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Cognitive Impairment: A Novel Risk Factor for Rapid Kidney Function Decline and Incident CKD in Middle-Aged Adults

--Manuscript Draft--

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Abstract:	Background: Emerging evidence suggests that better cognition is associated with a lower risk of CKD. However, whether early-onset cognitive impairment (CI) at baseline is linked to rapid estimated glomerular filtration rate (eGFR) decline or incident CKD remains unclear. Methods: We conducted a prospective cohort study of 5,761 World Trade Center (WTC) responders (mean age: 53.8 ± 7.9 years) without CKD at baseline, followed for a mean of 4.2 ± 1.9 years. CI was defined as a Montreal Cognitive Assessment (MoCA) score <23, with a subgroup analysis for baseline dementia (MoCA ≤18). Primary outcomes included annual eGFR change and rapid eGFR decline (< -5

	mL/min/1.73 m² per year). The secondary outcome was incident CKD (eGFR <60 mL/min/1.73 m² or diagnosis code). Multivariable Cox proportional hazards models and linear regressions were used for binary and continuous outcomes, respectively. Sensitivity analyses included looking at the effect of baseline mild cognitive impairment (MCI) (MoCA score 19-23), propensity matching for demographics, baseline age <60 years, removal of baseline post-traumatic stress disorder (PTSD)/ depression or baseline head trauma/stroke/cardiovascular disease and after exclusion of those who died during follow-up. Results: At baseline, 1,446 (25%) individuals had CI, while 89 (2%) had dementia. The mean baseline eGFR was 91.1 mL/min/1.73 m², with an overall decline of –1.2 mL/min/1.73 m² per year. Rapid eGFR decline occurred in 550 (10%) individuals. After adjusting for age, sex, race/ethnicity, comorbidities, WTC exposure, screened PTSD, and baseline eGFR, CI and dementia were significantly associated with rapid eGFR decline (adjusted hazard ratio [aHR]: 1.63 and 2.42, respectively; both p < 0.001) and faster annual eGFR decline. Findings were consistent across all sensitivity analyses. Additionally, 248 (4%) individuals developed incident CKD. Both baseline CI (aHR: 1.72, p < 0.001) and dementia (aHR: 2.77, p = 0.010) were significantly associated with incident CKD. Conclusions: Among middle-aged individuals without CKD, early-onset cognitive impairment was independently associated with rapid eGFR decline and incident CKD. These findings warrant validation in other cohorts.
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Title: Cognitive Impairment

Subtitle: A Novel Risk Factor for Rapid Kidney Function Decline and Incident CKD in Middle-Aged Adults

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List of Abbreviations:

WTC: World Trade Center, BMI: Body Mass Index; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease, DM: Diabetes Mellitus; ESKD: End Stage Kidney Disease, HTN: Hypertension; eGFR: Estimated Glomerular Filtration Rate; CI: Cognitive Impairment, MCI: Mild Cognitive Impairment, MoCA: Montreal Cognitive Assessment PCL: PTSD 17-item symptom checklist, PTSD: Post Traumatic Stress Disorder, PHQ-9: Patient Health Questionnaire-9 assessment.

Abstract:

Background: Emerging evidence suggests that better cognition is associated with a lower risk of chronic kidney disease (CKD). However, whether early-onset cognitive impairment (CI) at baseline is linked to rapid estimated glomerular filtration rate (eGFR) decline or incident CKD remains unclear.

Methods: We conducted a prospective cohort study of 5,761 World Trade Center (WTC) responders (mean age: 53.8 ± 7.9 years) without CKD at baseline, followed for a mean of 4.2 ± 1.9 years. CI was defined as a Montreal Cognitive Assessment (MoCA) score ≤23, with a subgroup analysis for baseline dementia (MoCA ≤18). Primary outcomes included annual eGFR change and rapid eGFR decline (< -5 mL/min/1.73 m² per year). The secondary outcome was incident CKD (eGFR <60 mL/min/1.73 m² or diagnosis code). Multivariable Cox proportional hazards models and linear regressions were used for binary and continuous outcomes, respectively. Sensitivity analyses included looking at the effect of baseline mild cognitive impairment (MCI) (MoCA score 19-23), propensity matching for demographics, baseline age <60 years, removal of baseline post-traumatic stress disorder (PTSD)/ depression or baseline head trauma/stroke/cardiovascular disease and after exclusion of those who died during follow-up.

Results: At baseline, 1,446 (25%) individuals had CI, while 89 (2%) had dementia. The mean baseline eGFR was 91.1 mL/min/1.73 m², with an overall decline of –1.2 mL/min/1.73 m² per year. Rapid eGFR decline occurred in 550 (10%) individuals. After adjusting for age, sex, race/ethnicity, comorbidities, WTC exposure, screened PTSD, and baseline eGFR, CI and dementia were significantly associated with rapid eGFR decline (adjusted hazard ratio [aHR]: 1.63 and 2.42, respectively; both $p < 0.001$) and faster annual eGFR decline. Findings were consistent across all sensitivity analyses. Additionally, 248 (4%) individuals developed incident CKD. Both baseline CI (aHR: 1.72, $p < 0.001$) and dementia (aHR: 2.77, $p = 0.010$) were significantly associated with incident CKD.

Conclusions: Among middle-aged individuals without CKD, early-onset cognitive impairment was independently associated with rapid eGFR decline and incident CKD. These findings warrant validation in other cohorts.

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Introduction:

A mild decline in estimated glomerular filtration rate (eGFR) of approximately 0.75 mL/min/1.73 m² per year is expected with normal kidney aging[1]. However, a greater-than-expected decline is a key indicator of chronic kidney disease (CKD) development and progression[2]. Well-established risk factors for rapid eGFR decline include age, sex, race, socioeconomic status, genetic predisposition, albuminuria, and comorbidities such as diabetes mellitus and hypertension[3,4]. Less is known about risk factors for rapid eGFR decline in middle-aged individuals with normal kidney function[3].

Patients with advanced CKD and end-stage kidney disease (ESKD) have a higher incidence of cognitive impairment (CI)[5-10], which are linked to poorer healthcare outcomes[11]. Furthermore, rapid eGFR decline has been associated with cognitive decline[7,10,12,13]. Cognitive dysfunction has been observed even in early eGFR decline, possibly due to vascular brain injury or related neuroinflammation[9]. Most studies have explored CKD as a predictor and CI as an outcome, often relying on cross-sectional designs. Yet even though mechanisms that are linked to CKD are also related to early neurodegenerative processes, few studies have considered the reverse hypothesis. One study that did reported that, in patients with CKD, the presence of CI was associated with more rapid eGFR decline[7]. Additionally, prior studies examining cognition and kidney disease have focused on older adults at a time (≥65 years old) when neurodegeneration has already commenced for most people [10,12-15]. A recent longitudinal study reported increased risk of CI in middle-aged individuals with CKD[16]. Thus, while robust epidemiological evidence links CKD to future cognitive decline, the potential role of neurocognitive impairments to predict eGFR decline in middle-aged individuals without CKD remains unclear.

CI has been linked to an increased risk of cardiovascular disease (CVD) [17,18], while higher cognitive function is associated with a lower risk of hypertension (HTN)[19]. Both CVD and HTN are well-established risk factors for CKD. A recent Mendelian randomization study suggested a causal association between better cognitive function and a lower risk of CKD[20]. Despite the strong epidemiological link between CKD and CI, whether baseline cognitive function predicts kidney function decline remains unclear. We hypothesized that baseline cognitive impairment is associated with an increased risk of rapid eGFR decline and incident CKD in middle-aged individuals without pre-existing kidney disease. To test this hypothesis, we analyzed data from the World Trade Center (WTC) responder cohort[21].

Methods:

Setting

The World Trade Center (WTC) responder cohort presents a unique opportunity to study this association in a relatively young population, where CKD is uncommon, yet early-onset CI is prevalent[22]. This setting allows us to examine the temporal relationship between CI and kidney function decline with minimized confounding. The WTC responder cohort undergoes protocolized annual assessments of eGFR and cognition, providing a unique opportunity to examine whether CI predicts future GFR decline and/or CKD.

Data Source and Study Population

Data were obtained from the WTC Health and Wellness Study, a prospective health monitoring program that follows first responders present at the WTC after the September 11, 2001, terrorist attacks, as previously described.[21] Participant screening and enrollment began one month after the response effort concluded, following the final extinguishment of fires. Annual assessments include medical history, physical examinations, and mental health evaluations. Serum creatinine (SCr) measurements became available in January 2015 due to electronic medical record (EMR) constraints, defining the starting point of this study. WTC responders undergo scheduled annual visits, during which data were collected for this study. This study was approved by the Stony Brook University Institutional Review Board (IRB: 604113; WTC Health & Wellness Study).

Inclusion and Exclusion criteria

Serum creatinine (SCr) measurements were obtained during routine *annual outpatient visits* per protocol, regardless of clinical status. SCr measurements during hospitalizations were excluded to ensure eGFR assessments reflected steady-state kidney function. Individuals were included if they had at least two outpatient SCr measurements between January 1, 2015, and December 31, 2022 (**Figure 1, Supplemental Figure 1**). Participants were excluded if they had a history of ESKD (defined as prior renal transplantation or dialysis before study initiation or during follow-up) or CKD at baseline (eGFR < 60 mL/min/1.73 m² or preexisting International Classification of Diseases (ICD) 9 or 10 CKD codes at the time of the first eGFR measurement). eGFR was calculated using the 2021 race-free CKD-EPI equation.[23] Participants were followed for a mean duration of 4.2 ± 1.9 years.

Exposure Measures

Global cognitive status was assessed using the Montreal Cognitive Assessment (MoCA), a 30-point screening tool evaluating short-term memory, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation[24]. The MoCA has shown high accuracy in diagnosing mild cognitive impairment (MCI) and was selected based on its proven sensitivity and reliability. To reduce test-retest bias, alternative versions were used at each testing occasion. A conservative cutoff of MoCA ≤23 was used to detect *cognitive impairment (CI)*, while severe CI, defined as *dementia*, was classified as MoCA ≤18[25,26]. MoCA scores were recorded at the start of the observation period (T_0), corresponding to the time of the initial eGFR measurement (**Supplemental Figure 1**). MoCA change per year was calculated as the total difference between last and first MoCA measurement divided by total-years of follow-up. MoCA change per year < 0 was classified as 'worsening MoCA scores', while ≥ 0 was classified as 'improving MoCA scores'.

Outcome Measures

The primary outcome measures were:

1. *Mean annual eGFR change*, calculated as the difference between the first (baseline) and last eGFR measurement, divided by the follow-up duration (years).
2. *Rapid eGFR decline*, defined as a mean annual eGFR change ≤ -5 mL/min/1.73 m²/year[27-29].

The secondary outcome measure was *incident CKD* defined as an eGFR < 60 mL/min/1.73 m² or the presence of a CKD diagnosis code at the last visit during the observation period.

Combining diagnosis codes with eGFR measurements has been shown to improve CKD classification accuracy[30]. (See Sensitivity Analyses for further validation.) Incident CKD was considered a secondary kidney outcome due to its lower incidence in this cohort (n = 248, 4%).

Covariates

Baseline demographics and health history were assessed at the time of the first eGFR measurement (T_0) (**Supplemental Figure 1**).

Race/Ethnicity: Participants were classified as: White: White/Non-Hispanic or Caucasian. Non-White: Black (Hispanic and Non-Hispanic), Hispanic (not Black)/Mexican, Asian (Non-Hispanic), or Other (Non-Hispanic).

WTC Exposure: Exposure assessments were conducted during WTC responders' intake visits using exhaustive self-reported questionnaires and validated in interviews conducted at responders' second visits. Exposure activities and experiences included location/duration of work, responder activities during cleanup, and types of exposures observed during response activities. The severity of exposure during WTC response efforts was categorized into five levels as previously described[22]: *No/Low* Exposure – No exposure or low exposure with protective personal equipment (PPE); *Mild* Exposure – Moderate duration of low-level exposure; *Moderate* Exposure – Prolonged low-level exposure; *High* Exposure – Moderate duration of high-risk activity; *Severe* Exposure – Prolonged high-risk activity; and *Unknown* – Insufficient exposure data.

Psychiatric Variables: Mental health symptom severity was also assessed at T_0 using validated inventories of behavioral symptoms. *Depression* was measured using the Patient Health Questionnaire-9 (PHQ-9) at annual WTC health visits. Individuals with PHQ-9 scores ≥10 were classified as having 'screened depression'.[31] *Post-traumatic stress disorder (PTSD)* was measured using the 17-item PTSD Checklist (PCL). Individuals with PCL scores ≥44 were classified as having 'screened PTSD'.[32]

Other Covariates: were defined as follows.

Educational Attainment: "BA/BS+" (≥4-year college degree) or "Less than BA/BS" (<4-year college degree).

Diabetes Mellitus (DM): ICD-9/10 codes, self-reported diagnosis (questionnaires), or fasting glucose >130 mg/dL.

Hypertension (HTN): ICD-9/10 codes, self-reported diagnosis, or recorded blood pressure of systolic >160 mmHg or diastolic >100 mmHg.

Cardiovascular Disease (CVD): Composite of stroke, angina, myocardial infarction, coronary artery disease, heart failure, or abnormal heart rhythm, determined via ICD-9/10 codes and self-reported diagnosis.

Obesity: ICD-9/10 codes or a recorded body mass index (BMI) >30 kg/m².

Statistical Analysis

Continuous variables were compared using the Student's t-test or Kruskal-Wallis test as appropriate. Categorical variables were compared using Chi-square (χ^2) tests or Fisher's Exact Test when applicable. Cox Proportional Hazards Models[33] were used to estimate hazard ratios (HR) for rapid eGFR decline and

incident CKD outcomes. These models were constructed in a series of successive steps, with cognitive impairment (CI) or dementia as the exposure variables (depending on the analysis) and binary kidney outcomes as the dependent variables.

The analysis began with an unadjusted model, followed by sequential adjustments for:

1. Demographics (age, sex, race/ethnicity)
2. Baseline comorbidities (diabetes, hypertension, cardiovascular disease, BMI)
3. WTC exposure
4. Screened baseline PTSD status (which is closely correlated with CI and dementia in previous WTC studies[34])
5. Baseline eGFR

The reference group for rapid eGFR decline was the 'stable' eGFR group, defined as a mean rate of eGFR change > -1 mL/min/1.73 m²/year. Linear regression models were used to estimate β-coefficients for the association between CI or dementia (depending on the analysis) and eGFR change per year, in a similar series of successive models. Individuals with missing data were removed from regressions, allowing for a complete-case analysis. Interactions between study variables were not assessed. Regression analyses were conducted in the same manner for main and sensitivity analyses.

Time-to-event data were used to generate unadjusted cumulative incidence curves for rapid eGFR decline during follow-up. The cumulative incidence function was estimated using the 1 - Kaplan-Meier estimate of the survival function[35], as no competing risks were evaluated in this study.

The Holm-Bonferroni correction was applied to regression analyses to account for adjustment for multiplicity testing, resulting in an adjusted p-value[36]. A two-tailed p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4[37] (Cary, NC, USA). Data visualization was done using the ggsurvfit[38] and forestplot[39] packages in R version 4.3.1[40].

Sensitivity analyses

To examine the importance of balancing participants, *propensity score matching (PSM)*[41] was employed using greedy nearest-neighbor matching to balance cohorts based on baseline age, sex, and race/ethnicity. To assess whether advanced baseline age acted as an effect modifier in the observed associations, sensitivity analyses were performed in which *individuals aged 60 years or older were excluded* from the overall cohort. An additional sensitivity analysis was conducted *excluding all individuals with baseline screened PTSD or depression*.

For those with baseline cognitive impairment (CI), the *incident CKD outcome was further analyzed using only the eGFR-based definition and the combined outcomes of incident CKD + eGFR decline.*

To determine whether an association was present between baseline mild cognitive impairment (MCI) and proposed kidney outcomes, additional subgroup analyses were performed for individuals with baseline MoCA scores ≥ 19, with baseline MCI defined as MoCA between 19-23[42]. Another sensitivity analysis assessed the association of worsening MoCA trajectories with rapid decline and incident CKD.

Additional sensitivity analyses were performed after excluding individuals who died during the observation period and those with removing traditional risk factors for CI development (stroke, head trauma, neurodegenerative disease, cardiovascular disease).

Results:

Participant Characteristics

In a cohort of 5,761 WTC responders, 1,446 (25%) had CI, and 89 (2%) had dementia at baseline (**Figure 1, Supplemental Table 1**). The mean age was 53.8 ± 7.9 years, 92% were male, and 84% were White/non-Hispanic. The mean baseline eGFR was 91.1 mL/min/1.73 m². Individuals without CI or dementia had slightly more eGFR measurements and a longer follow-up period. Overall, eGFR declined by -1.2 ± 4.0 mL/min/1.73 m² per year during the mean follow-up period of 4.2 ± 1.9 years. Those with CI were older, less likely to be White, had lower education, and higher WTC exposure, as well as a greater prevalence of diabetes, depression, and PTSD. A similar pattern was seen in individuals with dementia.

The association of baseline CI and dementia with change in eGFR per year

Individuals with CI (vs. no CI) experienced a greater annual eGFR decline (-1.5 ± 4.8 vs. -1.1 ± 3.7 mL/min/1.73 m²/year, p = 0.006) (**Table 1**). Those with dementia (vs. no dementia) had a more pronounced decline (-3.0 ± 5.3 vs. -1.2 ± 4.0 mL/min/1.73 m²/year, p = 0.002) (**Supplemental Table 1**).

After adjusting for demographics, comorbidities, WTC exposure, PTSD, and baseline eGFR, baseline CI (vs. no CI) (β = -0.34 [-0.58, -0.11], p-adjusted = 0.024) and baseline dementia (vs. no dementia) (β = -1.51 [-2.36, -0.66], p-adjusted = 0.004) were significantly associated with greater eGFR decline (**Figure 2, Supplemental Figure 2**).

Sensitivity analyses:

1) Propensity Score Matching (PSM) for Demographics: Individuals with baseline CI (vs. no CI) had greater eGFR decline (-1.9 ± 4.7 vs. -1.1 ± 3.6 mL/min/1.73 m²/year, p = 0.009) (**Table 2**). Among PSM-matched individuals, dementia did not significantly affect eGFR decline (**Supplemental Table 2**).

2) Baseline Age <60 Years: Individuals with CI and dementia had greater annual eGFR decline, compared to those without (**Table 3, Supplemental Table 3**). In multivariable analyses, baseline CI (vs. no CI) remained significantly associated with greater eGFR decline per year (β [95% CI]: -0.32 [-0.58, -0.07], p-adjusted = 0.039) (**Figure 2**). The association of baseline dementia (vs. no dementia) was of borderline statistical significance (β [95% CI]: -0.94 [-1.96, 0.06], p-adjusted = 0.064) (**Supplemental Figure 2**).

3) No PTSD or Depression at Baseline: CI and dementia were associated with greater annual eGFR decline (**Table 4, Supplemental Table 4**). In multivariable analyses, both baseline CI (vs. no CI) (β [95% CI]: -0.30 [-0.55, -0.05], p-adjusted = 0.040) (**Figure 2**) and baseline dementia (vs. no dementia) (β [95% CI]: -1.96 [-2.93, -0.98], p-adjusted = 0.001) (**Supplemental Figure 2**) were significantly associated with greater eGFR decline per year.

The association of baseline CI and dementia with rapid eGFR Decline

Of 5,761 responders, 550 (10%) experienced rapid eGFR decline. Individuals with CI (vs. no CI) were more likely to have rapid eGFR decline (13% vs. 8%, p < 0.001) (**Table 1, Figure 3**). Dementia (vs. no dementia) showed a more pronounced effect (25% vs. 9%, p < 0.001) (**Supplemental Table 1, Figure 4**).

Multivariable analysis showed that both CI (vs. no CI) (aHR: 1.61 [1.32, 1.96], p-adjusted < 0.001) and dementia (vs. no dementia) (aHR: 2.40 [1.46, 3.94], p-adjusted = 0.004) were significantly associated with rapid eGFR decline (**Figure 5, Supplemental Figure 3**).

Sensitivity analyses:

1) PSM for Demographics: Individuals with baseline CI (vs. no CI) had more rapid eGFR decline (12% vs. 9%, p = 0.003) (**Table 2**). Individuals with dementia (vs. no dementia) were also more likely to experience rapid eGFR decline (not statistically significant: 24% vs. 18%, p = 0.26) (**Supplemental Table 2**).

2) Baseline Age < 60 Years: Individuals with baseline CI and dementia were more likely to experience rapid eGFR decline (**Table 3**, **Supplemental Table 3**) compared to those without. In multivariable analyses, baseline CI (vs. no CI) (aHR: 1.55 [1.22, 1.97], p-adjusted = 0.003) (**Figure 5**) and dementia

(vs. no dementia) (aHR: 2.50 [1.28, 4.88], p-adjusted = 0.035) (**Supplemental Figure 3**) remained significantly associated with an increased hazard of rapid eGFR decline.

3) No PTSD or Depression at Baseline: Individuals with baseline CI and dementia were more likely to exhibit rapid eGFR decline, compared to those without (**Table 4**, **Supplemental Table 4**). In multivariable analyses, baseline CI (vs. no CI) (aHR: 1.56 [1.26, 1.93], p-adjusted < 0.001) (**Figure 5**) and dementia (vs. no dementia) (aHR: 2.68 [1.55, 4.62], p-adjusted = 0.004) (**Supplemental Figure 3**) remained significantly associated with an increased hazard of rapid eGFR decline.

The association of baseline CI/dementia with Incident CKD:

248 (4%) developed incident CKD. CI (vs. no CI) was associated with higher CKD risk (6% vs. 4%, p = 0.005) (**Table 1**), and dementia (vs. no dementia) showed a stronger association (10% vs. 4%, p = 0.007) (**Supplemental Table 1**). Multivariable models showed CI (vs. no CI) (aHR: 1.73 [1.29, 2.31], p-adjusted = 0.002) and dementia (vs. no dementia) (aHR: 2.80 [1.29, 6.09], p-adjusted = 0.038) were significantly linked to incident CKD (**Figure 6, Supplemental Figure 4**). Compared to individuals without baseline CI, those with CI had a greater incidence of CKD Stages 3b (0.6% vs. 0.4%) and 4 (0.1% vs. 0%). No individuals in the cohort developed incident CKD Stage 5 or ESKD.

Sensitivity analyses:

The low number of incident CKD cases based on ICD codes (0.8%) led to an alternative eGFR-based definition, confirming CI (vs. no CI) as significantly associated with incident CKD (aHR: 1.76 [1.29, 2.40], p-adjusted = 0.003) (**Figure 6**). All incident CKD cases in individuals with baseline dementia were determined only by eGFR.

Due to the low number of incident CKD cases, additional sensitivity analyses were not performed.

Other Sensitivity Analyses:

The association of baseline CI with Incident CKD and Rapid eGFR decline (combined outcome):

95 (2%) developed the combined outcome of incident CKD and rapid eGFR decline. CI (vs. no CI) was associated with higher risk (3% vs. 1%, p = 0.005). Multivariable models showed CI (vs. no CI) (aHR: 2.56 [1.66, 3.99], p < 0.001) was significantly linked to combined kidney outcome. The numbers of individuals with baseline dementia were too small for this analyses.

Association of Baseline MCI with kidney outcomes:

After excluding individuals with a baseline dementia (MoCA ≤ 19), 5672 individuals were eligible for analysis, of which 4315 (76%) did not have baseline MCI and 1357 (24%) were classified as baseline MCI. (**Supplemental Table 5**). Consistent with our primary cohort in fully adjusted models, baseline MCI (vs. no MCI) remained significantly associated with greater eGFR decline per year (**Supplemental Figure 5**), rapid eGFR decline (**Supplemental Figure 6**), and incident CKD (**Supplemental Figure 7**).

Exclusion of Mortality during Follow-up:

To prevent residual confounding from unmeasured variables leading to death, in a sensitivity analysis, we removed 62 (1%) individuals in our study who died by the end of follow-up. Consistent with our primary cohort, in fully adjusted models, both baseline CI (vs. no CI) and baseline dementia (vs. no dementia) remained significantly associated with greater eGFR decline per year (**Supplemental Figure 8**). rapid eGFR decline (**Supplemental Figure 9**). and incident CKD (**Supplemental Figure 10**).

Exclusion of pre-existing head trauma, stroke and cardiovascular disease:

After excluding 405 individuals with stroke, baseline cardiovascular disease, and head trauma, 5586 individuals were available for analysis of which 1391 (25%) were classified as having baseline CI and 85 (2%) were classified as having baseline dementia. Consistent with our primary cohort, in fully adjusted models, both baseline CI (vs. no CI) and baseline dementia (vs. no dementia) remained significantly associated with greater eGFR decline per year (**Supplemental Figure 11**). rapid eGFR decline (**Supplemental Figure 12**). and incident CKD (**Supplemental Figure 13**).

Association of Worsening MoCA Scores with Kidney Outcomes:

Of the 5761 individuals analyzed, 3022 (51%) showed worsening of MoCA scores over the follow-up period. Individuals with worsening MoCA scores did not have significantly different rates of either rapid decline (9 vs 10%, p = 0.087) or incident CKD (5% vs 4%, p = 0.198) (**Supplemental Table 6**). In fully adjusted models, worsening MoCA scores were not significantly associated with either rapid decline (aHR: 1.09 [0.99, 1.18], p = 0.068) or incident CKD (aHR: 1.12 [0.96, 1.30], p = 0.143) (**Supplemental Figure 14**). Based on our previous studies, while MoCA is very sensitive in detection of MCI or dementia, the trajectory of MoCA is not a reliable estimate of progressive cognitive decline.

Discussion:

We recently reported that WTC responders are at higher risk for early-onset mild cognitive impairment (MCI) and dementia[10,12-15]. Previous studies on cognition and kidney function have primarily focused on older populations[10,12-15], while those involving younger individuals have been limited by cross-sectional designs[6,43]. To our knowledge, this is the first study to report that, among middle-aged individuals without CKD, baseline cognitive impairment (CI) is associated with an increased risk of accelerated eGFR decline. This association remained significant after adjusting for multiple risk factors, as well as multiple sensitivity analyses: propensity score matching for demographics, in individuals younger than 60 years, and in those without baseline PTSD or depression, without baseline head trauma, stroke and cardiovascular disease and after exclusion of those who died during follow-up . Additionally, baseline CI was linked to an increased risk of incident CKD and the combined risk of incident CKD and rapid eGFR decline in multivariable models. Even mild impairment in cognition (MCI) was a risk factor for kidney outcomes. Severe CI (i.e., dementia) at baseline showed similar associations, although due to the very low sample size of individuals with baseline dementia, after propensity matching for demographics, the association with eGFR decline was not statistically significant. The association between baseline dementia and kidney outcomes requires replication in larger cohorts due to the limited subgroup size

A key strength of this study is the availability of longitudinal, granular data on mental health and protocolized annual GFR measurements from the WTC database, which enabled a robust analysis of the relationship between brain and kidney disease. Furthermore, the early onset of CI in WTC responders offers a unique opportunity to evaluate the impact of brain aging on kidney function in middle-aged individuals without pre-existing kidney disease.

Advanced CKD can lead to accelerated cognitive decline, potentially through vascular injury, inflammation, and uremic toxins[44,45]. Interestingly, similar inflammatory mechanisms are often linked to MCI and dementia, particularly in Alzheimer's disease and related dementias. However, the exact mechanism linking cognitive impairment to an increased risk of rapid kidney function decline in individuals without pre-existing kidney disease remains unclear. Our findings suggest that the association between eGFR decline, and CI is stronger in individuals with more severe cognitive impairment, i.e., dementia. A recent Mendelian randomization (MR) study involving 396,600 UK Biobank participants, all without baseline CKD or dementia, demonstrated that better cognitive function is causally associated with a lower risk of CKD[20]. Another MR study found that genetically predicted decreased kidney function is associated with biological aging (telomere attrition)[46]. Emerging evidence suggests a "systemic aging phenotype," in which physiological aging occurs concurrently in multiple organs, including the kidney and brain. Alzheimer's disease has been associated with accelerated aging in the kidneys[47]. Individuals

with CI may exhibit a systemic aging phenotype, in which brain and kidney function decline in parallel. We previously reported that early-onset CI in WTC responders is linked to cortical atrophy on brain imaging[48]. However, this form of dementia may be a tauopathy, distinct from typical Alzheimer's disease[49,50], and may involve neuroinflammation[51,52]. Systemic inflammation, a well-known contributor to CKD pathogenesis[53], could also play a role in kidney injury in these individuals. For example, the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome is known to be involved in the pathogenesis of both CKD[54] and Alzheimer's Disease[55]. Microvascular disease in the brain and kidneys has been correlated[9,56]. Additionally, endothelial dysfunction is associated with the progression of CKD[57] and neurodegenerative diseases[58]. CI is linked to a higher incidence of clinical risk factors of CKD, such as diabetes, hypertension, obesity and cardiovascular disease[17-19,59-62]. Finally, impaired cognition has been associated with reduced health literacy[63], which may influence health-related behaviors and contribute to kidney damage. Further research is needed to elucidate the pathophysiological pathways and patient-related factors linking neurodegenerative disorders with kidney aging and CKD.

We previously reported that exposure to toxic chemicals during the 9/11 rescue efforts (WTC exposure) is associated with early-onset dementia in WTC responders[22]. Emerging data suggests an association between chronic environmental toxin exposure and GFR decline or CKD[64]. WTC exposure lasted 9 months, which is long for an exposure event but relatively brief for occupational exposures. These exposures occurred 14 years before the start of our study, when individuals were still free of CKD. Although WTC exposures could have contributed to eGFR decline, the association between rapid GFR decline and incident CKD with CI remained independent of WTC exposure and baseline eGFR. Together, these results may imply that the relationship between CI and CKD is independent of exposure, potentially resulting from a shared inflammatory mechanism, or that exposures causing early-onset dementia may concurrently be damaging the kidneys.

PTSD and depression are both linked to CI[65,66] and eGFR decline[67,68]. We previously reported that PTSD is a risk factor for rapid eGFR decline in young WTC responders[68]. However, most studies on kidney and cognitive dysfunction have not accounted for comorbid PTSD or depression. In this study, we show that the association between eGFR decline and CI in middle-aged adults is independent of baseline screened PTSD and depression.

Our findings have important clinical implications. Rapid GFR decline, a hallmark of CKD progression toward kidney failure, may be slowed or halted with appropriate interventions[69]. Monitoring kidney function more closely in high-risk individuals, such as those with cognitive impairment , may enable the early initiation of preventive strategies. Given the association between kidney function decline and

cognitive impairment, clinicians may need to implement routine cognitive assessments in patients with CKD, particularly in populations with known environmental exposures. Additionally, integrating kidney function monitoring into neurological evaluations could allow for earlier interventions aimed at slowing both kidney dysfunction and neurodegeneration. Whether treatment of cognitive impairment can slow eGFR decline remains unknown, but it should be the focus of future interventional studies.

This study has several limitations. First, we lacked data on proteinuria, medications used for the treatment of CKD and CI, and drugs that can be toxic to the kidneys and brain. Second, the WTC cohort, which was almost universally employed in stable unionized jobs at the time of exposure, is relatively well-educated and mostly male and White. These factors limit the generalizability of our findings. Previous studies on cognitive function and CKD found that this association was not influenced by sex[10,11,20,70]. The influence of race/ethnicity in the association of CKD and dementia is less well studied and should be a focus of future research. Third, the relatively young age of our cohort and low prevalence of medical comorbidities resulted in few cases of incident CKD and baseline dementia. Advanced kidney outcomes, such as incident end-stage kidney disease (ESKD), were not evaluated. Moreover, our GFR calculation was based on serum creatinine which can be influenced by muscle mass. However, we have adjusted for BMI in all our multivariable models. Fourth, our diagnosis of CI and dementia relied on a sole screening tool (MoCA). However, as previously mentioned, MoCA has demonstrated high accuracy in diagnosing cognitive impairment and is associated with cortical atrophy on brain imaging. We used alternative versions at each testing occasion to reduce test-retest bias. Fifth, there are potential biases related to self-reported data. Sixth, individuals with baseline CI and dementia had less follow-up than those without. This was likely due to older age and poor cognition. Seventh, the competing of death and cardiovascular events were not assessed. Finally, it is important to acknowledge the possibility of residual confounding due to unmeasured variables. For example, health-related behaviors, which could influence both cognitive function and kidney health, was not accounted for in this study.

In conclusion, we report that prevalent CI is significantly associated with the risk of rapid eGFR decline in WTC responders without baseline kidney disease. CI may also be associated with the risk of incident CKD. These findings suggest that patients with CI may require close monitoring of kidney function, regardless of their age or comorbid psychiatric conditions. Furthermore, our results underscore the need for targeted screening strategies, particularly in high-risk occupational groups, and highlight the importance of refining CKD management guidelines to consider neurocognitive outcomes. Future studies should validate these findings in larger, more diverse cohorts and explore whether targeted interventions can mitigate the progression of both cognitive and kidney dysfunction.

References:

1. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest.* 1950;29(5):496-507.
2. Badve SV, Palmer SC, Hawley CM, Pascoe EM, Strippoli GF, Johnson DW. Glomerular filtration rate decline as a surrogate end point in kidney disease progression trials. *Nephrol Dial Transplant.* 2016;31(9):1425-1436.
3. Koraishy FM, Hooks-Anderson D, Salas J, Rauchman M, Scherrer JF. Fast GFR decline and progression to CKD among primary care patients with preserved GFR. *Int Urol Nephrol.* 2018;50(3):501-508.
4. Chang W-x, Arai S, Tamura Y, et al. Time-dependent risk factors associated with the decline of estimated GFR in CKD patients. *Clinical and experimental nephrology.* 2016;20:58-70.
5. Harhay MN, Xie D, Zhang X, et al. Cognitive Impairment in Non-Dialysis-Dependent CKD and the Transition to Dialysis: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis.* 2018;72(4):499-508.
6. Arafa A, Kawachi H, Matsumoto C, et al. The association between the estimated glomerular filtration rate and cognitive impairment: the Suita Study. *Hypertens Res.* 2024;47(3):672-676.
7. Kurella Tamura M, Yaffe K, Hsu CY, et al. Cognitive Impairment and Progression of CKD. *Am J Kidney Dis.* 2016;68(1):77-83.
8. Etgen T, Chonchol M, Forstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol.* 2012;35(5):474-482.
9. Tang X, Han YP, Chai YH, et al. Association of kidney function and brain health: A systematic review and meta-analysis of cohort studies. *Ageing Res Rev.* 2022;82:101762.
10. Xu H, Garcia-Ptacek S, Trevisan M, et al. Kidney Function, Kidney Function Decline, and the Risk of Dementia in Older Adults: A Registry-Based Study. *Neurology.* 2021;96(24):e2956-e2965.
11. Berger I, Wu S, Masson P, et al. Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med.* 2016;14(1):206.
12. Helmer C, Stengel B, Metzger M, et al. Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. *Neurology.* 2011;77(23):2043-2051.
13. Kurella Tamura M, Gaussoin SA, Pajewski NM, et al. Kidney Disease, Intensive Hypertension Treatment, and Risk for Dementia and Mild Cognitive Impairment: The Systolic Blood Pressure Intervention Trial. *J Am Soc Nephrol.* 2020;31(9):2122-2132.
14. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Kidney Dis.* 2008;52(2):227-234.
15. Hiramatsu R, Iwagami M, Nitsch D. Association between chronic kidney disease and incident diagnosis of dementia in England: a cohort study in Clinical Practice Research Datalink. *BMJ Open.* 2020;10(5):e033811.
16. Shang Y, Wang S, Wei C, et al. Association of chronic kidney disease with cognitive impairment risk in middle-aged and older adults: the first longitudinal evidence from CHARLS. *Scientific Reports.* 2024;14(1):23265.
17. Luksiene D, Sapranaviciute-Zabazlajeva L, Tamosiunas A, Radisauskas R, Bobak M. Lowered cognitive function and the risk of the first events of cardiovascular diseases: findings from a cohort study in Lithuania. *BMC Public Health.* 2021;21(1):792.
18. Leng X, Espeland MA, Manson JE, et al. Cognitive Function and Changes in Cognitive Function as Predictors of Incident Cardiovascular Disease: The Women's Health Initiative Memory Study. *J Gerontol A Biol Sci Med Sci.* 2018;73(6):779-785.

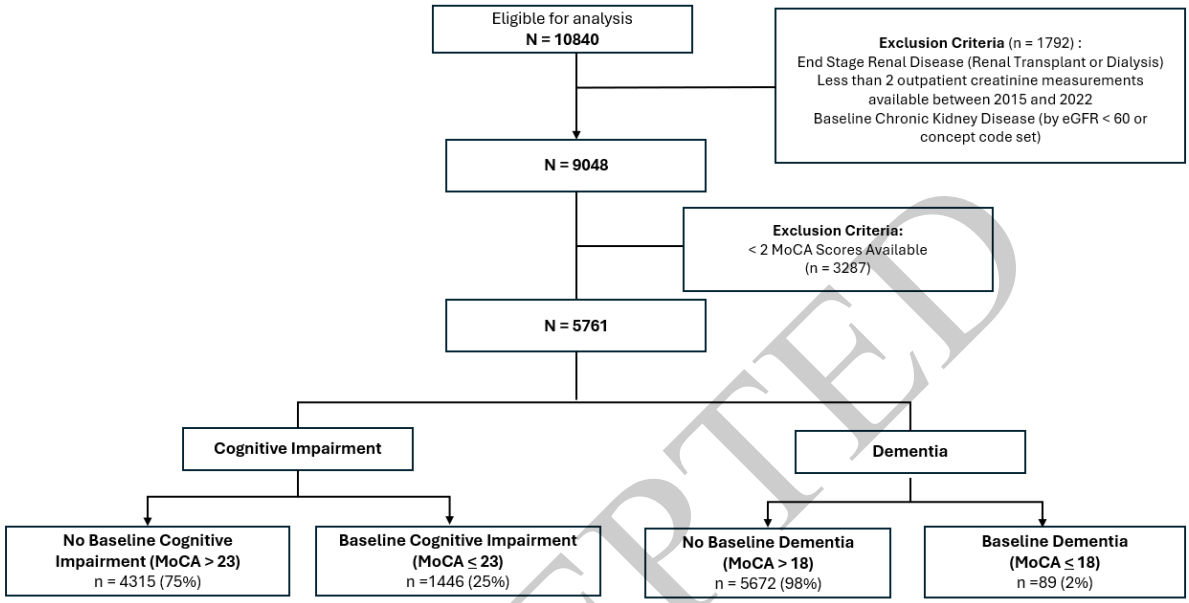
19. Altschul DM, Wraw C, Der G, Gale CR, Deary IJ. Hypertension Development by Midlife and the Roles of Premorbid Cognitive Function, Sex, and Their Interaction. *Hypertension.* 2019;73(4):812-819.
20. Yang S, Zhou C, Ye Z, et al. Association Between Cognitive Function and Risk of Chronic Kidney Disease: A Longitudinal Cohort and Mendelian Randomization Study. *Mayo Clin Proc.* 2024;99(9):1399-1410.
21. Dasaro CR, Holden WL, Berman KD, et al. Cohort Profile: World Trade Center Health Program General Responder Cohort. *Int J Epidemiol.* 2017;46(2):e9.
22. Clouston SAP, Mann FD, Meliker J, et al. Incidence of Dementia Before Age 65 Years Among World Trade Center Attack Responders. *JAMA Netw Open.* 2024;7(6):e2416504.
23. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med.* 2021;385(19):1737-1749.
24. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-699.
25. Ilardi CR, Menichelli A, Michelutti M, Cattaruzza T, Manganotti P. Optimal MoCA cutoffs for detecting biologically-defined patients with MCI and early dementia. *Neurological Sciences.* 2023;44(1):159-170.
26. Luis CA, Keegan AP, Mullan M. Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *Int J Geriatr Psychiatry.* 2009;24(2):197-201.
27. Levin A, Stevens PE, Bilous RW, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney international supplements.* 2013;3(1):1-150.
28. Hirst JA, Taal MW, Fraser SD, et al. Change in glomerular filtration rate over time in the Oxford Renal Cohort Study: observational study. *Br J Gen Pract.* 2022;72(717):e261-e268.
29. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol.* 2017;13(4):241-257.
30. Ramagopalan S, Leahy TP, Stamp E, Sammon C. Approaches for the identification of chronic kidney disease in CPRD-HES-linked studies. *J Comp Eff Res.* 2020;9(7):441-446.
31. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-613.
32. Karstoft KI, Andersen SB, Bertelsen M, Madsen T. Diagnostic accuracy of the posttraumatic stress disorder checklist-civilian version in a representative military sample. *Psychol Assess.* 2014;26(1):321-325.
33. The PHREG Procedure. In: *SAS/STAT® 13.2 User's Guide.* SAS Institute Inc., Cary, NC, USA; 2014.
34. Clouston SA, Kotov R, Pietrzak RH, et al. Cognitive impairment among World Trade Center responders: Long-term implications of re-experiencing the 9/11 terrorist attacks. *Alzheimers Dement (Amst).* 2016;4:67-75.
35. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation.* 2016;133(6):601-609.
36. Holm S. A Simple Sequentially Rejective Multiple Test Procedure. *Scandinavian Journal of Statistics.* 1979;6:65-70.
37. Solutions SDaA. SAS. SAS: Data and AI Solutions. https://www.sas.com/en_us/home.html. Published 2025. Accessed.

38. Daniel D. Sjoberg MB, Charlotta Fruechtenicht, Steven Haesendonckx, Tim Treis. Flexible Time-to-Event Figures. 2024. https://cran.r-project.org/web/packages/ggsurvfit/ggsurvfit.pdf.
39. Gordon M. Introduction to forest plots. 2024. https://cran.r-project.org/web/packages/forestplot/vignettes/forestplot.html.
40. Foundation R. The R Project for Statistical Computin. R Foundation. https://www.r-project.org/. Published 2025. Accessed.
41. Yuan Y, Yung YF, Stokes ME. Propensity Score Methods for Causal Inference with the PSMATCH Procedure. 2017.
42. Nasreddine Z. MoCA (Montreal Cognitive Assessment or The MoCA Test). https://mocacognition.com/faq/. Published 2025. Accessed2025.
43. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol.* 2007;18(7):2205-2213.
44. Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J Am Soc Nephrol.* 2013;24(3):353-363.
45. Miranda AS, Cordeiro TM, dos Santos Lacerda Soares TM, Ferreira RN, Simoes e Silva AC. Kidney–brain axis inflammatory cross-talk: from bench to bedside. *Clinical Science.* 2017;131(11):1093-1105.
46. Park S, Lee S, Kim Y, et al. A Mendelian randomization study found causal linkage between telomere attrition and chronic kidney disease. *Kidney Int.* 2021;100(5):1063-1070.
47. Oh HS, Rutledge J, Nachun D, et al. Organ aging signatures in the plasma proteome track health and disease. *Nature.* 2023;624(7990):164-172.
48. Clouston SAP, Deri Y, Horton M, et al. Reduced cortical thickness in World Trade Center responders with cognitive impairment. *Alzheimers Dement (Amst).* 2020;12(1):e12059.
49. Clouston SAP, Kritikos M, Huang C, et al. Reduced cerebellar cortical thickness in World Trade Center responders with cognitive impairment. *Transl Psychiatry.* 2022;12(1):107.
50. Kritikos M, Zhou JW, Huang C, et al. Exposure duration and cerebral amyloidosis in the olfactory cortex of World Trade Center responders: A positron emission tomography and magnetic resonance imaging study. *J Alzheimers Dis.* 2025;103(2):383-395.
51. Deri Y, Clouston SAP, DeLorenzo C, et al. Neuroinflammation in World Trade Center responders at midlife: A pilot study using [(18)F]-FEPPA PET imaging. *Brain Behav Immun Health.* 2021;16:100287.
52. Kuan PF, Clouston S, Yang X, et al. Single-cell transcriptomics analysis of mild cognitive impairment in World Trade Center disaster responders. *Alzheimers Dement (Amst).* 2021;13(1):e12154.
53. Amdur RL, Feldman HI, Gupta J, et al. Inflammation and Progression of CKD: The CRIC Study. *Clin J Am Soc Nephrol.* 2016;11(9):1546-1556.
54. Vilaysane A, Chun J, Seamone ME, et al. The NLRP3 inflammasome promotes renal inflammation and contributes to CKD. *J Am Soc Nephrol.* 2010;21(10):1732-1744.
55. Liang T, Zhang Y, Wu S, Chen Q, Wang L. The Role of NLRP3 Inflammasome in Alzheimer's Disease and Potential Therapeutic Targets. *Front Pharmacol.* 2022;13:845185.
56. Saji N, Kimura K, Yagita Y, et al. Deep Cerebral Microbleeds and Renal Dysfunction in Patients with Acute Lacunar Infarcts. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2015;24(11):2572-2579.
57. Roumeliotis S, Mallamaci F, Zoccali C. Endothelial Dysfunction in Chronic Kidney Disease, from Biology to Clinical Outcomes: A 2020 Update. *J Clin Med.* 2020;9(8).

58. Fang YC, Hsieh YC, Hu CJ, Tu YK. Endothelial Dysfunction in Neurodegenerative Diseases. *Int J Mol Sci.* 2023;24(3).
59. Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. *Arch Neurol.* 2008;65(1):89-93.
60. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Jr., Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ.* 2005;330(7504):1360.
61. Prasad R, Jha RK, Keerti A. Chronic Kidney Disease: Its Relationship With Obesity. *Cureus.* 2022;14(10):e30535.
62. Kumar M, Dev S, Khalid MU, et al. The Bidirectional Link Between Diabetes and Kidney Disease: Mechanisms and Management. *Cureus.* 2023;15(9):e45615.
63. Federman AD, Sano M, Wolf MS, Siu AL, Halm EA. Health literacy and cognitive performance in older adults. *J Am Geriatr Soc.* 2009;57(8):1475-1480.
64. Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD. *J Am Soc Nephrol.* 2018;29(1):218-230.
65. Severs E, James T, Letrondo P, Lovland L, Marchant NL, Mukadam N. Traumatic life events and risk for dementia: a systematic review and meta-analysis. *BMC Geriatr.* 2023;23(1):587.
66. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol.* 2011;7(6):323-331.
67. Zhang Z, He P, Liu M, et al. Association of Depressive Symptoms with Rapid Kidney Function Decline in Adults with Normal Kidney Function. *Clin J Am Soc Nephrol.* 2021;16(6):889-897.
68. Koraishy FM, Coca SG, Cohen BE, et al. The Association of Posttraumatic Stress Disorder With Longitudinal Change in Glomerular Filtration Rate in World Trade Center Responders. *Psychosom Med.* 2021;83(9):978-986.
69. Wuhl E, Schaefer F. Therapeutic strategies to slow chronic kidney disease progression. *Pediatr Nephrol.* 2008;23(5):705-716.
70. Iwata A, Iwatsubo T, Ihara R, et al. Effects of sex, educational background, and chronic kidney disease grading on longitudinal cognitive and functional decline in patients in the Japanese Alzheimer's Disease Neuroimaging Initiative study. *Alzheimer's & Dementia: Translational Research & Clinical Interventions.* 2018;4:765-774.

Figure Legends:

Figure 1. Flow Chart of Cohort. Abbreviations: MoCA = Montreal Cognitive Assessment.



Legend: Abbreviations: MoCA = Montreal Cognitive Assessment. eGFR = estimated glomerular filtration rate

Figure 2. Association of Baseline CI with eGFR Change Per Year. Forest plot displaying association between baseline CI and eGFR change per year for overall, < 60 years of age, and no PTSD/depression cohorts. Fully adjusted models adjusted for age, sex, race/ethnicity, comorbidities (diabetes, hypertension, cardiovascular disease, baseline BMI), WTC exposure, screened baseline PTSD (in overall and < 60 years of age cohorts), and baseline eGFR. Abbreviations: CKD = chronic kidney disease, PTSD = post-traumatic stress disorder, CI = cognitive impairment, 95% CI = 95% confidence interval.

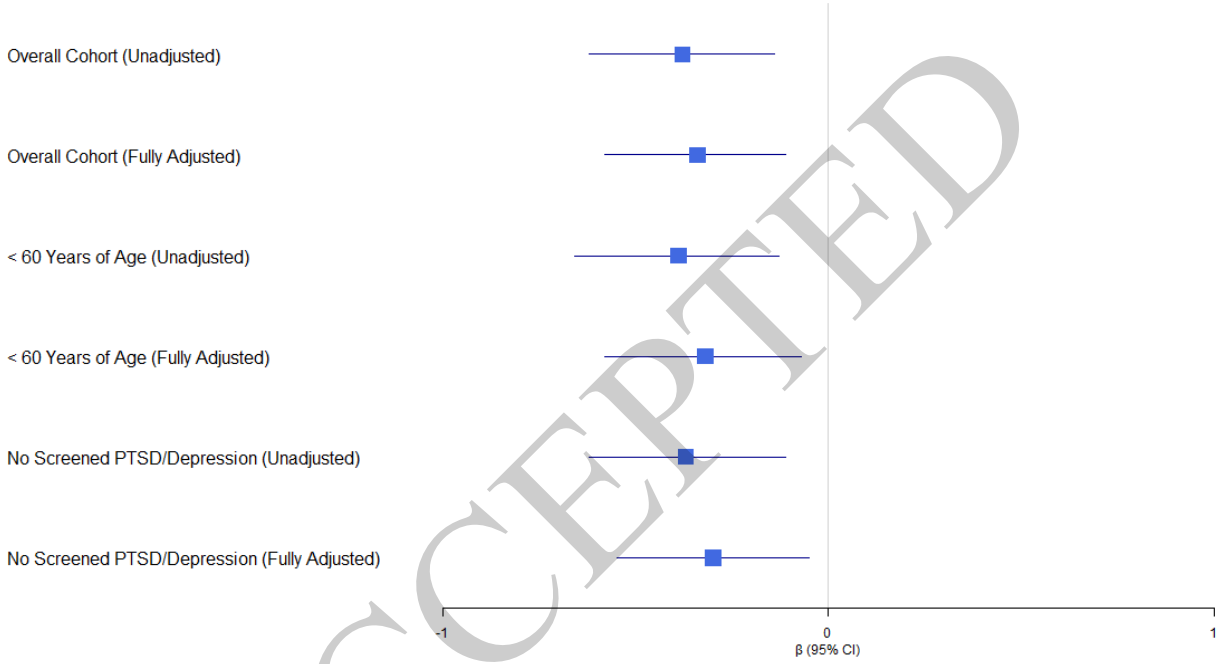


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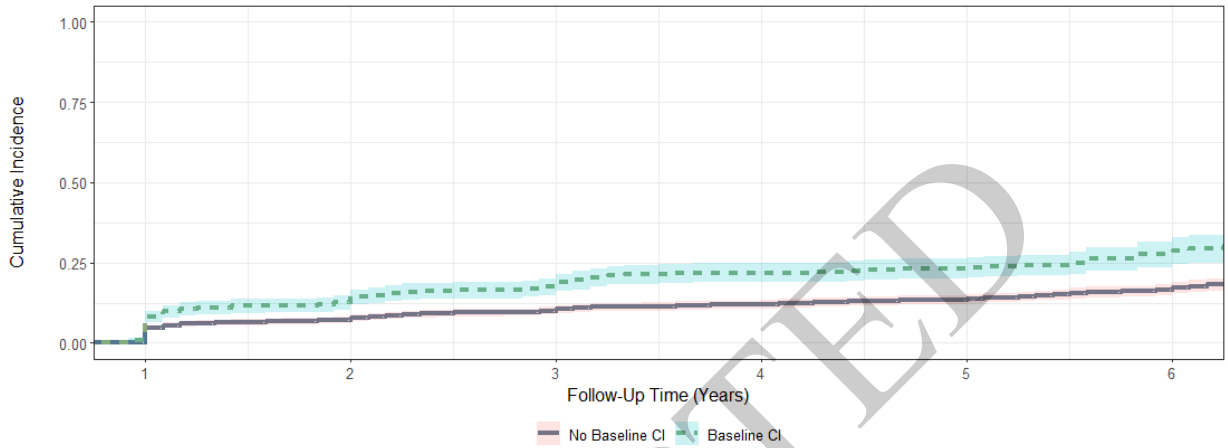
Figure 3. Cumulative Incidence Plot for Rapid eGFR Decline Outcome in individuals with and without Baseline CI. Cumulative (unadjusted) incidence plot for rapid GFR decline for individuals with (dashed) and without (solid) cognitive impairment during the observation period. Abbreviations: eGFR = estimated glomerular filtration rate, CI = cognitive impairment



No Baseline CI						
At Risk	2597	2184	1911	1588	1240	591
Events	123	200	259	289	317	350
Baseline CI						
At Risk	883	655	505	398	307	126
Events	73	121	151	168	175	188

Legend: Cumulative (unadjusted) incidence plot for rapid GFR decline for individuals with (dashed) and without (solid) cognitive impairment during the observation period. Abbreviations: eGFR = estimated glomerular filtration rate, CI = cognitive impairment

Figure 4. Cumulative Incidence Plot for Rapid eGFR Decline Outcome in individuals with and without Baseline Dementia. Cumulative (unadjusted) incidence plot for rapid GFR decline for individuals with (dashed) and without (solid) dementia during the observation period. Abbreviations: eGFR = estimated glomerular filtration rate

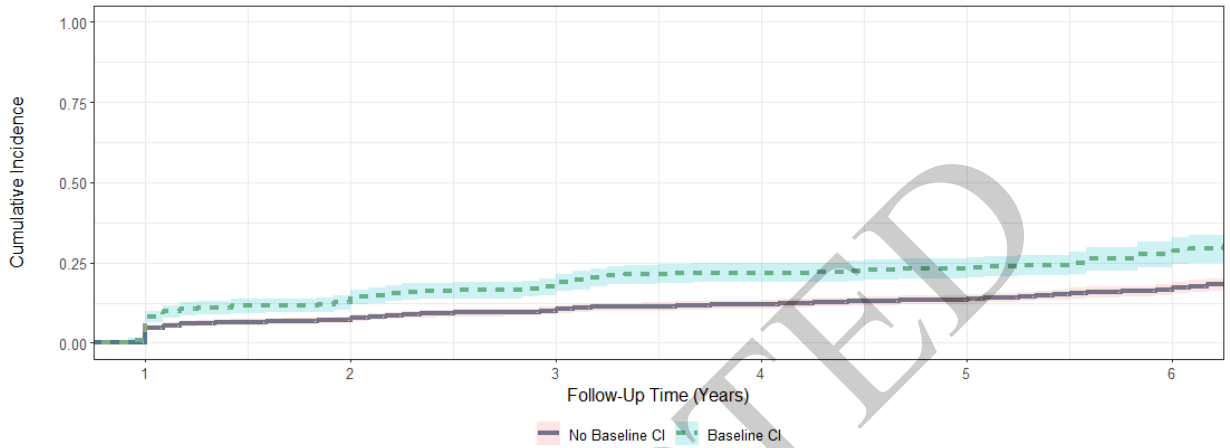


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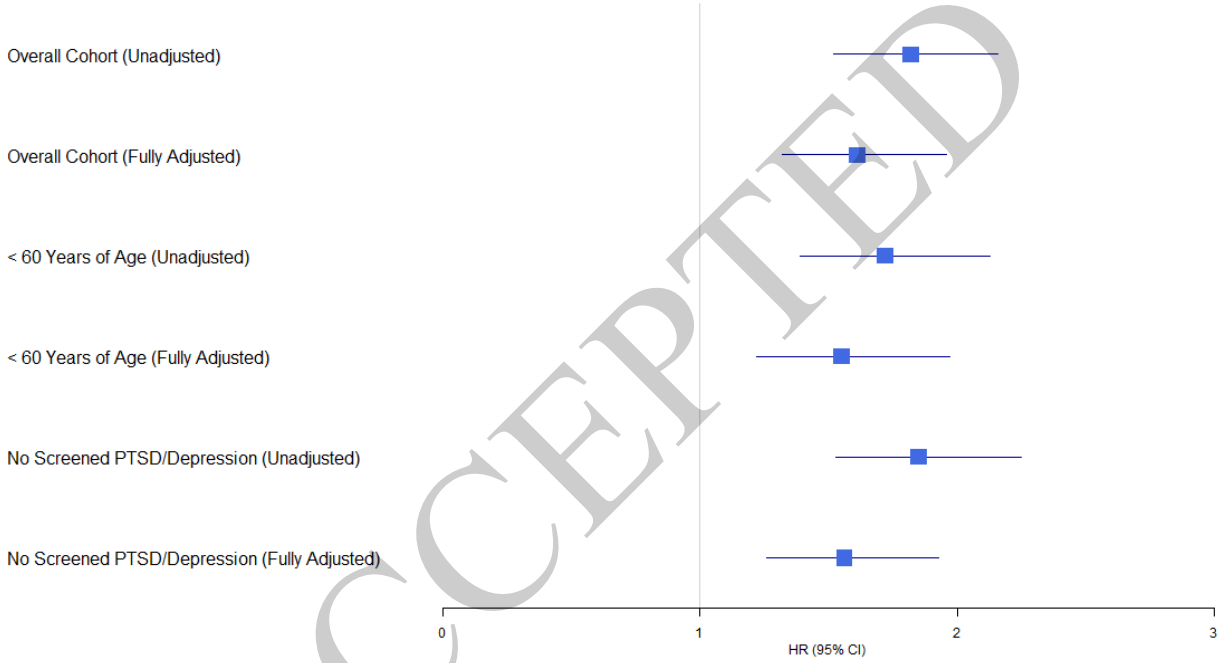
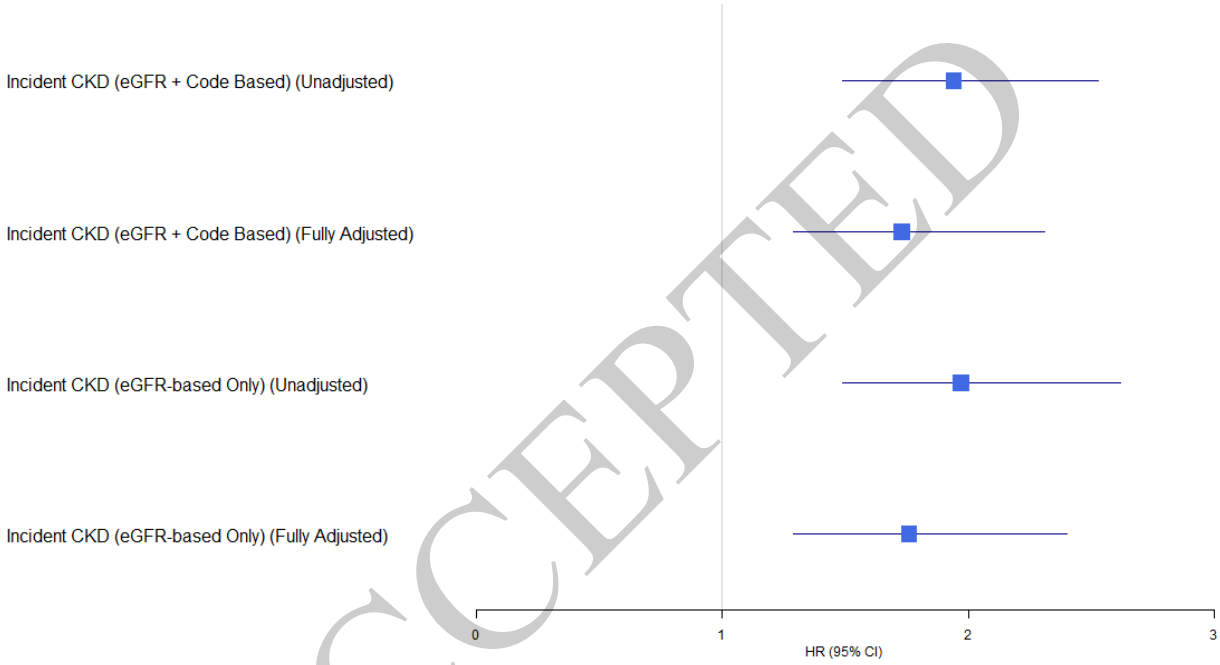
Figure 5 Association of Baseline CI with Rapid eGFR Decline (≤-5 mL/min/1.73 m2/year). Forest plot displaying association between baseline CI and rapid eGFR decline for overall, < 60 years of age, and no PTSD/depression cohorts. Fully adjusted models adjusted for age, sex, race/ethnicity, comorbidities (diabetes, hypertension, cardiovascular disease, baseline BMI), WTC exposure, screened baseline PTSD (in overall and < 60 years of age cohorts), and baseline eGFR. Abbreviations: CKD = chronic kidney disease, PTSD = post-traumatic stress disorder, CI = cognitive impairment, 95% CI = 95% confidence interval.



Legend: Forest plot displaying association between baseline CI and rapid eGFR decline for overall, < 60 years of age, and no PTSD/depression cohorts. Fully adjusted models adjusted for age, sex, race/ethnicity, comorbidities (diabetes, hypertension, cardiovascular disease, baseline BMI), WTC exposure, screened baseline PTSD (in overall and < 60 years of age cohorts), and baseline eGFR. Abbreviations: CKD = chronic kidney disease, PTSD = post-traumatic stress disorder, CI = cognitive impairment, 95% CI = 95% confidence interval.

Figure 6. Association of Baseline CI with Incident CKD. Forest plot displaying association between baseline CI and incident CKD (eGFR + code-based vs. eGFR-based only) among the overall cohort. Fully adjusted models adjusted for age, sex, race/ethnicity, comorbidities (diabetes, hypertension, , cardiovascular disease, baseline BMI), WTC exposure, screened baseline PTSD, and baseline eGFR. eGFR = estimated glomerular filtration rate, PTSD = post-traumatic stress disorder, CI = cognitive impairment, 95% CI = 95% confidence interval.



Legend: Forest plot displaying association between baseline CI and incident CKD (eGFR + code-based vs. eGFR-based only) among the overall cohort. Fully adjusted models adjusted for age, sex, race/ethnicity, comorbidities (diabetes, hypertension, cardiovascular disease, baseline BMI), WTC exposure, screened baseline PTSD, and baseline eGFR. eGFR = estimated glomerular filtration rate, PTSD = post-traumatic stress disorder, CI = cognitive impairment, 95% CI = 95% confidence interval

Supplemental Table of Contents

Supplemental Table 3. Characteristics and Outcomes of Individuals with and without Dementia in individuals with baseline age < 60 years old

Supplemental Table 4. Characteristics and Outcomes of Individuals with and without Dementia in individuals without baseline PTSD or Depression

Supplemental Table 5. Characteristics and Outcomes of Individuals with and without MCI

Supplemental Table 6. Characteristics and Outcomes of Individuals with Worsening MoCA Scores

Table 1. Characteristics and Outcomes of Individuals with and without Cognitive Impairment (overall Cohort)

	Overall *5761*	**No Baseline CI (MoCA > 23)** *4315 (75%)*	**Baseline CI (MoCA ≤ 23)** *1446 (25%)*	p-value
Age (years)	53.8 ± 7.9	53.1 ± 7.7	55.8 ± 8.2	<0.001
Sex				0.49
Male	5282 (92%)	3950 (92%)	1332 (92%)	
Female	479 (8%)	365 (8%)	114 (8%)	
Race/Ethnicity				<0.001
White (non-Hispanic)	4858 (84%)	3730 (86%)	1128 (78%)	
Non-White[1]	708 (12%)	481 (11%)	227 (16%)	
Missing	195 (3%)	104 (2%)	91 (6%)	
Education				<0.001
Less than BA/BS	3549 (62%)	2621 (61%)	928 (64%)	
BA/BS or higher	1633 (28%)	1317 (31%)	316 (22%)	
Missing	579 (10%)	377 (9%)	202 (14%)	
Comorbidities				
Cardiovascular Disease[2]	361 (6%)	247 (6%)	114 (8%)	0.003
Diabetes	594 (10%)	423 (10%)	171 (12%)	0.029
Hypertension	1834 (32%)	1360 (32%)	474 (33%)	0.37
Obesity	3080 (53%)	2315 (54%)	765 (53%)	0.62
BMI (kg/m^2)	31.2 ± 5.4	31.2 ± 5.4	31.1 ± 5.3	0.52
Missing	37 (0.6%)	22 (0.5%)	15 (1%)	
WTC Exposure				0.004
No Exposure/Low Exposure	272 (5%)	219 (5%)	53 (4%)	
Mild Exposure	2969 (52%)	2275 (53%)	694 (48%)	
Moderate Exposure	1836 (32%)	1334 (31%)	502 (35%)	
High Exposure	380 (7%)	275 (6%)	105 (7%)	
Severe Exposure	108 (2%)	80 (2%)	28 (2%)	
Missing	196 (3%)	132 (3%)	64 (4%)	
Screened Depression	647 (11%)	464 (11%)	183 (13%)	0.028
Missing	170 (3%)	109 (3%)	61 (4%)	
Screened PTSD	690 (12%)	474 (11%)	216 (15%)	<0.001
Missing	117 (2%)	82 (2%)	35 (2%)	
Baseline MoCA Score	25.2 ± 2.7	26.4 ± 1.7	21.5 ± 1.7	<0.001
eGFR Variables				
First eGFR Measurement (mL/min/1.73 m^2)	91.1 ± 12.8	91.5 ± 12.8	90.1 ± 12.9	<0.001
Last eGFR Measurement (mL/min/1.73 m^2)	86.7 ± 14.3	87.1 ± 14.1	85.7 ± 14.9	0.001
Number of eGFR Available	4.0 (3.0 - 6.0)	5.0 (3.0 - 6.0)	4.0 (3.0 - 5.0)	<0.001
Duration of Follow-Up (years)	4.2 ± 1.9	4.4 ± 1.8	3.7 ± 1.9	<0.001
Kidney Outcomes				
eGFR Change Per Year (mL/min/1.73 m^2/year)	-1.2 ± 4.0	-1.1 ± 3.7	-1.5 ± 4.8	0.006
Rapid eGFR Decline (≤ -5 mL/min/1.73 m^2/year)	550 (10%)	358 (8%)	192 (13%)	<0.001
Incident CKD	248 (4%)	167 (4%)	81 (6%)	0.005

Data expressed as mean ± standard deviation or frequency (percentage) as appropriate.
eGFR = estimated glomerular filtration rate, CI = cognitive impairment, MoCA = Montreal Cognitive Assessment, PTSD = post-traumatic stress disorder, PPE = protective personal equipment
[1]: Considered "non-white" if individuals reported themselves to be Black (Hispanic and Non-Hispanic), Hispanic (not Black)/Mexican, Asian (Non-Hispanic), or Other (non-Hispanic)
[2]: Cardiovascular disease was defined as a composite variable of stroke, angina, myocardial infarction, coronary artery disease, heart failure, or abnormal heart rhythm

Table 2. Characteristics and Outcomes of Individuals with and without Cognitive Impairment (Propensity Score Matched for Age, Sex and Race/Ethnicity)

	Overall *2652*	**No Baseline CI (MoCA > 23)** *1326 (50%)*	**Baseline CI (MoCA ≤ 23)** *1326 (50%)*	p-value
Age (years)	55.1 ± 7.5	55.0 ± 7.3	55.2 ± 7.6	0.43
Sex				1.00
Male	2436 (92%)	1218 (92%)	1218 (92%)	
Female	216 (8%)	108 (8%)	108 (8%)	
Race/Ethnicity				1.00
White (non-Hispanic)	2212 (83%)	1106 (83%)	1106 (83%)	
Non-White[1]	440 (17%)	220 (17%)	220 (17%)	
Education				<0.001
Less than BA/BS	1692 (64%)	808 (61%)	884 (67%)	
BA/BS or higher	685 (26%)	393 (30%)	292 (22%)	
Missing	275 (10%)	125 (9%)	150 (11%)	
Comorbidities				
Cardiovascular Disease[2]	181 (7%)	80 (6%)	101 (8%)	0.11
Diabetes	326 (12%)	166 (13%)	160 (12%)	0.72
Hypertension	915 (35%)	481 (36%)	434 (33%)	0.055
Obesity	1506 (57%)	803 (61%)	703 (53%)	<0.001
BMI (kg/m^2)	31.4 ± 5.4	31.8 ± 5.5	31.1 ± 5.3	<0.001
Missing	18 (0.7%)	6 (0.5%)	12 (0.9%)	
WTC Exposure				0.113
No Exposure/Low Exposure	130 (5%)	78 (6%)	52 (4%)	
Mild Exposure	1320 (50%)	669 (50%)	651 (49%)	
Moderate Exposure	879 (33%)	432 (33%)	447 (34%)	
High Exposure	176 (7%)	80 (6%)	96 (7%)	
Severe Exposure	57 (2%)	31 (2%)	26 (2%)	
Unknown	90 (3%)	36 (3%)	54 (4%)	
Screened Depression	333 (13%)	159 (12%)	174 (13%)	0.30
Missing	87 (3%)	33 (2%)	54 (4%)	
Screened PTSD	355 (13%)	151 (11%)	204 (15%)	0.002
Missing	56 (2%)	24 (2%)	32 (2%)	
Baseline MoCA Score	24.0 ± 2.9	26.3 ± 1.7	21.6 ± 1.7	<0.001
eGFR Variables				
First eGFR Measurement (mL/min/1.73 m^2)	90.2 ± 12.7	90.1 ± 12.5	90.4 ± 12.9	0.56
Last eGFR Measurement (mL/min/1.73 m^2)	85.8 ± 14.3	85.7 ± 14.0	85.8 ± 14.7	0.88
Number of eGFR Available	4.0 (3.0 - 6.0)	5.0 (3.0 - 6.0)	4.0 (3.0 - 5.0)	<0.001
Duration of Follow-Up	4.1 ± 1.9	4.3 ± 1.8	3.9 ± 1.9	<0.001
Kidney Outcomes				
eGFR Change Per Year (mL/min/1.73 m^2/year)	-1.3 ± 4.2	-1.1 ± 3.6	-1.9 ± 4.7	0.009
Rapid eGFR Decline (≤ -5 mL/min/1.73 m^2/year)	276 (10%)	114 (9%)	162 (12%)	0.003

Data expressed as mean ± standard deviation or frequency (percentage) as appropriate.
eGFR = estimated glomerular filtration rate, CI = cognitive impairment, MoCA = Montreal Cognitive Assessment, PTSD = post-traumatic stress disorder, PPE = protective personal equipment
[1]: Considered "non-white" if individuals reported themselves to be Black (Hispanic and Non-Hispanic), Hispanic (not Black)/Mexican, Asian (Non-Hispanic), or Other (non-Hispanic)
[2]: Cardiovascular disease was defined as a composite variable of stroke, angina, myocardial infarction, coronary artery disease, heart failure, or abnormal heart rhythm

Table 3. Characteristics and Outcomes of Individuals with and without Cognitive Impairment in individuals with baseline age < 60 years old

	Overall *4594*	**No Baseline CI (MoCA > 23)** *3542 (77%)*	**Baseline CI (MoCA ≤ 23)** *1052 (23%)*	p-value
Age (years)	50.8 ± 5.4	50.4 ± 5.5	51.9 ± 5.1	<0.001
Sex				0.94
Male	4173 (91%)	3218 (91%)	955 (91%)	
Female	421 (9%)	324 (9%)	97 (9%)	
Race/Ethnicity				<0.001
White (non-Hispanic)	3847 (84%)	3044 (86%)	803 (76%)	
Non-White[1]	617 (13%)	424 (12%)	193 (18%)	
Missing	130 (3%)	74 (2%)	56 (5%)	
Education				<0.001
Less than BA/BS	2880 (63%)	2179 (62%)	701 (67%)	
BA/BS or higher	1314 (29%)	1091 (31%)	223 (21%)	
Missing	400 (9%)	272 (8%)	128 (12%)	
Comorbidities				
Cardiovascular Disease[2]	213 (5%)	157 (4%)	56 (5%)	0.23
Diabetes	401 (9%)	294 (8%)	107 (10%)	0.059
Hypertension	1299 (28%)	988 (28%)	311 (30%)	0.29
Obesity	2522 (55%)	1923 (54%)	599 (57%)	0.13
BMI (kg/m^2)	31.3 ± 5.4	31.3 ± 5.4	31.5 ± 5.3	0.31
Missing	32 (0.7%)	19 (0.5%)	13 (1%)	
WTC Exposure				0.093
No Exposure/Low Exposure	212 (5%)	175 (5%)	37 (4%)	
Mild Exposure	2535 (55%)	1983 (56%)	552 (52%)	
Moderate Exposure	1356 (30%)	1026 (29%)	330 (32%)	
High Exposure	277 (6%)	207 (6%)	70 (7%)	
Severe Exposure	71 (2%)	53 (2%)	18 (2%)	
Unknown	143 (3%)	98 (3%)	45 (4%)	
Screened Depression	523 (11%)	383 (11%)	140 (13%)	0.015
Missing	121 (3%)	79 (2%)	42 (4%)	
Screened PTSD	561 (12%)	401 (11%)	160 (15%)	<0.001
Missing	88 (2%)	63 (2%)	25 (2%)	
Baseline MoCA Score	25.4 ± 2.6	26.5 ± 1.7	21.6 ± 1.6	<0.001
eGFR Variables				
First eGFR Measurement (mL/min/1.73 m^2)	92.8 ± 12.6	92.9 ± 12.5	92.3 ± 12.7	0.14
Last eGFR Measurement (mL/min/1.73 m^2)	88.6 ± 13.7	88.7 ± 13.6	88.1 ± 13.9	0.18
Number of eGFR Available	5.0 (3.0 - 6.0)	5.0 (3.0 - 6.0)	4.0 (3.0 - 5.0)	<0.001
Duration of Follow-Up	4.3 ± 1.8	4.5 ± 1.8	3.9 ± 1.9	<0.001
Kidney Outcomes				
eGFR Change Per Year (mL/min/1.73 m^2/year)	-1.1 ± 3.8	-1.0 ± 3.6	-1.4 ± 4.6	0.010
Rapid eGFR Decline (≤ -5 mL/min/1.73 m^2/year)	395 (9%)	273 (8%)	122 (12%)	<0.001

Data expressed as mean ± standard deviation or frequency (percentage) as appropriate.
eGFR = estimated glomerular filtration rate, CI = cognitive impairment, MoCA = Montreal Cognitive Assessment, PTSD = post-traumatic stress disorder, PPE = protective personal equipment
[1]: Considered "non-white" if individuals reported themselves to be Black (Hispanic and Non-Hispanic), Hispanic (not Black)/Mexican, Asian (Non-Hispanic), or Other (non-Hispanic)
[2]: Cardiovascular disease was defined as a composite variable of stroke, angina, myocardial infarction, coronary artery disease, heart failure, or abnormal heart rhythm

Table 4. Characteristics and Outcomes of Individuals with and without Cognitive Impairment in individuals without screened baseline PTSD or Depression

	Overall *4869*	**No Baseline CI (MoCA > 23)** *3686 (76%)*	**Baseline CI (MoCA ≤ 23)** *1183 (24%)*	p-value
Age (years)	53.7 ± 8.0	53.1 ± 7.8	55.8 ± 8.3	<0.001
Sex				0.42
Male	4497 (92%)	3398 (92%)	1099 (93%)	
Female	372 (8%)	288 (8%)	84 (7%)	
Race/Ethnicity				<0.001
White (non-Hispanic)	4122 (85%)	3198 (87%)	924 (78%)	
Non-White[1]	577 (12%)	396 (11%)	181 (15%)	
Missing	170 (3%)	92 (3%)	78 (7%)	
Education				<0.001
Less than BA/BS	2937 (60%)	2192 (59%)	745 (63%)	
BA/BS or higher	1432 (29%)	1163 (32%)	269 (23%)	
Missing	500 (10%)	331 (9%)	169 (14%)	
Comorbidities				
Cardiovascular Disease[2]	286 (6%)	198 (5%)	85 (7%)	0.020
Diabetes	465 (10%)	344 (9%)	121 (10%)	0.36
Hypertension	1502 (31%)	1129 (31%)	373 (32%)	0.56
Obesity	2560 (53%)	1949 (53%)	611 (52%)	0.46
BMI (kg/m^2)	31.0 ± 5.3	31.0 ± 5.3	30.9 ± 5.2	0.60
Missing	32 (0.7%)	19 (0.5%)	13 (1%)	
WTC Exposure				0.051
No Exposure/Low Exposure	232 (5%)	184 (5%)	48 (4%)	
Mild Exposure	2598 (53%)	2007 (54%)	591 (50%)	
Moderate Exposure	1514 (31%)	1113 (30%)	401 (34%)	
High Exposure	291 (6%)	215 (6%)	76 (6%)	
Severe Exposure	73 (2%)	55 (1%)	18 (2%)	
Missing	161 (3%)	112 (3%)	49 (4%)	
Baseline MoCA Score	25.3 ± 2.7	26.5 ± 1.7	21.6 ± 1.6	<0.001
eGFR Variables				
First eGFR Measurement (mL/min/1.73 m^2)	91.0 ± 12.8	91.4 ± 12.8	89.8 ± 13.0	<0.001
Last eGFR Measurement (mL/min/1.73 m^2)	86.7 ± 14.2	87.1 ± 14.0	85.5 ± 14.7	<0.001
Number of eGFR Available	4.0 (3.0 - 6.0)	5.0 (3.0 - 6.0)	4.0 (3.0 - 5.0)	<0.001
Duration of Follow-Up (years)	4.2 ± 1.9	4.4 ± 1.8	3.6 ± 1.9	<0.001
Kidney Outcomes				
eGFR Change Per Year (mL/min/1.73 m^2/year)	-1.2 ± 3.9	-1.1 ± 3.7	-1.5 ± 4.5	0.011
Rapid eGFR Decline (≤ -5 mL/min/1.73 m^2/year)	462 (9%)	303 (8%)	159 (13%)	<0.001

Data expressed as mean ± standard deviation or frequency (percentage) as appropriate.
eGFR = estimated glomerular filtration rate, CI = cognitive impairment, MoCA = Montreal Cognitive Assessment, PTSD = post-traumatic stress disorder, PPE = protective personal equipment
[1]: Considered "non-white" if individuals reported themselves to be Black (Hispanic and Non-Hispanic), Hispanic (not Black)/Mexican, Asian (Non-Hispanic), or Other (non-Hispanic)
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R. Bano reports the following:
Employer: Catholic Health Services of Long Island - St. Francis Hospital; Stony Brook University

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S. Clouston reports the following:
Employer: Renaissance School of Medicine at Stony Brook; and Ownership Interest: Google, Apple, Bank of Montreal, Bowhead, McDonald's Microsoft, Nike, NVidia, Anonos,.

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F. Mann reports the following:
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