 (7.9)	0.95	50 (8.7)	0.63
Race/Ethnicity (N, %)			0.79		0.25
White	1023 (89)	513 (88.6)		479 (91.0)	
Black	28 (2.5)	19 (3.3)		52 (9.0)	
Hispanic	72 (8.5)	36 (8.1)		44 (7.7)	
Education (high school degree) (N, %)	1077 (95.9)	540 (95.1)	0.43	552 (96.0)	0.92
PTSD (N, %)	163 (14.5)	113 (19.9)	0.005	97 (16.9)	0.20
Depression (N, %)	93 (8.3)	65 (11.5)	0.034	50 (8.7)	0.78
Smoking (N, %)			0.63		0.35
Current Smoker	79 (7)	44 (7.7)		31 (5.4)	
Former Smoker	312 (27.8)	167 (29.4)		154 (26.8)	
Never Smoker	732 (65.2)	357 (62.9)		390 (67.8)	
Alcohol overuse (N, %)	185 (16.5)	95 (16.7)	0.90	102 (17.7)	0.51
Hypertension (N, %)	341 (30.4)	164 (28.9)	0.53	169 (29.4)	0.68
Diabetes (N, %)	95 (8.5)	57 (10)	0.29	44 (7.7)	0.57
BMI (kg/m^2), Mean (SD)	31.4 (5.55)	30.99 (5.42)	0.32	31.05 (5.31)	0.31
Heart Attack (N, %)	192 (17.1)	82 (14.4)	0.16	73 (12.7)	0.018
Stroke (N, %)	7 (0.6)	9, (1.6)	0.052	11, (1.9)	0.014
Heart Failure (N, %)	201 (17.9)	91 (16.0)	0.34	75 (13.0)	0.010
Baseline GFR, Mean (SD) (ml/min/1.73m^2)	92.04 (13.43)	93.42 (13.23)	0.045	84.31 (13.43)	<0.001
≥90 (N, %)	683 (60.8)	375 (66)	0.017	204 (35.4)	<0.001
60-89 (N, %)	424 (37.8)	182 (32)		346 (60.2)	
< 60 (N, %)	16 (1.4)	11 (1.9)		25 (4.4)	
Rate of GFR decline, Mean (SD) (ml/min/1.73m^2/year)	−1.50 (1.45)	−8.00 (3.92)	<0.001	4.89 (3.79)	<0.001
Final GFR, Mean (SD) (ml/min/1.73m^2)	88.6 (13.65)	80.72 (14.25)	<0.001	91.85 (12.94)	<0.001
≥ 60 (N, %)	1093 (97.3)	530 (93.3)	<0.001	566 (98.4)	0.002
< 60 (N, %)	30 (2.7)	38 (6.7)		9 (1.6)	

Note. Means are reported with standard deviations in parentheses for variables with interval/ratio scales. Frequencies and percentages are reported for nominal variables.

Table 3.

Association of PTSD with GFR change

PTSD vs. No PTSD	Stable GFR	GFR Decline		GFR Rise	
		RR, [95% C.I.]	p-value	RR, [95% C.I.]	p-value
Unadjusted	1.00	1.67 [1.27-2.19]	<0.001	1.39 [1.05-1.83]	0.022
Adjusting for Age, Sex, Race/Ethnicity	1.00	1.68 [1.28-2.21]	<0.001	1.42 [1.07-1.88]	0.016
Additionally adjusting for diabetes, hypertension, stroke, heart attack, heart failure, and BMI	1.00	1.71 [1.30-2.26]	<0.001	1.42 [1.07-1.89]	0.015
Additionally adjusting for educational attainment, smoking status, and alcohol overuse	1.00	1.74 [1.32-2.30]	<0.001	1.47 [1.10-1.97]	0.009

Note. RR = risk ratio. 95% CI = 95% confidence interval. p-value = probability of the observed RR, if the null hypothesis is true (RR = 1).