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Final Report
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List of Terms and Abbreviations

ASCVD	atherosclerotic cardiovascular disease
B2M	beta-2 microglobulin
BMI	body mass index
Cd	Cadmium
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Consortium
CRP	C-reactive protein
CVD	cardiovascular disease
DD	diastolic dysfunction
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
GERD	gastro-esophageal reflux disease
HbA1c	hemoglobin A1c or glycosylated hemoglobin
Hg	mercury
Hs-CRP	high sensitivity C-reactive protein
IL	interleukin
IFγ	interferon gamma
KIM	kidney injury molecule
LV	left ventricle/ left ventricular
LVDD	left ventricular diastolic dysfunction
LVH	left ventricular hypertrophy
MCP	monocyte chemoattractant protein
MDRD	Modification of Diet in renal disease equations
MESA	Multi Ethnic Study of Atherosclerosis
NHANES	National Health and Nutrition Examination Study
NGAL	neutrophil gelatinase-associated lipocalin
OSA	obstructive sleep apnea
PAT	peripheral arterial tonometry
Pb	lead
PM	particulate matter
RV	right ventricle/ right ventricular
RHI	Reactive hyperemia index
TNFα	tissue necrosis factor- alpha
TNFR	tumor necrosis factor receptor
UACR	urine albumin: creatinine ratio
WTC	World Trade Center
YKL-40	chitinase 3-like1 or cartilage glycoprotein-39

Abstract

Significant associations between 9/11 exposure and several medical conditions, including obstructive sleep apnea (OSA) exist, but until now, studies of kidney damage are limited. Both kidney disease (characterized by albuminuria and impaired estimated glomerular filtration rate (eGFR)) and OSA are important public health issues due to their impact on cardiovascular outcomes. Prior researchers have found trends toward increased albuminuria in residents with higher PM exposure over 20 years. Mechanisms by which particulate matter (PM) causes toxic effects are not adequately understood, and different mechanisms may be responsible for acute vs. chronic effects.

Findings from this research addresses a critical knowledge gap about the risk of kidney damage among WTC-exposed individuals, and the association of chronic kidney disease (CKD) with a defined WTC-related diagnosis, OSA. Current evidence supports a strong interaction between OSA and CKD in those with end stage renal disease (ESRD), but evidence is lacking among those with early CKD. Our study provides a unique opportunity to analyze the relationship between prevalence of OSA and CKD in this unique population of middle-aged men and women with a relatively high prevalence of both conditions.

Between November 2017 and October 2020, a one-time evaluation was performed on 555 participants (513 WTC-exposed and 42 unexposed). Urine albumin:creatinine ratio (UACR) and eGFR were used to evaluate kidney function. Clinically relevant albuminuria was defined as UACR ≥30 mg/g and eGFR was calculated using the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equations. PM exposure was categorized into four levels based on proximity to Ground Zero, time of arrival, and duration of exposure (XP4). To investigate the association between kidney disease and OSA, participants underwent evaluation that included medical history, measurement of blood pressure, height, weight, waist, hip and neck circumference, lipid panel, complete blood count, HbA1c, serum creatinine and cystatin-C and sleep apnea screening (Berlin questionnaire). Participants never diagnosed with OSA and screened positive for high risk OSA were evaluated with home sleep apnea test device. Participants diagnosed with OSA provided latest sleep study results. To evaluate proposed mechanisms of kidney injury, biomarkers of inflammation (hsCRP, TNF-α, interferon-gamma and other cytokines), renal tubular injury (KIM-1, IL-18, B-2-microglobulin, NGAL, Uromodulin, MCP-1) and heavy metal assays were performed. Binary and categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation. Binary variables were compared between studies using logistic models and continuous variables were compared using general linear models.

WTC–exposed individuals were more likely to have decreased renal function (eGFR) compared with non-exposed New York cohort after adjusting for gender, ethnicity, race, smoking status, history of diabetes and hypertension (p=0.002). Moreover, WTC-exposed participants with OSA had decreased eGFR after adjusting for age, ethnicity, diabetes, hypertension and smoking (p=0.0491).

In light of the finding that reduction in kidney function was associated with exposure to particulate matter at Ground Zero, we recommend continued monitoring of kidney function in this population. These novel findings pave the way for future studies of environmental exposures in the pathogenesis of chronic kidney disease.

Section 1

Significant Key Findings

The primary objective of this study was to evaluate the risk of kidney disease among WTC Health Program Participants and to evaluate the association of kidney disease with a defined WTC-related diagnosis, obstructive sleep apnea (OSA). This study addresses a critical knowledge gap about the risk of kidney damage among WTC-exposed individuals, as well as potential pathways that could be targets for therapy. Renal function was assessed using serum creatinine and Cystatin C to calculate estimated glomerular filtration rate (eGFR) and spot urine albumin and creatinine to calculate urine albumin: creatinine ratio (UACR). We tested the hypothesis that eGFR and UACR correlate with intensity and duration of exposure to particulate matter at the WTC site. In order to assess effect of exposure level and renal tubular function as a cause of kidney disease, we measured urine and plasma biomarkers of renal tubular injury and inflammation.

Renal Function in WTC-exposed individuals compared to non-exposed

1. Participants exposed to WTC particulate matter (PM) were more likely to have decreased renal function compared with non-exposed New York cohort as defined by eGFR using creatinine equation (mean 86.02 vs 97.16 ml/min/1.73m2) after adjusting for gender, ethnicity, race, smoking status, history of diabetes and hypertension (p=0.002).
2. The presence of renal dysfunction as defined by eGFR by creatinine equation (p=0.019) and eGFR by both creatinine and cystatin C equation (p= 0.0322) correlates with degree of exposure to PM in this population.
3. Participants exposed to WTC PM had higher UACR compared with non-exposed New York cohort (mean 102.1 vs. 40.8 ug/mg, p=0.0601)

OSA and Kidney Disease in WTC-exposed Participants

1. WTC–exposed individuals were significantly more likely to have a diagnosis of OSA (p<0.0001) or score as High Risk for OSA (p=0.0008) compared to unexposed individuals. OSA diagnosis is significantly associated with Exposure to particulate matter (p<0.0001).
2. A primary analysis was a comparison of renal disease in those with OSA compared with those without OSA. We found that WTC-exposed participants with OSA were more likely to have decreased eGFR using CKDepi-cystatin and creatinine equation, after adjusting for age, ethnicity, diabetes, hypertension and smoking (p=0.0491).

Proximal and Distal Renal Tubular Function assessed by urine biomarkers and plasma inflammatory markers

1. The presence of proximal tubular dysfunction as defined by Beta-2 microglobulin (B2M) differed by exposure level (p=0.0041), and was markedly increased in the highest exposure group.
2. The presence of distal tubular dysfunction as defined by Neutrophil Gelatinase-Associated Lipocalin (NGAL) differed by exposure level (p=0.0387).

Noteworthy Renal Pathology

1. We developed a repository of data of WTC responders with a spectrum of renal disorders. The following relatively rare diseases occurred in this population: Alport syndrome, angiomyolipoma, kidney infections, anti-GBM monotypic atypical nephritis, retroperitoneal fibrosis, Wegener's granulomatosis with renal involvement. We also noted: focal segmental glomerulosclerosis (FSGS) in 4 subjects; Renal cancer in 8 subjects and end-stage renal disease (ESRD) in 21 subjects.

2. **IgA Nephropathy occurred in 11 subjects and was associated with WTC exposure (XP4) (p=0.0230)**
   IgA nephropathy (IgAN), a cause of end-stage renal disease, is linked to a generalized hyper-reactivity of the immune system. It is an autoimmune disease where immune complexes consisting of IgA1 with an autoantigen and anti-glycan autoantibodies deposit in the glomeruli and induce renal injury. Both clinical and experimental research has shown antigens from respiratory or gastrointestinal tract to be involved in the pathogenesis of IgA nephropathy.

   Interactions between the immune system, genetics and environmental exposure contribute to autoimmune disorders. Several autoimmune disorders are associated with dust cloud exposure at the WTC. The incidence of 11 cases of IgAN among 513 persons is 2.2 %, which is higher than expected in otherwise healthy adults (1.29 in 100000 persons). This novel finding has important implications for those who worked and volunteered at the WTC disaster area.

3. **Kidney Stones occurred in 109 subjects (19.6% of participants). Diagnosis of kidney stones was more likely in people who had diagnosis of OSA compared to those who did not have OSA (p= 0.0166).** Environmental exposures have been shown to correlate with kidney stones. Studies have also shown OSA and cardiovascular risk factors like hypertension and metabolic syndrome can cause kidney stones which can lead to significant morbidity (infection, impaired kidney function). Further exploration of this finding is warranted.

Translation of Findings

Kidney disease results in significant morbidity and mortality in the United States. The findings of small increases in albuminuria or declines in eGFR in the study participants, may lead to important clinical outcomes. Similar changes in kidney function have been associated with increased risk of cardiovascular events in other populations. In light of the findings that reduction in eGFR was associated with exposure to particulate matter at Ground Zero, this finding should translate into continued surveillance of eGFR in those who sustained high-exposure to particulate matter at Ground Zero. Surveillance, early detection and timely referral to kidney specialists would mitigate long-term kidney and CVD risk.

Obstructive Sleep Apnea is a highly prevalent condition among WTC participants. Importantly, this study highlights the significant association between OSA and decreased renal function, after controlling for age, ethnicity, hypertension, diabetes and smoking. Blood and urine tests for renal tubular function and inflammation (urine KIM-1, Uromodulin, and plasma TNFR1) were higher in OSA patients supporting mechanistic pathways involved in clinical outcomes.

Research Outcomes/Impact

This study rigorously investigates the risk of kidney damage among WTC individuals exposed to the WTC disaster. **Participants exposed to WTC particulate matter (PM) were more likely to have decreased renal function compared with non-exposed individuals. Importantly, WTC–exposed individuals with obstructive sleep apnea (OSA) are more likely to have kidney dysfunction, after adjusting for age, ethnicity, diabetes, hypertension and smoking**. In addition, the incidence of autoimmune-related kidney disease, specifically IgA nephropathy, is higher than expected compared to the general population. A higher incidence of kidney stones among participants with OSA compared to those without OSA is a novel finding. These findings warrant further investigation.

In regard to improved practices of occupational safety and health, periodic monitoring of kidney function should be performed in workers with exposure to inhaled particulate matter. Specifically these findings should impact current screening and evaluation of WTC Health Program participants.

Section 2 Scientific Report

A. Background and Significance

More than 410,000 individuals were directly exposed to the 9/11 World Trade Center (WTC) disaster[1], including more than 91,000 rescue and recovery workers and volunteers who sustained exposure to thousands of tons of coarse and fine particulate matter (PM), including cement dust, glass fibers, silica, asbestos, lead, hydrochloric acid, organochlorine pesticides, polychlorinated biphenyls, and dioxins.[2-5] These individuals, followed regularly at the WTC Health Program, represent a unique population of subjects with PM exposure related to a discrete event, with the potential to provide insight into the long-term health effects of PM exposure both for WTC responders and for other individuals with significant occupational or environmental exposure. In 2017, the prevalence of CKD was estimated as 9.1% in the world's population and was the 12th leading cause of death worldwide.[6] In the United States, the prevalence of CKD has most recently been estimated as 14.8% of the population per the 2013-2016 NHANES and most (9 in 10) adults with CKD do not know they have it. [7-8] The prevalence of CKD is rising in tandem with the prevalence of hypertension and diabetes, the two major risk factors.[9] However, not all individuals with hypertension or diabetes develop significant CKD, and not all individuals with CKD have these traditional risk factors.[10] In the Atherosclerosis Risk in Communities (ARIC) Study, an observational cohort, the risk for CKD rose with increasing quartiles of inflammatory markers independent of traditional risk factors. [11] Exposure to silica, dioxins and heavy metals, such as found in WTC dust, is known to contribute to CKD. Evidence is now building that nontraditional risk factors (including air pollution and inhaled PM) may be involved in CKD pathogenesis. [12-13]

Significant associations between 9/11 exposure and several medical conditions, including obstructive sleep apnea exist, [14] but studies of kidney damage are limited. We previously evaluated 406 participants in the CDC-NIOSH funded observational study, "Renal and Cardiovascular Impairment in WTC Responders: Implications for Diagnosis and Treatment (WTC-RENAL), NCT02246101." As part of that study, we have identified first responders with abnormal kidney function, defined by reduced estimated glomerular filtration rate (eGFR) or increased urine albumin:creatinine ratio (UACR). Albuminuria is a marker of systemic endothelial dysfunction and early CKD. Obstructive sleep apnea (OSA), a prevalent disorder in WTC-exposed individuals, is defined by CDC/NIOSH as a "WTC-related" diagnosis. OSA consists of episodes of intermittent hypoxemia, oxidative stress, and endothelial dysfunction. Both albuminuria and OSA are important public health issues due to their impact on cardiovascular outcomes. Findings from this research address a critical knowledge gap about the risk of kidney damage among WTC responders, the progression of CKD since exposure, and the association of CKD with a defined WTC-related diagnosis, OSA.

Inhaled particulate matter and kidney disease

The current body of literature can verify that long term PM exposure is associated with increased risk of CKD and recent findings have shown that the global burden of CKD attributable to exposure to PM is substantial. [15] In a subset of patients from the ARIC study followed for a median of 17.7 years, higher annual average PM exposure was associated with increased albuminuria and a higher risk of CKD. [16] In the Multi-Ethnic Study of Atherosclerosis (MESA), the authors found a trend toward increased albuminuria in residents of field centers with higher PM exposure over 20 years, after adjustment for demographic and cardiovascular risk factors.[17] The investigators speculated that PM-induced endothelial dysfunction causes disruption of the glomerular basement membrane. The mechanisms by which PM causes these toxic effects are not adequately understood, and different mechanisms may be responsible for acute and chronic effects.

Kidney disease and OSA

Patients with CKD have an increased prevalence of OSA that has been associated with an increased risk for cardiovascular events and mortality. [18] The increased risk of CVD events is observed across all stages of CKD, including small increases in albuminuria or declines in eGFR. In a study of mostly male US veterans, those diagnosed with incident OSA had higher incidence of CKD compared with those without OSA.[19] Current evidence supports a strong interaction between OSA and CKD in those with end stage renal disease (ESRD), but evidence

is lacking among those with early CKD. Our study provided a unique opportunity to analyze the relationship between prevalence of OSA and CKD in this unique population of middle-aged men and women with a relatively high prevalence of both conditions.

Plausible mechanisms for kidney damage resulting from PM exposure

Prior studies of WTC responders have focused primarily on the incidence of adverse health outcomes; however, a number of potential mechanisms have been hypothesized. Inhaled PM has been shown to deposit in the microvasculature, and exposure has been associated with elevated markers of systemic inflammation. A study to evaluate WTC responders with high and low exposure to PM using dynamic magnetic resonance imaging to evaluate differences in atherosclerosis demonstrated that high exposure to PM might be associated with plaque neovascularization, which may indicate worsening endothelial dysfunction in WTC responders with high exposure to PM.[20] This research evaluated the innovative hypothesis that systemic inflammation and endothelial dysfunction mediate the relationship between PM exposure and CKD. In addition, PM from the WTC site contained heavy metals, including several that have been associated with CKD. In particular, environmental or occupational exposure to lead, cadmium, and mercury have all been reproducibly associated with nephrotoxicity manifesting in early stages as proximal tubular dysfunction.[21]

***Figure 1*: Effects of PM Exposure on Kidneys: Potential mechanism**

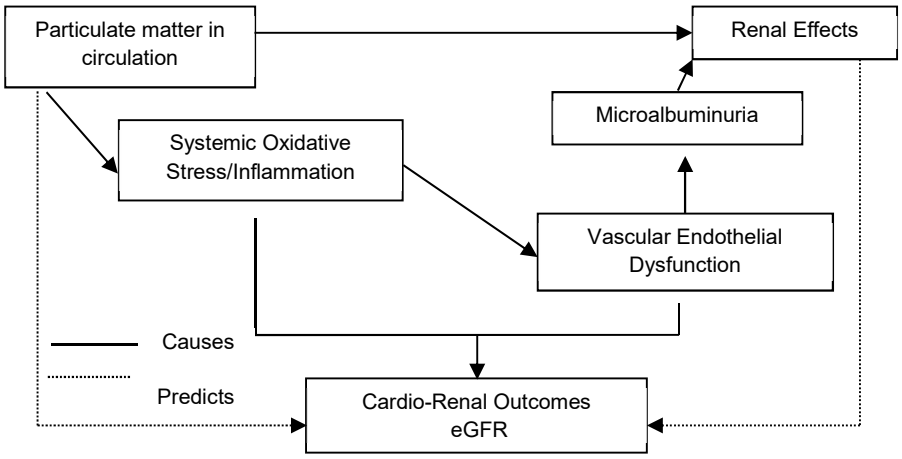
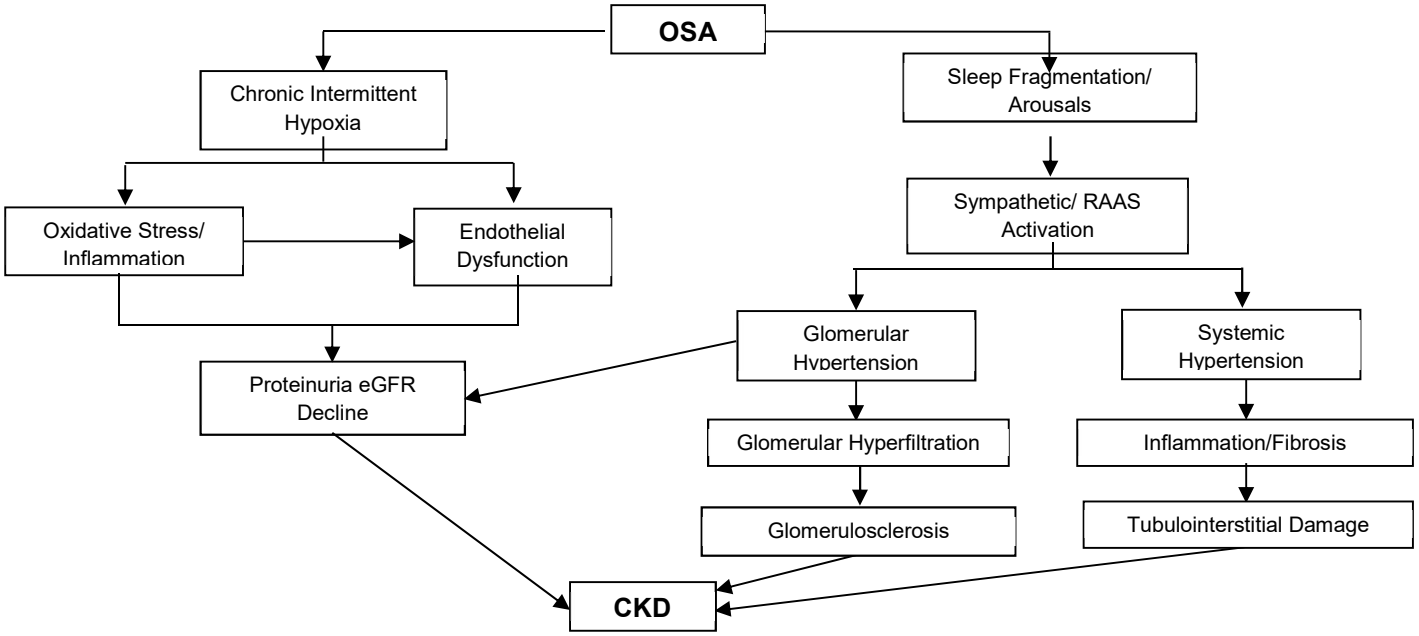


***Figure 2*: Conceptual framework linking OSA and CKD**



Preliminary Data

Prevalence of impaired kidney function in WTC Responders

From our previous U01 study, we recruited 406 WTC first responders to participate in a more detailed evaluation of CKD prevalence and risk factors. The mean age of participants was 54 years and most were males (80.5%), white (72%) and never smokers (71.43%). Our data demonstrated a high prevalence of mildly decreased eGFR with 68% of participants having an eGFR between 60 - 90 ml/min/1.73m^2 and 5% of participants having an eGFR < 60 ml/min/1.73m^2. The prevalence of albuminuria, defined as a urine albumin: creatinine ratio (UACR) > 30 mg/g, was approximately 9%.

Association between 9/11 exposure and kidney function

From our previous U01 study of 406 WTC first responders, we found a significant association between eGFR and exposure (using the 4-level exposure score previously described by our colleagues, Wisnivesky et al [22]). Those with very high exposure had significantly lower eGFR compared to those with intermediate exposure (p=0.03) and low exposure (p=0.02) even after adjustment for pertinent covariates.

In an earlier pilot study of 183 consecutively enrolled subjects from the WTC-CHEST study, we evaluated the association of albuminuria with WTC exposure. Participants provided detailed information about PM exposure, and exposure score was calculated as previously described. We measured spot UACR and performed a multivariable regression analysis evaluating the association with exposure score, adjusting for age, gender, race, smoking status, body mass index, HbA1c, and self-reported hypertension. Results are notable for a significant linear trend (p=0.009) between level of exposure to PM and UACR. Participants with the highest PM exposure had a UACR of 207ug/mg greater than the low exposure group (95% CI 69 to 345, p= 0.003) after controlling for traditional risk factors.[23]

Prevalence of OSA in WTC responders

It is estimated that 26% of Americans between the ages of 30 and 70 years have sleep apnea.[24] A study of 4,576 WTC firefighters and emergency medical personnel found the prevalence of high risk for OSA to be 36.6%. At average follow-up of 1.4 years, 16.9% of those previously not at high risk became high risk for OSA, as defined by screening evaluations.[25] In our evaluation of 1540 WTC-Law Enforcement Officers, 653 (42%) were found to be high-risk for OSA based on screening with the Berlin Questionnaire.[26] Based on a review of the WTC data center as of March 2016, of the 20,253 subjects assigned to Mount Sinai WTC-Health Program, 2,052 have a WTC-certified diagnosis of OSA (includes verified sleep study in addition to a WTC-related diagnosis of chronic sinusitis or GERD) and an additional 3,355 have self-reported a physician diagnosis of OSA.

Inflammatory response to particulate matter

Studies have shown that short and long-term exposures to PM are associated with markers of inflammation. A study in Switzerland determined short and long-term exposure to PM_{10} were directly associated with interleukin 1-beta (IL-1B), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a) but not with C-reactive protein (CRP). The authors hypothesized that the possible pathophysiological mechanism linking PM and systemic inflammation could be the increase in production of these pro-inflammatory cytokines. [27] In a study of 2,086 women enrolled in the US SWAN study, a one-year exposure to $PM_{2.5}$ was associated with high-sensitivity CRP (hs-CRP). [28]

Inflammation is linked with endothelial dysfunction and promotes development of CVD.[29,30] For example, the infiltration and retention of LDL in the artery wall initiates an inflammatory response which is pivotal in the atherosclerotic disease cascade.[31] Other mediators of cardiac risk, including air pollution, induce an inflammatory response as indicated by increased expression of C-reactive protein (CRP).[32,33] Our previous study of 406 first responders demonstrates elevated hs-CRP levels (mean 2.99 mg/dl).

Heavy metal levels in WTC responders

There are only a limited number of studies regarding heavy metal levels among WTC responders. An earlier study among fire fighters showed higher blood lead (Pb) and urine antimony (Sb) among WTC exposed firefighters compared to the control firefighters and a higher urine cadmium (Cd) level in those who have a higher exposure to the WTC dust particles compared to those with lower exposure. [34] In a study of pregnant women exposed to the WTC dust particles, no significant associations of heavy metals with exposure were seen. [35]

Data from our previous U01 study demonstrated elevated urine cadmium levels, consistent with prior exposure. The mean urine cadmium level in our sample (0.389 ng/mL) was substantially higher than population norms (comparison group based on NHANES data). Urine cadmium levels were also higher in participants with albuminuria than in those without, although this difference did not reach statistical significance.

Blood lead levels were within the normal range in the majority of participants enrolled (mean 1.13ug/dL); After adjustment for age, sex, race, ethnicity and smoking, blood lead had a dose-response relationship with exposure, with significantly higher blood lead levels in participants with very high exposure than those with intermediate and low exposure . Both blood and urine lead levels increase significantly with age, and non-Hispanics have a significantly higher blood lead than Hispanics.

Urine mercury levels were within the normal range, and we did not observe any significant association with kidney disease or WTC exposure.

B. Specific Aims

Specific Aim 1: To quantify the risk of kidney damage and the relationship to 9/11 exposure among WTC Health Program participants. Exposure to PM at the WTC site has not previously been associated with kidney damage. Based on our preliminary finding of an association between the intensity of exposure and albuminuria, we tested the working hypothesis that PM exposure causes delayed kidney damage. We predicted that albuminuria and decreased eGFR will be more common in WTC-exposed participants than in the general population (Aim 1a). We further hypothesized that albuminuria and eGFR will correlate with the intensity of PM exposure (Aim 1b). We expect that these studies will demonstrate a strong association between PM exposure and markers of kidney damage, including albuminuria and decreased eGFR.

Aim1a. We hypothesized that CKD, defined by the presence of albuminuria or decreased eGFR, will occur more frequently in WTC participants than in the general population and will correlate with the degree of exposure as defined by the previously defined WTC exposure score (adjusting for demographics, family history of CKD, and diagnosed, treated or laboratory confirmed diabetes and hypertension). As CKD can result from damage to the glomerular, tubular, or interstitial compartment, we assessed established urine biomarkers of tubular function and tubulointerstitial inflammation in WTC responders.

Aim1b. We created a repository of WTC responders with established CKD (including relatively rare disease) to qualitatively evaluate and describe the spectrum of kidney disease in the entire WTC population and compare to patterns of kidney disease in the general population.

Specific Aim 2: Evaluate the association of kidney disease and the established WTC-related condition, OSA. CKD and OSA share a similar risk profile, including hypertension and diabetes, the two most common determinants of CKD. OSA has deleterious effects on the cardiovascular, endocrine and nervous systems. We predicted that a faster rate of eGFR decline will be observed in those diagnosed with OSA.

Aim2a. OSA is particularly prevalent among WTC cohorts, and higher rates of OSA have also been observed among patients with CKD. We hypothesized that there is an independent association between prevalent OSA and prevalent CKD in WTC responders.

Aim2b.We hypothesized that OSA independently contributes to the progression of CKD. We will assess the temporal relationship eGFR decline to presence and severity of OSA, using longitudinal data from the WTC data center.

Specific Aim 3: To evaluate potential mechanisms of kidney injury in WTC Health Program participants. Exposure to PM has been associated with markers of systemic inflammation. Systemic inflammation has been proposed as both a mediator and a consequence of CKD. We and other investigators have demonstrated evidence of endothelial dysfunction in WTC responders. Our working hypothesis is that systemic inflammation and endothelial dysfunction mediate the relationship between PM exposure and kidney and cardiovascular damage. We evaluated the potential contribution of systemic inflammation to CKD by measuring biomarkers that have been associated with both CKD and OSA, a WTC-related condition that has itself been linked to CKD in the general population. Based on our preliminary data, we also considered the hypothesis that heavy metal toxicity contributes to the development of CKD in a broader sample of WTC responders.

Aim3a. In order to understand the role of chronic inflammation, we evaluated established plasma inflammatory markers which have been implicated as potential mediators of both OSA and CKD, including tumor necrosis factor (TNF-a), high sensitivity C-reactive protein (hs-CRP), interleukin (IL-6), and white blood cell count (WBC).

Aim3b. Based on our preliminary data noting increases in heavy metal levels in urine and blood, we narrowed the focus to evaluate the role of cadmium and lead in the development of CKD with evaluations of lead content in bone (marker of long-term exposure) as well as in blood. Since study participants included law enforcement personnel (with known exposure to lead), the characterization of bone lead levels will have an important health impact, whether or not a relationship to 9/11 is detected.

Aim3c. In a registry cohort of WTC responders with established CKD we explored potential mechanisms as determined by the observed patterns of disease by developing a comprehensive repository of data on WTC Health Program participants with common and rare kidney diseases, we defined specific clinical profiles and identified potential mechanisms that warrant future study. Importantly, we attempted to develop a process across all WTC Health Programs (inclusive of approximately 50,000 individuals), to monitor those with early CKD as well as those with biopsy-proven kidney disease at any stage.

C. Methodology

Study Population:

WTC patients participating in any WTC Health Program (WTCHP), and over the age of 18 years were eligible for enrollment into the study. In addition, unexposed comparator group (urban individuals of similar demographics who worked in New York City since 9/11 but not exposed to the 9/11 attacks) were also enrolled.

The main study enrolled 555 participants (513 exposed and 42 unexposed) from November 2017 to October 2020. Out of the 513 WTC-exposed patients, 171 had known kidney disease. An additional 66 subjects were enrolled in to be part of the registry cohort. The study was approved by the Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects and written informed consent was obtained.

Individuals with an occupation possibly involving chronic exposure to inhaled PM were not excluded but were asked to complete a questionnaire regarding type of work and duration to adjust for confounding factors.

Definition of albuminuria**:** Urine samples were collected on 2 occasions for albumin and creatinine. Clinically relevant albuminuria was defined as a random UACR ≥30 mg/g.

Calculation of eGFR**:** eGFR was calculated using the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations. The CKD-EPI eGFR equations were selected because of improved accuracy in the normal range.[36-37] The study evaluated differences in the combined creatinine-cystatin C eGFR, which provides the most accurate estimate of GFR, and the creatinine-based CKD-EPI eGFR, which is more practical for use in clinical practice and in monitoring programs. Values > 200 will be set to 200mL/min/1.73m^2.

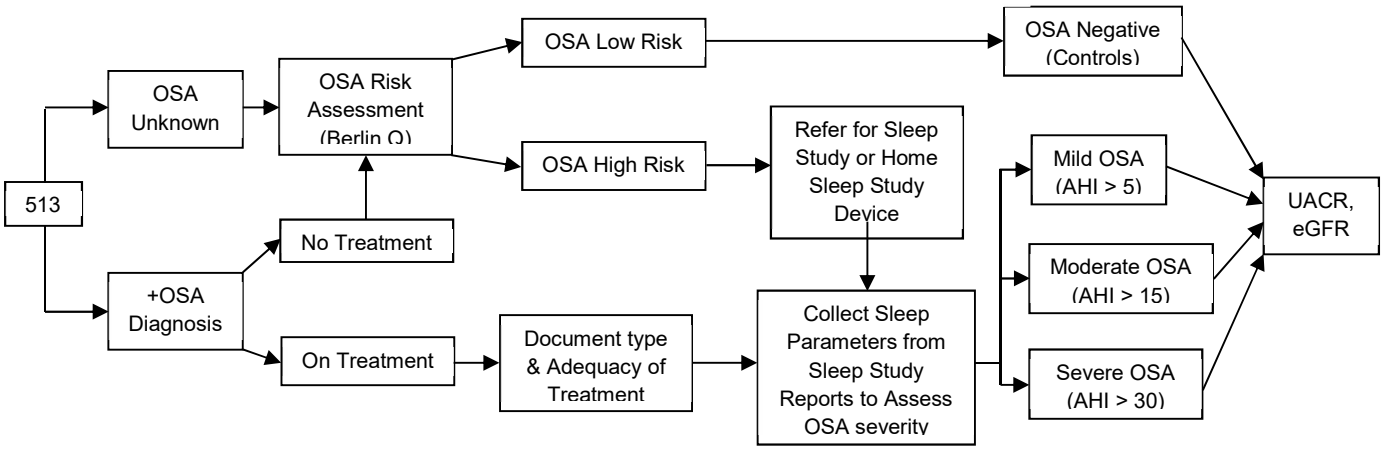
Assessment of tubular injury: Three established urine biomarkers of proximal tubular injury, including β2-microglobulin, kidney injury molecule (KIM)-1, and interleukin 18 (IL-18), as well as markers of distal tubular function (neutrophil gelatinase-associated lipocalin (NGAL)), Loop of Henle function (Uromodulin (UMOD)), and tubulointerstitial inflammation (monocyte chemotactic protein (MCP-1)) were measured.

Registry (Aim1c): A repository of WTC Health Program participants with established CKD (including relatively rare disease) was done to explore possible patterns of disease that may be associated with the exposure. We enlisted those participants in any WTC Health Program site, with a verified physician diagnosis of CKD, and prospectively collected data, including pathology specimen(s), if available. We qualitatively evaluated and described the spectrum of kidney disease in this population and compared it to patterns in the general population. This exploratory study will determine the need for future definitive studies.

Cardiovascular Disease Risk Screening In order to identify an independent relationship between CKD and OSA, we comprehensively evaluated potential confounders. Participants underwent an evaluation of traditional risk factors for CVD and CKD as accounted for in both the traditional Framingham Risk Score [38] ASCVD score, and Reynold's score[39] (medical history, medication use and baseline risk for CVD: smoking status, family history of premature coronary disease, blood pressure, heart rate, height, weight, waist, hip and neck circumference). Laboratory evaluation included: lipid panel, hs-CRP, complete blood count, HbA1C, serum creatinine, and cystatin C. In addition, all participants completed standard questionnaires on depression (Patient Health Questionnaire), stress (Perceived Stress Scale, PTSD Checklist: PCL-S), and sleep apnea (Berlin Questionnaire – reported sensitivity 86%, specificity 77%).[40]

Participants who were never diagnosed with OSA and screened positive for high risk OSA (using the Berlin questionnaire) underwent sleep apnea testing using an ambulatory home device (Watch PAT100). The Watch PAT100 (WP100, Itamar Medical; Caesarea, Israel) is a four-channel unattended ambulatory device based on the peripheral arterial tone (PAT) signal with three additional channels: heart rate (derived from the PAT signal), pulse oximetry, and actigraphy (both are embedded in the device). The PAT signal measures the arterial pulsatile volume changes of the finger that are regulated by the α-adrenergic innervations of the smooth muscles of the vasculature of the finger, and thus reflects sympathetic nervous system activity. The WP100 indirectly detects apnea/hypopnea events by identifying surges of sympathetic activation associated with the termination of these events. This information is further combined with heart rate and pulse oximetry data that are analyzed by the automatic algorithm of the system. This detects respiratory events and calculates the PAT Respiratory Disturbance Index (PRDI).

***Figure 3*: OSA and Kidney Disease: Flowchart**



Inflammatory Markers Traditional CKD risk factors have been associated with endothelial dysfunction, however, there is considerable heterogeneity in the magnitude of dysfunction observed in individuals with similar risk factor profiles.[41] Therefore, novel CKD risk factors, including inhaled PM, likely account for some of the observed variability. An established marker of systemic inflammation, serum hs-CRP [42], was measured and was included in an expanded panel of inflammatory biomarkers.

We measured a robust set of plasma inflammatory markers including tumor necrosis factor-alpha (TNF), an inflammatory biomarker that has been shown to be elevated in the setting of both CKD and OSA [43], interferon-gamma (INFγ), KIM-1, and other cytokines **(**IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13) [44].

Heavy Metals Prior studies have identified heavy metals in the dust collected at the WTC disaster site. Among these potential environmental toxins, lead, cadmium, and mercury have been previously associated with kidney damage, including proximal tubular dysfunction. We explored the hypothesis that heavy metal toxicity contributes to kidney damage among our population by measuring blood levels of lead and urine levels of cadmium and mercury (Agilent 8800 Triple Quad Dynamic Reaction Cell-Inductively Coupled Plasma-Mass Spectrometer) in all participants. Heavy metal assays were performed in the Molecular Environmental Health Laboratory using certified reference materials. Heavy metal levels were compared between participants with and without CKD.

Because blood lead levels reflect more recent exposure and may be confounded by occupational exposure in first responders (i.e. firing range in police and security officers), we also measured bone lead as a more stable indicator of prior exposure in a subgroup of participants. Bone lead measurements using a non-invasive technique (X-ray fluorescence) were performed under the supervision of Dr. Andy Todd, an international expert in the assessment and health effects of lead exposure.

Statistical Approach For specific Aim 1, the primary analysis was a comparison of the mean eGFR across the four levels of PM exposure and the unexposed group. Power calculations were utilized in order to determine the necessary sample size to detect what is considered a clinically significant change in eGFR between any two levels of exposure levels, at the 5% level using a two-sided significance test. To enable these calculations, the distribution of exposure levels in the pilot sample (406 of whom had an eGFR measurement) was used, as was the standard deviation of eGFR. The overall sample size was fixed so as to be able to detect differences with at least 80% power. A sample size of 550 new participants will provide at minimum 80% power to detect a difference of 5mL/min/1.73m^2 between the two highest categories of exposure, with greater power to detect differences between those with very high and intermediate or low exposure.

Each exposure group was compared with the unexposed group using generalized linear models, adjusting for age, sex and race. Differences were summarized by the mean and 95% confidence interval (CI). An overall test of association between exposure and mean eGFR was carried out using multiple linear regression, adjusting for age, gender, race, and co-morbidities such as diabetes or hypertension. If appropriate, the trend, adjusted for confounders, across the exposure categories was computed. Secondary analyses were repeated for UACR.

For specific aim 2, the primary analysis was a comparison of the prevalence of OSA in WTC-Health Program participants with and without evidence of kidney damage, as indicated by decreased creatinine-based eGFR or the presence of albuminuria. Assuming a fixed sample size of 550 new participants and a two-sided significance test with alpha of 5%, with a power of 90% to detect a 2.5-fold increase in the prevalence of OSA (i.e. 45% *vs* 20%) in this sample of participants with more detailed assessment of kidney function. OSA prevalence was compared between participants with and without CKD using non-parametric tests as well as univariate and multiple logistic regression models, adjusted for demographics and traditional CVD/ CKD and OSA risk factors.

For specific aim 3, we evaluated trends and differences in eGFR and albuminuria. Heavy metal levels (blood and urine level of lead, cadmium and mercury including bone lead in a subgroup of participants) and biomarkers were compared between participants with and without CKD using non-parametric tests.

Results and Discussion

Specific Aim 1: To quantify the risk of kidney damage and the relationship to 9/11 exposure among WTC Health Program participants

Table 1A summarizes the comparison of WTC-exposed and unexposed participants. There was no difference in age, education, smoking status, history of diabetes, body mass index (BMI), mean blood pressures, lipid profiles, HbA1c, hs-CRP, serum cystatin-C, urine albumin creatinine ratio (UACR) between the exposed and unexposed groups. There were significant differences in gender, ethnicity, marital status, alcohol intake, obstructive sleep apnea diagnosis, history of hypertension, waist circumference, serum creatinine

Serum creatinine was significantly higher in the exposed group (mean 1.03 vs 0.81 mg/dL, p=<0.0001). Kidney function was significantly lower in the exposed group with eGFR using CKD-epi equation (86.02 vs 97.16 ml/min/1.73m^2) (p=<0.0001) and eGFR using MDRD equation (88.64 vs 99.67 ml/min/1.73m^2) (p=0.0005). This remained statistically significant after adjusting for gender, ethnicity, race, smoking status, diabetes and hypertension (p=0.0002)

The incidence of albuminuria (UACR>30) was higher in the unexposed group (23.8% vs 14.4%) but not statistically significant. The mean UACR was higher in the exposed group (102.1 vs 40.8 ug/mg) and trended towards statistical significance (p=0.0601).

Table 1B summarizes the comparison of WTC-exposed and unexposed participants according to the different exposure groups (XP4). There were no significant differences in the history of diabetes, BMI, blood pressure measurements, lipid profile (total cholesterol, HDL and LDL), hs-CRP, HbA1c, cystatin-C, UACR among the 4 groups of exposed and unexposed participants. There were significant differences in age, gender, ethnicity, race, smoking status, alcohol intake, OSA diagnosis, history of hypertension, incidence of ESRD, IgA nephropathy, renal cyst and triglycerides.

Serum creatinine (1.28 (very high) vs 0.97(high) vs 1.01 (intermediate) vs 1.04 (low) vs. 0.81(unexposed) ml/min/1.73m^2) was significantly different among the exposure groups. (p=0.0428)

Kidney function was significantly different among the groups with eGFR using CKD-epi equation (84.2 (very high) vs 86.6 (high) vs 85.9 (intermediate) vs 86.3 (low) vs 97.2 (unexposed) ml/min/1.73m^2) (p=0.0119).

Among the exposed groups, blood and urine heavy metals as well as bone lead measurements did not have any significant differences. Although most biomarkers were within the normal range, there were statistically significant differences in urine levels of beta-2 microglobulin (B2M) (p=0.0041) and NGAL (p=0.0387) and plasma interferon-gamma (0.0005). Mean urine Beta-2-microglobulin (3,933,958 pg/mL) was abnormal/elevated in the highest exposure group (normal value is <300,000 pg/mL). Studies have shown B2M levels can be used to detect tubular injury due to various toxins and has been used as a marker of tubular dysfunction in subjects with heavy metal exposure such as cadmium.[45]

Table 1A: Comparison of WTC-Exposed and Unexposed Participants

	Unexposed	Exposed	*p*-Value
n	42	513	
Age (years)	53.5 (11.0)	56.4 (7.3)	0.0946
Gender (Males - %)	20 (47.6%)	423 (82.5%)	**<0.0001**
Ethnicity (Hispanic -%)	18 (42.9%)	128 (24.9%)	**0.0008***
Race			
White	20 (47.6)	347 (67.6)	**<0.0001***
Black	11 (26.2%)	70 (13.7)	
American Indian	0	3 (0.6%)	
Asian	3 (7.1%)	15 (2.9%)	
Other	8 (19.1)	78 (15.2%)	
Education			
Less than 12 years	0	14 (2.7%)	0.5746
HS/GED	8 (19.0)\%)	69 (13.6%)	
College-no degree	10 (23.8%)	151 (29.7%)	
Associate degree	4 (9.5%)	57 (11.2%)	
Bachelor degree	12 (28.6%)	154 (30.2%)	
Advanced degree	8 (19.1)	64 (12.6%)	
Marital Status			
Single	15 (35.7%)	84 (16.4%)	**0.0176**
Married/Partner	23 (54.8%)	346 67.6%)	
Divorced/separated	3 (7.1%)	64 (12.5%)	
Other	1 (2.4%)	18 (3.5%)	
Work Status			
employed	35 (83.3%)	262 (51.3%)	**<0.0001**
retired	3 (7.1%)	234 (45.8%)	
unemployed	4 (9.5%)	15 (2.9%)	
Smoking Status‡			
never smoked	25 (59.5%)	366 (71.4%)	0.1324
ex-smoker(former)	14 (33.3%)	133 (25.9%)	
current smoker	3 (7.1%)	14 (2.7%)	
Alcohol Intake			
Never	16 (38.1%)	138 (26.9%)	**0.0033***
Less than 1 drink/week	14 (33.3%)	174 (34.0%)	
None in past year (former)	0	7 (1.4%)	
More than 1 drink/week	12 (28.6%)	193 (37.7%)	
PHQ9	3.71 (5.05)	3.99 (5.18)	0.7380
PTSD(PCL-Q) > 44	2 (4.8%)	77 (15.2%)	0.0638
PTSD(PCL-Q) > 50	1 (2.4%)	50 (9.9%)	0.1079
OSA Diagnosis§ (Yes)	6 (14.3%)	281 (54.8%)	**<0.0001**
OSA High Risk$^{\Delta}$	13 (31.7%)	300 (58.6%)	**0.0008**
Hypertension§ (Yes)	17 (40.5%)	313 61.0%)	**0.0092**
Diabetes § (Yes)	8 (19.05%)	116 (22.61%)	0.5939
Dyslipidemia§ (Yes)	15 (35.71%)	275 (53.61%)	**0.0256**
BMI (kg/m^2) Mean	31.1 (6.8)	30.3 (5.5)	0.4784
BMI ≥ 30	16 (38.1%)	241 (47.1%)	0.2622
Waist Circ (in)	37.2 (5.3)	39.3 (6.0)	**0.0224**
Neck Circ (in)	15.2 (1.3)	15.6 (1.7)	0.1027
W:H ratio	0.88 (0.07)	1.09 (3.58)	0.1681
SBP(mmHg)	121.0 (10.8)	123.3 (14.8)	0.2122
DBP (mmHg)	75.7 (8.0)	77.6 (8.1)	0.1374
Total Cholesterol (mg/dL)	178.4 (38.9)	188.2 (42.6)	0.1489
LDL (mg/dL)	109.3 (32.9)	134.3 (391.2)	0.1657
HDL (mg/dL)	48.26 (13.79)	48.19 (12.75)	0.9703
Triglycerides (mg/dL)	104.1 (51.0)	114.4 (60.1)	0.2812
hsCRP (mg/L)	3.74 (5.05)	3.54 (5.88)	0.8299
HbA1c (%)	6.15 (1.26)	5.82 (0.97)	0.1129
Creatinine (mg/dL)	0.81 (0.15)	1.03 (0.62)	**<0.0001**
Serum cystatin-C (mg/L)	0.77 (0.13)	1.07 (3.66)	0.0721
UACR (µg/mg)-mean	40.8 (89.50	102.1 (667.2)	0.0601
UACR>30	10 (23.8%)	74 (14.4%)	0.1041
eGFRCKDep_creati$^{\Omega}$	97.16 (14.81)	86.02 (19.75)	**<0.0001**
eGFRMDRD$^{\infty}$	99.67 (18.22)	88.64 (23.46)	**0.0005**
Blood Lead (ug/dL)	-	1.350 (1.034)	
Urine Lead (ug/L)	-	0.541 (0.518)	

Blood Cadmium (ug/L)	-	0.286 (0.270)	
Urine Cadmium (ug/L)	-	0.403 (0.449)	
Urine Mercury (ng/mL)	-	1.104 (1.086)	
Bone Lead	-	N=281 7.60 (7.02)	
Urine Biomarkers (pg/mL)			
Proximal tubular function			
IL-18	-	43.47 (75.03)	
KIM-1	-	1616 (1965)	
B2M	-	612816 (4037194)	
Distal Tubular function			
NGAL	-	34246 (116772)	
Loop of Henle			
Uromodulin	-	4294839 (2506467)	
Tubular inflammation			
MCP-1	-	161.38 (183.10)	
Tubular recovery			
YKL-40	-	2459 (285595)	
EGF	-	9023 (7156)	
Plasma Biomarkers (pg/mL)			
KIM-1	-	81.02 (162.68)	
TNFR1	-	2207 (1694)	
TNFR2	-	7303 (4656)	
IFNγ	-	7.237 (13.702)	
IL-10	-	0.297 (0.948)	
IL-12p70 (n=219)	-	0.209 (0.378)	
IL-13 (n=235)	-	0.573 (0.635)	
IL-2 (n=303)	-	0.262 (0.751)	
IL-4 (n=363)	-	0.017 (0.703)	
IL-6	-	0.938 (1.139)	
IL-8	-	3.833 (3.903)	
TNF α	-	2.238 (0.970)	

Continuous variables are expressed as mean (standard deviation); categorical variables are expressed as number of patients (percent %) *Fisher's exact test used

Body Mass Index-BMI; waist hip ratio=W:H; Systolic Blood Pressure = SBP; Diastolic Blood Pressure = DBP; Low Density Lipoprotein Cholesterol = LDL; High Density Lipoprotein Cholesterol = HDL; High-sensitivity C-Reactive Protein = hsCRP; Glycosylated hemoglobin = HbA1c; Urine Albumin/Creatinine Ratio = UACR; interleukin=IL; Kidney injury molecule= KIM-1; monocyte chemoattractant protein= MCP; chitinase 3-like 1= YKL-40; beta-2 microglobulin= B2M; epidermal growth factor= EGF; neutrophil gelatinase-associated lipocalin= NGAL; tumor necrosis factor receptor=TNFR; interferon gamma= IFNγ; tumor necrosis factor alpha= TNFα

§Self-reported, physician diagnosis

ΔDefined by Berlin Questionnaire, 2 or more categories positive

ΩDefined by CKD-EPI equation ∞Defined by MDRD equation

Table 1B: Comparison of Characteristics According to Exposure Score (XP4)

	WTC Exposure XP4					
	Very High	**High**	**Intermediate**	**Low**	**Unexposed**	***p*-Value**
n	18	118	301	76	42	
Age (years)	53.7 (5.2)	57.2 (7.0)	56.5 (7.3)	55.6 (7.7)	53.5 (11.0)	**0.0342**
Gender (Males - %)	15 (83.3%)	99 (84.0%)	245 (81.4%)	64 (84.2%)	20 (47.6%)	**<0.0001**
Ethnicity(Hispanic%)	3 (16.7%)	32 (27.1%)	76 (25.2%)	17 (22.4%)	18 (42.9%)	**<0.0001***
Race						
White	13 (72.2%)	74 (62.7%)	216 (71.8%)	44 (57.9%)	20 (47.6%)	**<0.0001***
Black	2 (11.1%)	18 (15.2%)	34 (11.3%)	16 (21.0%)	11 (26.2%)	
American Indian	0	2 (1.7%)	1 (0.3%)	0	0	
Asian	0	4 (3.4%)	5 (1.7%)	6 (7.9%)	3 (7.1%)	
Other	3 (16.7%)	20 (17.0%)	45 15.0%)	1013.2%)	8 (19.1%)	
Education						
Less than 12 years	0	4 (3.4%)	8 (2.7%)	2 (2.7%)	0	**<0.0001***
HS/GED	3 (16.7%)	15 (12.7%)	35 (11.7%)	16 (21.6%)	8 (19.0%)	
College-no degree	7 (38.9%)	33 (28.0%)	99 (33.1%)	12 (16.2%)	10 (23.8%)	
Associate degree	2 (11.1%)	14 (11.9%)	30 (10.0%)	11 (14.9%)	4 (9.5%)	
Bachelor degree	4 (22.2%)	37 (31.3%)	91 (30.4%)	22 (29.7%)	12 (28.6%)	
Advanced degree	2 (11.1%)	15 (12.7%)	36 (12.0%)	11 (15.3%)	8 (19.0	
Marital Status						
Single	5 (27.8%)	19 (16.1%)	46 (15.3%)	14 (18.4%)	15 (35.7%)	**<0.0001***
Married/Partner	12 (66.7%)	79 (67.0%)	208 (69.3%)	47 (61.8%)	23 (54.8%)	
Divorced/separated	1 (5.6%)	18 (15.2%)	33 (11.0%)	12 (15.8%)	3 (7.1%)	
Other	0	2 (1.7%)	13 (4.3%)	3 (4.0%)	1 (2.4%)	
Work Status						
employed	14 (77.8%)	54 (45.8%)	158 (52.7%)	36 (48.0%)	35 (83.3%)	**<0.0001***
retired	4 (22.2%)	62 (52.4%)	133 (44.3%)	35 (46.7%)	3 (7.1%)	
unemployed	0	2 (1.7%)	9 (3.0%)	4 (5.3%)	4 (9.5%)	
Smoking Status‡						
never smoked	15 (83.3%)	89 (75.4%)	213 (70.8%)	49 (64.5%)	25 (59.6%)	**<0.0001***
ex-smoker(former)	3 (16.7%)	29 (24.6%)	74 (24.6%)	27 (35.5%)	14 (33.3%)	
current smoker	0	0	14 (4.6%)	0	3 (7.1%)	
Alcohol Intake						
Never	3 (16.7%)	34 (28.8%)	82 (27.3%)	19 (25.0%)	16 (38.1%)	**<0.0001***
Less than 1 drink/wk	10 (55.6%)	46 (39.0%)	93(31.0%)	25 (32.9%)	14 (33.3%)	
None pastyr (former)	0	1 (0.8%)	3 (1.0%)	3 (4.0%)	0	
More than 1 drink/wk	5 (27.8%)	37 (31.4%)	122 (40.7%)	29 (38.1%)	12 (28.6%)	
PHQ9	2.94 (3.73)	4.19 (5.07)	3.84 (5.13)	4.51 (5.84)	3.70 (5.05)	0.7271
(PCL-Q) > 44	3 (16.7%)	19 (16.1%)	44 (14.9%)	11 (14.9%)	2 (4.8%)	0.4660
(PCL-Q) > 50	1 (5.6%)	14 (11.9%)	28 (9.4%)	7 (9.5%)	1 (2.4%)	0.4611
OSADiagnosis§(Yes)	10 (55.6%)	69 (58.5%)	165 (54.8%)	37 (48.7%)	6 (14.3%)	**<0.0001**
OSA High Risk$^{\Delta}$	10 (55.6%)	66 (55.9%)	177 (59%)	47 (61.8%)	13 (31.7%)	**0.0179**
Hypertension§ (Yes)	8 (44.4%)	82 (69.5%)	180 (59.8%)	43 (56.6%)	17 (40.4%)	**0.0105**
Diabetes § (Yes)	3 (16.7%)	25 (21.2%)	70 (23.3%)	18 (23.7%)	8 (19.1%)	0.9229
Dyslipidemia§ (Yes)	10 (55.6%)	63 (53.4%)	160 (53.2%)	42 (55.3%)	15 (35.7%)	0.2753
Kidney Disease						
CKD	1 (5.56%)	4 (3.39%)	24 (7.97%)	8 (10.53%)	0	0.1025
ESRD	2 (11.11%)	1(0.85%)	1 (0.33%)	2 (2.63%)	0	**0.0004***
FSGS	0	1 (0.85%)	2 (0.66%)	1 (1.32%)	0	0.1035
IgA nephropathy	0	1 (0.85%)	7 (2.33%)	0	0	**0.0230***
Cyst	1 (5.56%)	9 (7.63%)	15 (4.98%)	6 (7.89%)	0	**0.0005***
Stone	4 (22.22%)	24 (20.34%)	47 (15.61%)	9 (11.84%)	6 (14.29%)	0.5217
PKD	0	0	4 (1.33%)	0	0	0.0857
Cancer	0	1 (0.85%)	2 (0.66%)	1 (1.32%)	0	0.1035
Congenital	0	1 (0.85%)	2 (0.66%)	0	0	0.1880
Other†	0	3 (2.54%)	11 (3.65%)	3 (3.95%)	0	**0.0073***

BMI (kg/m^2) -Mean	32.2 (5.8)	30.1 (5.1)	30.5 (5.7)	29.8 (5.2)	31.1 (6.8)	0.4211
BMI ≥ 30	8 (44.4%)	56 (47.5%)	145 (48.3%)	32 (42.1%)	16 (38.1%)	0.6881
Waist Circ (in)	41.5 (7.0)	39.3 (5.5)	39.4 (6.2)	38.5 (5.3)	37.2 (5.3)	0.0516
Neck Circ (in)	15.8 (1.7)	15.5 (1.7)	15.6 (1.7)	15.4 (1.4)	15.2 (1.3)	0.5112
W:H ratio	0.94 (0.08)	1.63 (7.46)	0.94 (0.08)	0.93 (0.08)	0.88 (0.07)	0.4338
SBP(mmHg)	128.7(15.5)	123.8 (14.0)	122.9 (15.7)	122.6(12.4)	121.0(10.8)	0.4257
DBP (mmHg)	80.1 (7.8)	78.4 (9.2)	77.5 (7.8)	76.3 (7.6)	75.7(8.0)	0.1381
TChol (mg/dL)	195.4 (33.2)	186.3 (41.8)	188.9 (44.0)	186.2 (40.1)	178.4 (38.9)	0.5445
LDL (mg/dL)	118.3 (23.8)	115.4 (35.9)	117.3 (39.2)	118.3 (36.4)	109.3 (33.0)	0.7332
HDL (mg/dL)	47.33 (10.27)	46.69 (12.76)	48.80 (13.23)	48.25 (11.26)	48.26 (13.7)	0.6680
TG (mg/dL)	148.6 (92.9)	121.0 (61.1)	113.3 (57.8)	100.7 (53.9)	104.1 (51.0)	**0.0122**
hsCRP (mg/L)	5.3 (4.5)	3.8 (7.8)	3.5 (5.3)	2.9 (5.1)	3.7 (5.0)	0.5970
HbA1c (%)	6.0 (1.0)	5.9 (1.0)	5.8 (1.0)	5.9 (0.8)	6.1 (1.3)	0.2255
Creatinine (mg/dL)	1.28 (1.46)	0.97 (0.28)	1.03 (0.65)	1.04 (0.58)	0.81 (0.15)	**0.0428**
UACR (µg/mg)Mean	125.4 (460.9)	59.4 (210.4)	126.9 (842.7)	64.4 (273.7)	40.8 (89.5)	0.8083
UACR>30	2 (11.1%)	13 (11.0%)	48 (16.0%)	11 (14.5%)	10 (23.8%)	0.3498
eGFRCKDepi$^{\Omega}$						
eGFR_creat_	84.2 (24.1)	86.6 (18.2)	85.9 (19.9)	86.3 (20.5)	97.2 (14.8)	**0.0119**
eGFR_cyst	91.3 (26.9)	96.8 (20.4)	95.0 (22.2)	98.9 (26.5)	103.3 (16.3)	0.1362
eGFR_both	88.5 (25.9)	93.2 (19.5)	91.7 (21.1)	93.7 (22.5)	102.3 (15.6)	**0.0322**
eGFRMDRD$^{\infty}$	87.1 (30.4)	89.9 (23.6)	88.3 (23.3)	88.5 (22.4)	99.7 (18.2)	0.0551
Cystatin-C (mg/L)	1.07 (0.88)	0.92 (0.70)	1.18 (4.75)	0.87 (0.40)	0.77 (0.13)	0.9109
Blood Pb (ug/dL)	1.71 (1.86)	1.22 (0.64)	1.38 (1.05)	1.36 (1.17)	-	0.2345
Urine Pb (ug/L)	0.60 (0.60)	0.55 (0.56)	0.54 (0.52)	0.52 (0.43)	-	0.9314
Blood Cd (ug/L)	0.26 (0.21)	0.24 (0.13)	0.31 (0.33)	0.29 (0.17)	-	0.1608
Urine Cd (ug/L)	0.33 (0.35)	0.40 (0.42)	0.41 (0.48)	0.41 (0.37)	-	0.9065
Urine Hg (ng/mL)	0.78 (0.50)	1.16 (1.16)	1.04 (1.02)	1.35 (1.28)	-	0.0736
Urine (pg/mL)						
Proximal tubule						
IL-18	35.93 (30.41)	51.96 (122.98)	41.56 (55.62)	39.54 (45.05)	-	0.5541
KIM-1	1500 (1330)	1559 (1648)	1605 (1868)	1774 (2756)	-	0.8817
B2M	3933958 (15903625)	260291 (1125031)	558491 (3026393)	587298 (3504484)	-	**0.0041**
Distal Tubule						
NGAL	111906 (346331)	31677 (109917)	30348 (93751)	35174 (101218)	-	**0.0387**
Loop of Henle						
UMod	3989333 (2756307)	4373441 (2530119)	4344923 (2548918)	4048110 (2256833)	-	0.7447
Tubule inflammation						
MCP-1	175.98 (166.40)	157.44 (150.00)	160.53 (177.98)	167.37 (243.73)	-	0.9679
Tubule recovery						
YKL-40	2359 (6355)	778 (1350)	1490 (11212)	8903 (70728)	-	0.2030
EGF	6921 (6175)	9808 (7540)	8807 (7188)	9151 (6599)	-	0.3528
Plasma (pg/mL)						
KIM-1	81.78(74.41)	62.01(46.38)	89.78(200.20)	75.69(121.11)	-	0.4643
TNFR1	3135 (4973)	2035 (854)	2228 (1483)	2172 (1948)	-	0.0819
TNFR2	8812 (9080)	6991 (3482)	7383 (4677)	7111 (4705)	-	0.4523
IFNγ	5.324 (2.199)	11.826 (26.184)	5.692 (4.859)	6.685 (8.524)	-	**0.0005**
IL-10	0.234 (0.166)	0.414 (1.243)	0.272 (0.953)	0.224 (0.237)	-	0.4689
IL-12p70 (n=219)	0.080 (0.099)	0.259 (0.366)	0.210 (0.411)	0.160 (0.199)	-	0.5379
IL-13 (n=235)	0.358 (0.280)	0.683 (0.740)	0.537 (0.565)	0.568 (0.755)	-	0.3810
IL-2 (n=303)	0.083 (0.065)	0.230 (0.581)	0.257 (0.540)	0.372 (1.453)	-	0.6292
IL-4 (n=363)	0.010 (0.009)	0.019 (0.079)	0.017 (0.075)	0.015 (0.029)	-	0.9585
IL-6	1.000 (0.768)	1.019 (1.256)	0.940 (1.216)	0.795 (0.560)	-	0.6054
IL-8	3.15 (1.40)	3.97 (2.62)	4.04 (4.75)	2.98 (1.25)	-	0.1624
TNF α	2.64 (1.04)	2.32 (0.98)	2.20 (0.97)	2.16 (0.91)	-	0.1931
Bone XRF	n=11 7.99 (6.00)	n=67 7.45 (7.58)	n=154 7.59 (7.05)	n=49 7.77 (6.27)	-	0.9930

Continuous variables are expressed as mean (standard deviation); categorical variables are expressed as number of patients (percent %)

Chronic Kidney Disease=CKD, End stage renal disease= ESRD, Focal segmental glomerulosclerosis =FSGS, polycystic kidney disease=PKD

† Other kidney disease (included AKI, Alport syndrome, angiomyolipomakidney infection, anti-GBM monotypic atypical nephritis, kidney infection, retroperitoneal fribrosis, unilateral kidney secondary to trauma, wegener's granulomatosis with renal involvement

Body Mass Index-BMI; waist hip ratio=W:H; Systolic Blood Pressure = SBP; Total cholesterol=TChol; Diastolic Blood Pressure = DBP; Low Density Lipoprotein Cholesterol = LDL; High Density Lipoprotein Cholesterol = HDL; Triglycerides=TG; High-sensitivity C-Reactive Protein = hsCRP; Glycosylated hemoglobin = HbA1c; Urine Albumin/Creatinine Ratio = UACR; Lead=Pb; Cadmium=Cd; Mercury=Hg; interleukin=IL; Kidney injury molecule= KIM-1; monocyte chemoattractant protein= MCP; chitinase 3-like 1= YKL-40; beta-2 microglobulin= B2M; epidermal growth factor= EGF; neutrophil gelatinase-associated lipocalin= NGAL; Uromodulin=UMod; tumor necrosis factor receptor=TNFR; interferon gamma= IFNγ; tumor necrosis factor alpha= TNFα

§Self-reported, physician diagnosis

ΔDefined by Berlin Questionnaire, 2 or more categories positive

ΩDefined by CKD-EPI equation ∞Defined by MDRD equation

<u>Specific Aim 2: Evaluate the association of kidney disease and the established WTC-related condition, OSA.</u>

Table 2 summarizes the comparison of WTC-exposed patients with versus without OSA. There was no significant difference in age, race, level of PM exposure, smoking status, waist:hip ratio and hs-CRP There were statistically significant differences in gender, ethnicity, history of hypertension and diabetes, BMI, blood pressure and HbA1c.

Participants with OSA had higher percentage of CKD (38.57% vs 27.16%, p=0.0065) and lower eGFR (using ckdepi-cystatin and creatinine equation): 90.17 vs 94.71 ml/min/1.73m^2 (p=0.0155). The association remained significant after adjusting for age, ethnicity, smoking, diabetes and hypertension (p=0.0491).

This association trended towards significance in patients with albuminuria (17.14% vs 11.21, p=0.0572)

A novel finding in our cohort was that patients with OSA had higher incidence of kidney stones compared to those without OSA (p=0.0166). A recent study in young males explored the association of OSA and risk of kidney stones and found that patients with sleep apnea and concomitant cardiovascular co-morbidities are at greater risk for kidney stone formation.[46]

There was a significant association between OSA and urine KIM-1 (p=0.0294) and uromodulin (p=0.0017) as well as plasma TNFR1 (p=0.0188). These findings can help inform treatment strategies by using these markers as treatment outcomes.

Although not specified in this aim, we found an association between OSA and PTSD. Patients with OSA had higher incidence of PTSD risk based on PCL questionnaires cut off >44 (p=0.0012) and cut off >50 (p=0.0208).

Table 2: Comparison of WTC-exposed patients with vs without OSA

	Without OSA	With OSA	*p*-Value
n	232	281	
Age (years)	56.0 (7.6)	56.8 (7.0)	0.2701
Gender (Males - %)	180 (77.59%)	243 (86.48%)	**0.0084**
Ethnicity (Hispanic -%)	57(24.57%)	71 (25.27%)	**0.0438***
Race			
White	155 (66.81%)	192 (68.33%)	0.8906
Black	31 (13.36%)	39 (13.88%)	
American Indian	1 (0.43%	2 (0.71%)	
Asian	6 2.59%)	9 (3.2%)	
Other	39 (16.81)	39 (13.88%)	
Education			
Less than 12 years	6 (2.6%)	8 (2.88%)	0.5455
HS/GED	24 (10.39%)	45 (16,19%)	
College-no degree	70 (30.30%)	81 (29.14%)	
Associate degree	26 (11.26%)	31 (11.15%)	
Bachelor degree	73 (31.60%)	81 (29.14%)	
Advanced degree	32 (13.85%)	32 (11.51%)	
Marital Status			
Single	45 (19.48%)	39 (13.88%)	0.1864
Married/Partner	152 (65.80%)	194 (69.04%)	
Divorced/separated	29 (12.55%)	35 (12.46%)	
Other	5 (2.16%)	13 (4.63%)	
Work Status			
employed	133 (57.83%)	129 (45.91%)	**0.0169**
retired	93 (40.43%)	141 (50.18%)	
unemployed	4 (1.74%)	11 (3.91%)	
WTC Exposure (XP4)			
Very High	8 (3.45%)	10 (3.57%)	0.6163
High	49 (21.12%)	69 (24.64%)	
Intermediate	136 (58.62%)	164 (58.57%)	
Low	39 (16.81%)	37 (13.21%)	
Smoking Status			
Never smoked	172 (74.1%)	194 (69.0%)	0.4109
Ex-smoker(former)	55 (23.7%)	78 (27.8%)	
Current smoker	5 (2.2%)	9 (3.2%)	
PHQ9	3.0 (4.6)	5.0 (5.4)	**<0.0001**
PTSD (PCL-Q) > 44	22 (9.57%)	55 (19.93%)	**0.0012**
PTSD (PCL-Q) > 50	15 (6.52%)	35 (12.68%)	**0.0208**
Hypertension§ (Yes)	118 (50.86%)	195 (69.40%)	**<0.0001**
Diabetes § (Yes)	29 (12.50%)	87 (30.96%)	**0.0001**
Dyslipidemia§ (Yes)	109 (46.69%)	166 (59.07%)	**0.0063**
Kidney Disease			
CKD	16 (6.90%)	21 (7.47%)	0.8016
ESRD	2 (0.86%)	4 (1.42%)	0.6943
FSGS	2 (0.86%)	2 (0.71%)	1.000
IgA nephropathy	1 (0.43%)	7 (2.49%)	0.0782
Cyst	15 (6.47%)	16 (5.69%)	0.7151
Stone	28 (12.07%)	56 (19.93%)	**0.0166**
PKD	1 (0.43%)	3 (1.07%)	0.6304
Cancer	2 (0.86%)	2 (0.71%)	1.000
Congenital	2 (0.86%)	2 (0.71%)	1.000
Other	8 (3.45%)	9 (3.20%)	0.8772
Gout	13 (5.60%)	40 (14.23%)	**0.0014**
BMI (kg/m^2) Mean	28.6 (4.7)	31.8 (5.7)	**<0.0001**
Waist Circ (in)	37.3 (5.3)	41.0 (6.0)	**<0.0001**
Neck Circ (in)	15.0 (1.5)	16.0 (1.7)	**<0.0001**
W:H ratio	0.92 (0.08)	1.25 (4.84)	0.2508
SBP(mmHg)	120.5 (13.1)	125.6 (15.8)	**<0.0001**
DBP (mmHg)	75.9 (7.8)	79.0 (8.2)	**<0.0001**
hsCRP (mg/L)	3.36 (7.19)	3.68 (4.52)	0.5574
HbA1c (%)	5.65 (0.8)	5.97 (1.06)	**0.0002**
Cystatin-C (mg/L)	0.85 (0.28)	1.25 (4.94)	0.1697
Creatinine (mg/dL)	0.99 (0.54)	1.06 (0.68)	0.3076
UACR (µg/mg)-mean	106.2 (899.4)	98.6 (383.1)	0.9044

UACR>30	26 (11.21%)	48 (17.14%)	0.0572
eGFRCKDepi$^{\Omega}$			
eGFR_creat mean	87.12 (18.55)	85.10 (20.68)	0.2481
eGFR<90	102 (43.97%)	140 (49.82%	0.1860
eGFR_cyst mean	99.12 (20.66)	93.20 (23.95)	**0.0028**
eGFR<90	50 (21.55%)	93 (33.21%)	**0.0034**
eGFR_both mean	94.71 (19.86)	90.17 (21.92)	**0.0155**
eGFR<90	63 (27.16%)	108 (38.57%)	**0.0065**
eGFRMDRD$^{\infty}$ mean	88.84 (21.24)	88.47 (25.18)	0.8582
eGFR<90	108 (46.55%)	145 (51.60%)	0.2549
Blood Lead (ug/dL)	1.416 (1.384)	1.296 (0.938)	0.1968
Urine Lead (ug/L)	0.551 (0.569)	0.532 (0.473)	0.6901
Blood Cadmium (ug/L)	0.280 (0.270)	0.291 (0.271)	0.6498
Urine Cadmium (ug/L)	0.407 (0.479)	0.400 (0.424)	0.8713
Urine Mercury (ng/mL)	1.096 (1.137)	1.110 (1.043)	0.8879
Bone Lead	7.79 (7.57)	7.46 (6.52)	0.6964
Urine Biomarkers (pg/mL)			
Proximal tubule function			
IL-18	45.580 (103.4)	41.709 (37.988)	0.5891
KIM-1	1414 (1623)	1783 (2191)	**0.0294**
B2M	412285 (2891710	779566 (4784474	0.2857
Distal tubule function			
NGAL	37445 (122698)	31585 (111757)	0.5727
Loop of Henle			
UMod	4680684 (2704665)	3973992 (2284558)	**0.0017**
Tubular inflammation			
MCP-1	152.9 (180.0)	168.4 (184.8)	0.3400
Tubular recovery/repair			
YKL-40	1636 (12660)	3142 (36971)	0.5246
EGF	9452 (7705)	8666 (6662)	0.2230
Plasma Biomarkers (pg/mL)			
KIM-1	71.932 (157.6)	88.528 (166.5)	0.2503
TNFR1	2024. (1056)	2358 (2068)	**0.0188**
TNFR2	6913 (3912)	7625 (5177)	0.0773
IFNγ	6.984 (14.423)	7.446 (13.099)	0.7044
IL-10	0.240 (0.269)	0.342 (1.254)	0.1834
IL-12p70 (n=219)	0.257 (0.518)	0.171 (0.184)	0.1169
IL-13 (n=235)	0.572 (0.630)	0.574 (0.641)	0.9753
IL-1β (n=244)	0.157 (0.586)	0.116 (0.363)	0.5100
IL-2 (n=303)	0.208 (0.287)	0.307 (0.985)	0.2210
IL-4 (n=363)	0.022 (0.103)	0.014 (0.017)	0.3167
IL-6	0.925 (1.398)	0.950 (0.870)	0.8096
IL-8	3.989 (4.613)	3.704 (3.204)	0.4265
TNF α	2.161 (0.927)	2.301 (1.001)	0.1022

Continuous variables are expressed as mean (standard deviation); categorical variables are expressed as number of patients (percent %) *Fisher's exact test used

Chronic Kidney Disease=CKD, End stage renal disease= ESRD, Focal segmental glomerulosclerosis =FSGS, polycystic kidney disease=PKD

† Other kidney disease (included AKI, Alport syndrome, angiomyolipomakidney infection, anti-GBM monotypic atypical nephritis, kidney infection, retroperitoneal fribrosis, unilateral kidney secondary to trauma, wegener's granulomatosis with renal involvement

Body Mass Index-BMI; waist hip ratio=W:H; Systolic Blood Pressure = SBP; Total cholesterol=TChol; Diastolic Blood Pressure = DBP; High-sensitivity C-Reactive Protein = hsCRP; Glycosylated hemoglobin = HbA1c; Urine Albumin/Creatinine Ratio = UACR; interleukin=IL; Kidney injury molecule= KIM-1; monocyte chemoattractant protein= MCP; chitinase 3-like 1= YKL-40; beta-2 microglobulin= B2M; epidermal growth factor= EGF; neutrophil gelatinase-associated lipocalin= NGAL; Uromodulin=UMod; tumor necrosis factor receptor=TNFR; interferon gamma= IFNγ; tumor necrosis factor alpha= TNFα

§Self-reported, physician diagnosis

$^{\Delta}$Defined by Berlin Questionnaire, 2 or more categories positive

$^{\Omega}$Defined by CKD-EPI equation $^{\infty}$Defined by MDRD equation

Specific Aim 3: To evaluate potential mechanisms of kidney injury in WTC Health Program participants.

Inflammation plays a key role in atherosclerosis and is likely a precursor of endothelial dysfunction.[31] Mediators of cardiac and kidney disease (i.e. dyslipidemia, smoking) induce an inflammatory response that increases the expression of acute phase proteins (e.g. hs-CRP), as well as soluble mediators. This inflammatory response is present throughout the continuum of atherosclerotic disease. The systemic expression of inflammatory markers and other related biomarkers in the plasma and/or serum represents an opportunity to identify and correlate biomarker patterns to disease expression.[47-48]

Table 3A demonstrated that those with albuminuria had significantly higher levels of blood lead and lower level of urine mercury. The albuminuria correlated with higher levels of biomarkers of tubular injury.

Tables 3B to 3E Compared participants with normal and abnormal kidney function using the different equations to calculate for eGFR (CKD-epi equations using creatinine, cystatin-C, both and MDRD equation). Those with abnormal kidney function had significantly higher blood lead (short-term measure of accumulation) and bone lead (long term measure of accumulation). The decrease in kidney function also correlated with biomarkers renal tubular injury.

Although TNF-alpha levels were normal, it was higher in those with albuminuria and abnormal kidney function ($p<0.0001$).

Urine epidermal growth factor (EGF) was significantly lower in those with albuminuria and abnormal kidney function ($p<0.0001$). EGF is a prototypical peptide growth factor of the egf/egf receptor signaling pathway, which plays important roles in proliferation, differentiation and migration of variety of cell types, especially epithelial cells. It promotes tubular cell proliferation and has been linked to modulating the recovery and repairing process of renal tissues. [49] Decreased renal expression and urinary excretion of EGF has been observed in various human kidney diseases, including diabetic nephropathy, IgA nephropathy, acute kidney injury and lupus nephritis. [50]

Table 3A: Comparative analysis of potential mechanisms between WTC–exposed subjects with and without albuminuria

		No albuminuria (UACR≤30)		Albuminuria (UACR>30)	
	n	Mean (SD)	n	Mean (SD)	*P* value
hs-CRP (mg/L)	436	3.23 (4.46)	74	5.25 (10.87)	0.1193
Bone lead	238	7.49 (6.13)	43	9.93 (8.53)	0.0789
Urine lead (ug/L)	437	0.538 (0.486)	73	0.567 (0.686)	0.7273
Blood lead (ug/dL)	438	1.273 (0.877)	74	1.508 (1.627)	**0.0074**
Urine cadmium (ug/L)	437	0.408 (0.455)	73	0.377 (0.416)	0.5838
Blood cadmium (ug/L)	438	0.280 (0.283)	74	0.317 (0.177)	0.1436
Urine mercury (ng/mL)	437	1.144 (1.115)	73	0.876 (0.867)	**0.0214**
Urine biomarkers (pg/mL)					
Proximal tubular function					
IL-18	437	36.82 (34.09)	73	83.45 (175.9)	**0.0270**
KIM-1	437	1473 (1539)	73	2484 (3458)	**0.0162**
B2M	437	144550 (542963)	73	3287937 (10191427)	**0.0103**
Distal Tubular function					
NGAL	437	22846 (53513)	73	102785 (271453)	**0.0144**
Loop of Henle					
Uromodulin	437	4458020 (2465212	73	3361351 (2552379	**0.0005**
Tubular inflammation					
MCP-1	437	143.6 (124.5)	73	268.9 (358.7)	**0.0042**
Tubular recovery/repair					
YKL-40	437	711 (1050)	73	12943 (75228)	0.1691
EGF	437	9797 (7216)	73	4494 (4720)	**<0.0001**
Plasma biomarkers (pg/mL)					
KIM-1	438	57.99 (110.5)	74	215.1 (301.0)	**<0.0001**
TNFR1	438	1888 (561)	74	4065 (3754)	**<0.0001**
TNFR2	437	6346 (2313)	74	12865 (9076)	**<0.0001**
IFNγ	438	6.62 (8.58)	74	10.94 (29.32)	0.2115
IL-10	436	0.299 (1.203)	74	0.284 (0.275)	0.8026
IL-12p70	187	0.211 (0.396)	31	0.195 (0.202)	0.7288
IL-13	201	0.599 (0.664)	34	0.418 (0.391)	**0.0298**
IL-2	257	0.252 (0.752)	45	0.325 (0.760)	0.5449
IL-4	311	0.018 (0.076)	51	0.016 (0.014)	0.7326
IL-6	438	0.897 (1.149)	74	1.164 (1.047)	**0.0611**
IL-8	438	3.677 (3.216)	74	4.742 (6.629)	0.1791
TNF α	438	2.108 (0.824)	74	2.972 (1.346)	**<0.0001**

Urine Albumin/Creatinine Ratio = UACR; High-sensitivity C-Reactive Protein = hsCRP;
IL interleukin, KIM-1 Kidney injury molecule, MCP monocyte chemoattractant protein, YKL-40 chitinase 3-like 1, B2M beta-2 microglobulin, EGF epidermal growth factor, NGAL neutrophil gelatinase-associated lipocalin, TNFR tumor necrosis factor receptor, IFNγ interferon gamma, TNFα tissue necrosis factor alpha

Table 3B: Comparative analysis of potential mechanisms between WTC–exposed subjects with and without abnormal kidney function (based on CKD-epi equation using serum creatinine)

		Normal kidney function (eGFR≥90)		Abnormal kidney function (eGFR<90)	
	n	Mean (SD)	n	Mean (SD)	*P* value
hs-CRP (mg/L)	271	3.37 (4.96)	240	3.73 (6.78)	0.5031
Bone lead	154	7.06 (6.20)	127	8.83 (6.95)	**0.0257**
Urine lead (ug/L)	271	0.581 (0.533)	240	0.496 (0.499)	0.0645
Blood lead (ug/dL)	271	1.207 (0.852)	242	1.511 (1.872)	**0.0011**
Urine cadmium (ug/L)	271	0.440 (0.485)	240	0.361 (0.403)	**0.0476**
Blood cadmium (ug/L)	271	0.273 (0.272)	242	0.301 (0.268)	0.2350
Urine mercury (ng/mL)	271	1.234 (1.210)	240	0.957 (0.905)	**0.0033**
Urine biomarkers (pg/mL)					
Proximal tubular function					
IL-18	271	44.17 (55.45)	240	42.68 (92.41)	0.8277
KIM-1	271	1679 (1947)	240	1543 (1977)	0.4345
B2M	271	121376 (109021)	240	1167735 (5846679)	**0.0060**
Distal Tubular function					
NGAL	271	23622 (54552)	240	46240 (159570)	**0.0375**
Loop of Henle					
Uromodulin	271	4608191 (2475982)	240	3941011 (2498640)	**0.0026**
Tubular inflammation					
MCP-1	271	158.4 (144.1)	240	164.7 (218.3)	0.7046
Tubular recovery/repair					
YKL-40	271	745 (982)	240	4394 (41688)	0.1766
EGF	271	11060 (7797)	240	6722 (5534)	**<0.0001**
Plasma biomarkers (pg/mL)					
KIM-1	271	59.99 (138.2)	242	104.6 (183.6)	**0.0022**
TNFR1	271	1744 (409)	242	2725 (2324)	**<0.0001**
TNFR2	270	5951 (2001)	242	8811 (6096)	**<0.0001**
IFNγ	271	6.45 (9.01)	242	8.12 (17.51)	0.1814
IL-10	270	0.329 (1.279)	241	0.259 (0.273)	0.3780
IL-12p70	109	0.194 (0.352)	110	0.225 (0.395)	0.5465
IL-13	124	0.527 (0.544)	111	0.625 (0.722)	0.2444
IL-2	159	0.226 (0.472)	144	0.302 (0.970)	0.3930
IL-4	186	0.011 (0.009)	177	0.024 (0.099)	0.0697
IL-6	271	0.882 (1.072)	242	1.002 (1.207)	0.2315
IL-8	271	4.017 (4.806)	242	3.626 (2.533)	0.2424
TNF α	271	2.022 (0.848)	242	2.480 (1.041)	**<0.0001**

High-sensitivity C-Reactive Protein = hsCRP; estimated glomerular filtration rate = eGFR;
IL interleukin, KIM-1 Kidney injury molecule, MCP monocyte chemoattractant protein, YKL-40 chitinase 3-like 1, B2M beta-2 microglobulin, EGF epidermal growth factor, NGAL neutrophil gelatinase-associated lipocalin, TNFR tumor necrosis factor receptor, IFNγ interferon gamma, TNFα tissue necrosis factor alpha

Table 3C: Comparative analysis of potential mechanisms between WTC–exposed subjects with and without abnormal kidney function (based on CKD-epi equation using serum cystatin-C)

		Normal kidney function (eGFR≥90)		Abnormal kidney function (eGFR<90)	
	n	Mean (SD)	n	Mean (SD)	*P* value
hs-CRP (mg/L)	368	3.01 (4.50)	142	4.91 (8.35)	**0.0112**
Bone Lead	204	7.39 (6.29)	77	9.09 (7.25)	0.0541
Urine lead (ug/L)	369	0.523 (0.478)	141	0.589 (0.612)	0.2512
Blood lead (ug/dL)	369	1.227 (0.885)	143	1.671 (1.296)	**0.0002**
Urine cadmium (ug/L)	369	0.395 (0.435)	141	0.426 (0.486)	0.4976
Blood cadmium (ug/L)	369	0.266 (0.239)	143	0.339 (0.333)	**0.0168**
Urine mercury (ng/mL)	369	1.116 (1.094)	141	1.079 (1.068)	0.7295
Urine biomarkers (pg/mL)					
Proximal tubule function					
IL-18	369	38.58 (48.58)	141	56.54 (118.6)	0.0831
KIM-1	369	1457 (1694)	141	2039 (2488)	**0.0112**
B2M	369	119355 (187634)	141	1908499 (7546321	**0.0056**
Distal Tubular function					
NGAL	369	20406 (48349)	141	70700 (204149)	**0.0044**
Loop of Henle					
Uromodulin	369	4590010 (2433915)	141	3535672 (2545404)	**<0.0001**
Tubular inflammation					
MCP-1	369	142.9 (131.4)	141	210.9 (269.3)	**0.0046**
Tubular recovery/repair					
YKL-40	369	672 (852)	141	7150 (54298)	0.1588
EGF	369	10144 (7382)	141	6135 (5601)	**<0.0001**
Plasma biomarkers (pg/mL)					
KIM-1	369	57.73 (118.7)	143	141.5 (231.7)	**<0.0001**
TNFR1	369	1748 (389)	143	3395 (2826)	**<0.0001**
TNFR2	368	5821 (1621)	143	11135 (7119)	**<0.0001**
IFNγ	369	6.45 (11.14)	143	9.30 (18.69	0.0886
IL-10	368	0.309 (1.111)	142	0.262 (0.189)	0.4294
IL-12p70	151	0.212 (0.406)	67	0.207 (0.294)	0.9332
IL-13	174	0.508 (0.531)	60	0.752 (0.847)	**0.0392**
IL-2	212	0.246 (0.569)	91	0.299 (1.064)	0.6559
IL-4	256	0.014 (0.046)	106	0.026 (0.108)	0.2690
IL-6	369	0.856 (1.157)	143	1.154 (1.068)	**0.0079**
IL-8	369	3.726 (4.153)	143	4.102 (3.184)	0.2734
TNF α	369	1.973 (0.756)	143	2.927 (1.118)	**<0.0001**

High-sensitivity C-Reactive Protein = hsCRP; estimated glomerular filtration rate = eGFR;
IL interleukin, KIM-1 Kidney injury molecule, MCP monocyte chemoattractant protein, YKL-40 chitinase 3-like 1, B2M beta-2 microglobulin, EGF epidermal growth factor, NGAL neutrophil gelatinase-associated lipocalin, TNFR tumor necrosis factor receptor, IFNγ interferon gamma, TNFα tissue necrosis factor alpha

Table 3D: Comparative analysis of potential mechanisms between WTC–exposed subjects with and without abnormal kidney function (based on CKD-epi equation using serum cystatin-C and creatinine)

		Normal kidney function (eGFR≥90)		Abnormal kidney function (eGFR<90)	
	n	Mean (SD)	n	Mean (SD)	*P* value
hs-CRP (mg/L)	340	3.05 (4.62)	170	4.54 (7.74)	**0.0215**
Bone Lead	194	7.40 (6.34)	87	8.88 (7.07)	0.0816
Urine lead (ug/L)	341	0.524 (0.485)	169	0.578 (0.579)	0.2984
Blood lead (ug/dL)	341	1.207 (0.832)	171	1.637 (1.308)	**0.0001**
Urine cadmium (ug/L)	341	0.388 (0.434)	169	0.435 (0.479)	0.2706
Blood cadmium (ug/L)	341	0.264 (0.247)	171	0.330 (0.309)	**0.0153**
Urine mercury (ng/mL)	341	1.153 (1.123)	169	1.009 (1.002)	0.1588
Urine biomarkers (pg/mL)					
Proximal tubule function					
IL-18	341	39.42 (50.09)	169	51.86 (109.1)	0.1596
KIM-1	341	1486 (1728)	169	1886 (2344)	**0.0499**
B2M	341	122170 (194243)	169	1606394 (6922332)	**0.0059**
Distal tubule function					
NGAL	341	21147 (49938)	169	60874 (187826)	**0.0075**
Loop of Henle					
Uromodulin	341	4588302 (2471553)	169	3713801 (2484665)	**0.0002**
Tubular inflammation					
MCP-1	341	146.1 (134.4)	169	193.1 (251.1)	**0.0237**
Tubular recovery/repair					
YKL-40	341	671 (855)	169	6079 (49626)	0.1584
EGF	341	10379 (7537)	169	6324 (5408)	**<0.0001**
Plasma biomarkers (pg/mL)					
KIM-1	341	58.92 (124.0)	171	125.4 (214.3)	**0.0002**
TNFR1	341	1731 (385)	171	3158 (2642)	**<0.0001**
TNFR2	340	5799 (1623)	171	10308 (6801)	**<0.0001**
IFNγ	341	6.64 (11.68)	171	8.45 (17.04)	0.2118
IL-10	340	0.309 (1.148)	170	0.272 (0.259)	0.5676
IL-12p70	139	0.219 (0.420)	79	0.194 (0.278)	0.5886
IL-13	158	0.531 (0.552)	76	0.653 (0.777)	0.2200
IL-2	194	0.256 (0.592)	109	0.274 (0.974)	0.8613
IL-4	232	0.011 (0.009)	130	0.029 (0.116)	0.0862
IL-6	341	0.829 (1.114)	171	1.159 (1.162)	**0.0020**
IL-8	341	3.795 (4.295)	171	3.904 (2.998)	0.7387
TNF α	341	1.995 (0.725)	171	2.827 (1.122)	**<0.0001**

High-sensitivity C-Reactive Protein = hsCRP; estimated glomerular filtration rate = eGFR;
IL interleukin, KIM-1 Kidney injury molecule, MCP monocyte chemoattractant protein, YKL-40 chitinase 3-like 1, B2M beta-2 microglobulin, EGF epidermal growth factor, NGAL neutrophil gelatinase-associated lipocalin, TNFR tumor necrosis factor receptor, IFNγ interferon gamma, TNFα tissue necrosis factor alpha

Table 3E: Comparative analysis of potential mechanisms between WTC–exposed subjects with and without abnormal kidney function (based on MDRD equation using serum creatinine)

		Normal kidney function (eGFR≥90)		Abnormal kidney function (eGFR<90)	
	n	Mean (SD)	n	Mean (SD)	*P* value
hs-CRP (mg/L)	260	3.34 (4.99)	251	3.74 (6.69)	0.4424
Bone Lead	152	7.38 (6.27)	129	8.43 (6.95)	0.1829
Urine lead (ug/L)	259	0.579 (0.532)	252	0.501 (0.502)	0.0855
Blood lead (ug/dL)	260	1.223 (0.861)	253	1.481 (1.173)	**0.0047**
Urine cadmium (ug/L)	259	0.419 (0.467)	252	0.386 (0.430)	0.4058
Blood cadmium (ug/L)	260	0.272 (0.276)	253	0.301 (0.264)	0.2220
Urine mercury (ng/mL)	259	1.206 (1.199)	252	0.999 (0.946)	**0.0299**
Urine biomarkers (pg/mL)					
Proximal tubule function					
IL-18	259	44.45 (56.36)	252	42.25 (90.40)	0.7646
KIM-1	259	1704 (1984)	252	1523 (1934)	0.2963
B2M	259	133142 (217586)	252	1105815 (5708525)	**0.0073**
Distal tubule function					
NGAL	259	22690 (48972)	252	46121 (157991)	**0.0251**
Loop of Henle					
Uromodulin	259	4596610 (2460130)	252	3984685 (2520598)	**0.0057**
Tubular inflammation	259				
MCP-1		160.0 (146.7)	252	162.8 (213.6)	0.8626
Tubular recovery/repair	259				
YKL-40	259	737 (919)	252	4228 (40688)	0.1745
EGF		10863 (7811)	252	7130 (5856)	**<0.0001**
Plasma biomarkers (pg/mL)					
KIM-1	260	62.99 (141.6)	253	99.55 (180.1)	**0.0111**
TNFR1	260	1750 (426)	253	2676 (2282)	**<0.0001**
TNFR2	259	5960 (2003)	253	8677 (6008)	**<0.0001**
IFNγ	260	6.42 (9.10)	253	8.07 (17.17)	0.1764
IL-10	260	0.335 (1.302)	251	0.256 (0.270	0.3433
IL-12p70	103	0.201 (0.360)	116	0.216 (0.387)	0.7679
IL-13	122	0.519 (0.540)	113	0.632 (0.721)	0.1810
IL-2	153	0.225 (0.479)	150	0.299 (0.952)	0.3913
IL-4	179	0.011 (0.009)	184	0.023 (0.098)	0.0876
IL-6	260	0.892 (1.086)	253	0.986 (1.191)	0.3544
IL-8	260	4.012 (4.886)	253	3.649 (2.521)	0.2895
TNF α	260	2.025 (0.843)	253	2.457 (1.043)	**<0.0001**

High-sensitivity C-Reactive Protein = hsCRP; estimated glomerular filtration rate = eGFR;
IL interleukin, KIM-1 Kidney injury molecule, MCP monocyte chemoattractant protein, YKL-40 chitinase 3-like 1, B2M beta-2 microglobulin, EGF epidermal growth factor, NGAL neutrophil gelatinase-associated lipocalin, TNFR tumor necrosis factor receptor, IFNγ interferon gamma, TNFα tissue necrosis factor alpha

Specific Aim 1C: Develope a repository of data of WTC responders with a spectrum of renal disorders to explore possible patterns of disease that may be associated with exposure.

The Registry included 171 participants from the main study with known kidney disease and an additional 66 subjects that only participated in the Registry (n= 237 subjects).

Table 4 is a summary of the characteristics of the WTC Health program participants with known kidney disease.

The following relatively rare diseases occurred in this population: Alport syndrome, angiomyolipoma, kidney infections, anti-GBM monotypic atypical nephritis, retroperitoneal fibrosis, Wegener's granulomatosis with renal involvement. The following also occurred: Focal Segmental glomerulosclerosis (FSGS) occurred in 4 subjects. Renal cancer noted in 8 subjects in this cohort. End-stage renal disease (ESRD) noted in 21 subjects.

There was a higher percentage (p=0.0004) of ESRD patients and significantly higher markers of renal tubular injury (beta-2-microalbumin (p=0.0067) and NGAL (p=0.0370)) in the very high exposure compared to the other exposure groups.

IgA Nephropathy (IgAN) occurred in 11 subjects and was associated with WTC exposure (XP4) (p=0.0230). IgAN is linked to a generalized hyper-reactivity of the immune system. It is an autoimmune disease where immune complexes consisting of IgA1 with an autoantigen and anti-glcan autoantibodies deposit in the glomeruli and induce renal injury. Both clinical and experimental research has shown antigens from respiratory or gastrointestinal tract to be involved in the pathogenesis of IgA nephropathy. IgAN is a cause of end- stage renal disease. Of note, other immune diseases have been documented in WTC exposed individuals. The incidence of 11 cases among 513 persons is 2.2 %, which is higher than expected in otherwise healthy adults (1.29 in 100000 persons). [51]

Kidney Stones occurred in 109 subjects (19.6% of participants). Diagnosis of kidney stones was more likely in people who had diagnosis of OSA compared to those who did not have OSA (p= 0.0166). Environmental exposures have been shown to correlate with kidney stones, and kidney stones can cause significant morbidity (infection, impaired kidney function)

Table 4: Baseline Characteristics of Registry Participants (WTC-Exposed patients with Kidney Disease)

	Total	Very High	High	Intermediate	Low	*p*-Value
n	237	11	53	136	37	
Age (years)	58.3 (7.8)	55.5 (5.0)	60.3 (8.1)	57.7 (7.5)	58.4 (9.1)	0.1293
Gender (Males-%)	209 (88.2%)	9 (81.8%)	47 (88.7%)	120 (88.2%)	33 (89.2%)	0.9240
Ethnicity(Hispanic%)	46 (19.4%)	0	11 (20.8%)	27 (19.8%)	8 (21.6%)	**0.0001***
Race						
White	164 (69.2%)	9 (81.8%)	36 (67.9%)	98 (72.1%)	21 (56.8%)	
Black	38 (16.0%)	0	8 (15.1%)	21 (15.4%)	9 (24.3%)	**<0.0001***
American Indian	1 (0.4%)	0	1 (1.9%)	0	0	
Asian	6 (2.6%)	0	2 (3.8%)	1 (0.7%)	3 (8.1%)	
Other	28 (11.8%)	2 (18.2%)	6 (11.3%)	16 (11.8%)	4 (10.8%)	
Education						
Less than 12 yrs	9 (3.8%)	0	4 (7.6%)	4 (3.0%)	1 (2.8%)	
HS/GED	44 (18.8%)	4 (36.3%)	11 (20.7%)	22 (16.3%)	7 (20.0%)	
College-no degree	70 (29.9%)	3 (27.3%)	16 (30.2%)	41 (30.4%)	10 (28.6%)	**<0.0001***
Associate degree	23 (9.8%)	1 (9.1%)	7 (13.2%)	10 (7.4%)	5 (14.3%)	
Bachelor degree	67 (28.6%)	3 (27.3%)	13 (24.5%)	41 (30.4%)	10 (28.6%)	
Advanced degree	21 (9.0%)	0	2 (3.8%)	17 (12.5%)	2 (5.7%)	
Marital Status						
Single	36 (15.19%)	2 (18.18%)	5 (9.43%)	21 (15.44%)	8 (21.62%)	
Married/Partner	155 (65.40%)	8 (72.73%)	38 (71.70%)	89 (65.44%)	20 (54.05%)	**<0.0001***
Divorce/separated	35 (14.77%)	1 (9.09%)	8 (15.09%)	20 (14.71%)	6 (16.22%)	
Other	11 (4.64%)	0	2 (3.77%)	6 (4.41%)	3 (8.11%)	
Work Status						
employed	98 (41.35%)	4 (36.36%)	17 (32.08%)	64 (47.06%)	13 (35.14%)	**<0.0001***
retired	131 (55.27%)	6 (54.55%)	36 (67.92%)	67 (49.26%)	22 (59.46%)	
unemployed	8 (3.38%)	1 (9.09%)	0	5 (3.68%)	2 (5.41%)	
Smoking Status‡						
never smoked	159 (67.09%)	8 (72.73%)	35 (66.04%)	90 (66.18%)	26 (70.27%)	**0.0006***
ex-smoker(former)	73 (30.80%)	3 (27.27%)	17 (32.08%)	42 (30.88%)	11 (29.73%)	
current smoker	5 (2.11%)	0	1 (1.89%)	4 (2.94%)	0	
Alcohol Intake						
Never	75 (31.65%)	1 (9.09%)	17 (32.08%)	46 (33.82%)	11 (29.73%)	
Less than 1 drink/wk	89 (37.55%)	7 (63.64%)	17 (32.08%)	51 (37.50%)	14 (37.84%)	**<0.0001***
Nonepastyr (former)	5 (2.11%)	2 (18.18%)	0	3 (2.21%)	0	
More than 1 drink/wk	68 (28.69%)	1 (9.09%	19 (35.95%)	36 (26.48%)	12 (32.43%)	
PHQ9 mean score	5.2 (5.7)	7.1 (7.7)	4.5 (4.4)	5.4 (5.9)	4.9 (6.0)	0.5343
(PCL-Q) > 44	46 (19.91%)	3 (27.27%)	8 (15.09%)	29 (21.97%)	6 (17.14%)	0.6450
(PCL-Q) > 50	33 (14.29%)	2 (18.18%)	6 (11.32%)	20 (15.15%)	5 (2.16%)	0.8970
OSADx§(Yes)	148 (62.45%)	8 (72.73%)	33 (62.26%)	84 (61.76%)	23 (62.16%)	0.9134
OSA High Risk$^{\Delta}$	159 (68.24%)	9 (81.82%)	34 (64.15%)	93 (69.92%)	23 (14.47%)	0.6077
Hypertension§(Yes)	172 (72.57%)	6 (54.55%)	46 (86.79%)	92 (67.65%)	28 (75.68%)	**0.0291**
Dyslipidemia§ (Yes)	149 (62.87%)	8 (72.73%)	37 (69.81%)	79 (58.09%)	25 (67.57%)	0.3570
Diabetes § (Yes)	73 (30.80%)	3 (27.27%)	17 (32.08%)	44 (32.35%)	9 (24.32%)	0.8045
Kidney Disease						
CKD	52 (21.94%)	1 (9.09%)	6 (11.32%)	34 (25%)	11 (29.73%)	0.0856
ESRD	21 (8.86%)	4 (36.36%)	5 (9.43%)	9 (6.62%)	3 (8.11%)	**0.0004***
FSGS	4 (1.69%)	0	1 (1.89%)	2 (1.47%)	1 (2.7%)	0.1405
IgA nephropathy	11 (4.64%)	0	1 (1.89%)	10 (7.35%)	0	**0.0086***
Cyst	45 (18.99%)	1 (9.09)	11 (20.75%)	23 (16.91%)	10 (27.03%)	0.4329
Stone	109 (45.99%)	7 (63.64%)	27 (50.94%)	60 (44.12%)	15 (40.54%)	0.4687
PKD	6 (2.53%)	0	1 (1.89%)	5 (3.68%)	0	0.0826
Cancer	8 (3.38%)	0	2 (3.77%)	4 (2.94%)	2 (5.41%)	0.0571
Congenital	3 (1.27%)	0	1 (1.89%)	2 (1.47)	0	0.2221
Other	23 (9.70%)	0	6 (11.32%)	14 (10.29%)	3 (8.11%)	**0.0142***
	n=171	n=7	n=40	n=98	n=26	
BMI (kg/m^2)Mean	30.97 (5.83)	32.86 (6.72)	30.23 (5.18)	31.05 (6.24)	31.31 (4.89)	0.6885
BMI ≥ 30	97 (51.32%)	4 (57.14%)	21 (46.67%)	58 (53.70%)	14 (48.28%)	**0.0045***
Waist Circ (in)	40.2 (6.2)	41.8 (7.0)	39.9 5.4)	40.4 (6.4)	39.9 (6.1)	0.8799
Neck Circ (in)	15.7 (1.7)	15.6 (1.7)	15.6 (1.5)	15.8 (1.7)	15.7 (1.7)	0.9478
W:H ratio	0.95 (0.08)	0.93 (0.09)	0.96 (0.07)	0.95 (0.08)	0.95 (0.08)	0.7799
SBP(mmHg)	125.3 (14.8)	130.0 (18.7)	123.6 (12.4)	125.8 (15.7)	124.6 (13.6)	0.7072
DBP (mmHg)	77.7 (8.9)	79.6 (8.2)	77.6 (9.9)	78.0 (8.9)	76.3 (6.9)	0.7886
TCholesterol (mg/dL)	185.7 (50.0)	180.0 (19.3)	180.6 (42.4)	190.2 (53.4)	177.9 (52.5)	0.5841

LDL (mg/dL)	114.4 (44.6)	107.6 (18.8)	109.8 (38.0)	118.4 (47.3)	108.5 (47.2)	0.6111
HDL (mg/dL)	47.53 (12.80)	52.14 (10.45)	45.42 (12.25)	47.97 (13.17)	47.88 (12.66)	0.5479
Triglyceride(mg/dL)	119.9 (62.5)	101.3 (49.9)	127.0 (73.1)	120.1 (54.1)	113.6 (76.0)	0.7063
hsCRP (mg/L)	3.78 (5.34)	5.63 (5.48)	2.51 (2.78)	4.34 (6.40)	3.18 (3.60)	0.2158
HbA1c (%)	5.86 (0.80)	5.62 (0.38)	5.93 (0.94)	5.58 (0.78)	5.86 (0.76)	0.8294
Creatinine (mg/dL)	1.27 (0.93)	1.77 (2.34)	1.08 (0.36)	1.30 (0.94)	1.34 (0.90)	0.2673
UACR(µg/mg)mean	259.6 (1139.1)	288.4 (741.1)	99.2 (285.1)	347.4 (1453)	167.4 (455.4)	0.6713
UACR>30	48 (28%)	1 (14%)	8 (20%)	32 (33%)	7 (27%)	0.3742
eGFRCKDepi$^{\Omega}$						
eGFR_creat_	75.37 (25.44)	77.43 (34.87)	79.25 (22.32)	73.96 (25.48)	74.19 (27.19)	0.7218
eGFR_cyst	83.94 (28.55)	85.14 (40.42)	90.27 (25.12)	81.09 (28.31)	84.62 (30.97)	0.3987
eGFR_both	80.38 (27.31)	82.14 (38.81)	85.95 (23.98)	77.94 (27.01)	80.54 (29.86)	0.4814
eGFRMDRD∞	77.58 (28.22)	81.43 (40.77)	82.72 (28.47)	75.50 (27.06)	76.46 (28.54)	0.5668
Cystatin-C (mg/L)	1.07 (0.57)	1.38 (1.41)	0.94 (0.33)	1.10 (0.54)	1.07 (0.62)	0.2166
Blood Lead (ug/dL)	1.43 (1.24)	1.93 (2.59)	1.27 (0.73)	1.43 (1.21)	1.57 (1.45)	0.5470
Urine Lead (ug/L)	0.48 (0.39)	0.51 (0.14)	0.45 (0.35)	0.48 (0.42)	0.50 (0.36)	0.9515
Blood cadmium (ug/L)	0.325 (0.363)	0.322 (0.317)	0.238 (0.142)	0.366 (0.456)	0.310 (0.134)	0.3132
UrineCadmium (ug/L)	0.405 (0.475)	0.470 (0.524)	0.307 (0.257)	0.429 (0.540)	0.448 (0.455)	0.5128
Urine Hg (ng/mL)	0.996 (1.004)	0.699 (0.359)	0.951 (1.129)	0.964 (0.999)	1.271 (0.836)	0.4345
Urine(pg/mL)						
Proximal Tubule						
IL-18	45.76 (47.13)	42.07 (34.28)	39.39 (31.16)	46.71 (46.20)	52.99 (69.01)	0.7001
KIM-1	1893 (2412)	2035 (1791)	1912 (2128)	1732 (1785)	2433 (4320)	0.6227
B2M	1534009 (6657842)	9943611 (25448433)	269527 (853964)	1457858 (5177979)	1502274 (5958843)	**0.0067**
Distal Tubule						
NGAL	56908 (170312)	236564 (551153)	33289 (75909)	51981 (147236)	63446 (166597)	**0.0370**
Loop of Henle						
Uromodulin	3918627 (2478723)	4732017 (3529273)	4064913 (2047323)	3941805 (2693102)	3387212 (1836658)	0.5540
Tubule inflammation						
MCP-1	195.19 (253.02)	251.53 (235.5)	166.45 (129.99)	197.35 (247.47)	216.07 (387.77)	0.7898
Tubule recovery						
YKL-40	6040 (49117)	5435 (9801)	861 (1252)	3252 (19509)	24679 (120885)	0.2159
EGF	7623 (7279)	8406 (9238)	8410 (7078)	7301 (7168)	7415 (7481)	0.8586
Plasma (pg/mL)						
KIM-1	136.55 (268.79)	100.23 (88.7)	75.89 (58.25)	167.5 (335.5)	123.0 (196.7)	0.3203
TNFR1	2957 (2683)	5082 (7918)	2352 (1193)	3069 (2305)	2893 (3195)	0.0896
TNFR2	9556 (6899)	12649 (14198)	7939 (4584)	9969 (6938)	9657 (7073)	0.2694
IFNγ	7.98 (14.02)	5.01 (1.83)	12.80 (26.56)	6.14 (5.55)	8.31 (9.61)	0.0841
IL-10	0.241 (0.210)	0.313 (0.226)	0.277 (0.296)	0.228 (0.184)	0.218 (0.121)	0.4444
IL-12p70 (n=78)	0.207 (0.287)	0.077 (0.076)	0.269 (0.466)	0.199 (0.193)	0.157 (0.182)	0.5950
IL-13 (n=78)	0.567 (0.633)	0.357 (0.259)	0.846 (0.935)	0.415 (0.333)	0.609 (0.764)	0.0724
IL-1β (n=78)	0.109 (0.277)	0.136 (0.071)	0.066 (0.047)	0.146 (0.365)	0.038 (0.039)	0.4896
IL-2 (n=103)	0.314 (1.082)	0.098 (0.601)	0.326 (0.952)	0.202 (0.307)	0.799 (2.526)	0.2910
IL-4 (n=124)	0.022 (0.101)	0.016 (0.014)	0.012 (0.011)	0.028 (0.129)	0.021 (0.045)	0.9033
IL-6	0.959 (0.791)	1.202 (1.002)	0.905 (0.766)	0.983 (0.803)	0.882 (0.723)	0.7575
IL-8	4.26 (5.25)	2.95 (1.59)	3.76 (2.44)	4.82 (6.68)	3.25 (1.27)	0.4126
TNF α	2.54 (1.08)	3.07 (1.52)	2.38 (0.85)	2.56 (1.09)	2.55 (1.23)	0.4455
Bone XRF (n=87)	8.43 (7.18)	9.20 (7.32)	7.35 (6.89)	8.38 (7.06)	9.83 (7.78)	0.7354

Continuous variables are expressed as mean (standard deviation); categorical variables are expressed as number of patients (percent %) *Fisher's exact test used

Chronic Kidney Disease=CKD, End stage renal disease= ESRD, Focal segmental glomerulosclerosis =FSGS, polycystic kidney disease=PKD † Other kidney disease (include AKI, Alport syndrome, angiomyolipomakidney infection, anti-GBM monotypic atypical nephritis, kidney infection, retroperitoneal fibrosis, wegener's granulomatosis with renal involvement)

Body Mass Index-BMI; waist hip ratio=W:H; Systolic Blood Pressure = SBP; Diastolic Blood Pressure = DBP; Low Density Lipoprotein Cholesterol = LDL; High Density Lipoprotein Cholesterol = HDL;High-sensitivity C-Reactive Protein = hsCRP; Glycosylated hemoglobin = HbA1c; Urine Albumin/Creatinine Ratio = UACR; Mercury=Hg; interleukin=IL; Kidney injury molecule= KIM-1; monocyte chemoattractant protein= MCP; chitinase 3-like 1= YKL-40; beta-2 microglobulin= B2M; epidermal growth factor= EGF; neutrophil gelatinase-associated lipocalin= NGAL; tumor necrosis factor receptor=TNFR; interferon gamma= IFNγ; tumor necrosis factor alpha= TNFα

§Self-reported, physician diagnosis ΔDefined by Berlin Questionnaire, 2 or more categories positive

ΩDefined by CKD-EPI equation ∞Defined by MDRD equation

D. Conclusions/Limitations and Future Directions

The primary objective of this study was to quantify the risk of kidney impairment and the relationship to particulate matter exposure among individuals exposed to the WTC attack. Kidney function, as measured by eGFR, as well as kidney damage, as measured by albuminuria (UACR), are both associated with increased risk of kidney disease progression, as well as risk of mortality. Current clinical guidelines suggest measurement of eGFR to stage level of CKD and consideration of adding measurement of UACR to all levels of eGFR.

This study confirmed a significant association between eGFR and PM exposure across the four levels of exposure group and more importantly have shown a significant difference in kidney function between exposed and non-exposed individuals. Although we did not reach the sample size planned for the comparison group, the association remained significant after adjusting for confounding factors. This finding thus supports studies showing particulate matter exposure as a risk factor for kidney disease.

One specific aim not presented in this report but will be pursued in later publications is to quantify change in renal function over time by analyzing eGFR at WTC Health Program Visit 1 (V1) and subsequent visits, adjusting for demographics and known co-morbid conditions. We hypothesize that initial exposure to 9/11 contributed to reduction in renal function over time. If proven, then this will be a stronger evidence to support WTC-exposure as a risk factor for kidney disease.

The secondary objective was to evaluate the association of kidney disease and OSA. Current evidence supports the association of OSA with end stage renal disease but not early CKD. Obstructive Sleep Apnea is a highly prevalent condition among WTC participants. Importantly, this study highlights the significant association between OSA and decreased renal function, after controlling for age, ethnicity, hypertension, diabetes and smoking. Blood and urine tests for renal tubular function and inflammation (urine KIM-1, Uromodulin, and plasma TNFR1) were higher in OSA patients supporting mechanistic pathways involved in clinical outcomes.

Another specific aim not presented in this report is the evaluation of the temporal relationship of eGFR decline to presence and severity of OSA, using longitudinal data. This will be posted in later publications.

Another objective is to explore plausible mechanisms. This study has shown that kidney damage secondary to PM exposure may be due to renal tubular injury as evidenced by the increased level of urine beta-2-microglobbulin and higher NGAL in those with albuminuria and abnormal kidney function. It confirmed the role of inflammation in the development of kidney disease with higher TNFα levels and lower epidermal growth factor (EGF) in those with kidney impairment. It demonstrated an established pathway of heavy metal-induced kidney damage due to higher levels of blood and bone lead in those with abnormal kidney function.

Lastly, the registry has shown the spectrum of kidney disease in the WTC population. The finding of IgA nephropathy is significant and warrants further exploration. The prevalence of kidney stones and its association with OSA is a novel finding that needs to be examined.

This study rigorously investigated the risk of kidney damage among WTC-exposed individuals. In light of the findings that reduction in eGFR was associated with exposure to particulate matter at Ground Zero, this finding should translate into continued surveillance of eGFR in those who sustained high-exposure to particulate matter at Ground Zero. Surveillance, early detection and timely referral to kidney specialists would mitigate long-term kidney and CVD risk.

E. Publications

Manuscripts in preparation (Expected December 2021):

1. Risk of CKD in WTC participants with Obstructive Sleep Apnea (OSA)
2. World Trade Center Exposure and Risk of IgA Nephropathy
3. Renal Stones among WTC Responders – what is the link?

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