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Invisible Threat: How Air Pollution Fuels Primary Glomerular Disease

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Kidney Int Rep (2024) **9,** 2591–2593; https://doi.org/10.1016/j.ekir.2024.07.023

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Environmental pollution has a significant impact on global disease burden, health care costs, and mortality. Air pollution, especially fine particulate matter (PM2.5), has been increasingly recognized as a significant environmental risk factor for various health conditions. The impact of PM2.5 on global life expectancy is comparable to that of smoking, more than 3 times that of alcohol use and unsafe water, more than 5 times that of transport injuries such as car crashes, and more than 7 times that of HIV/AIDS.[1] The World Health Organization and the U.S. Environmental Protection Agency have been keenly studying the effects of pollution on health and have developed laws and regulations to curb its impact on global health. The World Health Organization recently revised its guidelines for coarse and particulate matter levels in 2021 and reduced target PM2.5 levels by half of what was proposed in 2005.[2] The average annual concentration of PM2.5 in the United States was 7.8 $\mu g/m^3$ in 2022. This was above the World Health Organization target of 5 $\mu g/m^3$.[2]

Even though pulmonary and cardiac conditions are recognized as major effects of air pollution, its impact on the kidneys is often overlooked. Kidney disease prevalence has been substantially increasing worldwide and it is estimated that more than 1.3 million deaths in 2019 were related to kidney dysfunction.[3] Therefore, it is imperative to identify modifiable risk factors for kidney disease to come up with targeted prevention approaches. The study published in a recent issue by Troost *et al.*[4] examined the associations of particulate matter air pollution and decline in estimated glomerular filtration rate in glomerulronephritis.[4]

The effect of air pollution on kidney function has lately been a topic of interest and numerous studies have been published on the association between PM2.5, PM10, heavy metals, greenhouse gases, etc., and the incidence of acute kidney injury, progression of chronic kidney disease (CKD), and the incidence of end-stage kidney disease. In an observational study of 2.5 million veterans without CKD, Bowe *et al.*[5] noted that every 10 $\mu g/m^3$ increase in PM2.5 was associated with a 26% to 28% higher risk of incident CKD, CKD progression, and end-stage kidney disease.[5] They also estimated that air pollution could have caused about 45,000 new cases of CKD and 2438 patients were started on dialysis during the study period.[5]

Another study investigated 71,151 renal biopsy samples obtained in 282 cities across China between 2004 and 2014.[6] During this period, the researchers found that the prevalence of membranous nephropathy increased from 12% to 24% whereas other major glomerular diseases remained stable. Interestingly, long-term exposure to high levels of PM2.5 was associated with an increased risk of membranous nephropathy in a nonlinear pattern. Each 10 $\mu g/m^3$ increase in PM2.5 concentration was associated with 14% higher odds of a patient developing membranous nephropathy (odds ratio, 1.14; 95% confidence interval: 1.10–1.18) in regions with PM2.5 levels $>$ 70 $\mu g/m^3$.[6] A recent review article elucidates the interplay of short-term and long-term exposure to PM2.5 and the prevalence and progression of CKD and incidence of end-stage kidney disease. The majority of the studies included in the review denote a positive correlation between air pollution and kidney disease.[3]

Troost *et al.*[4] studied the relation of PM2.5, black carbon (BC) - an indicator of traffic-related pollution, and sulfates - indicators of coal combustion, with kidney disease progression in 5 different primary glomerulopathies in a pooled cohort of patients from the Nephrotic Syndrome Study Network (NEPTUNE) and Cure

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Glomerulonephropathy (CureGN) studies in the US. They estimated ambient air quality for study participants by residential census data by merging the ambient air quality estimates derived from satellite, simulation, and ground monitor sources. Although the nationwide trends in the levels of PM2.5 have seen a 42% decrease from 2000 to 2022,[7] the levels of PM 2.5, BC, and sulfates remained stable during the study period. Unsurprisingly, the subjects exposed to levels above the median of these pollutants were generally older, more likely to be Black and had lower baseline estimated glomerular filtration rate. This distribution highlights the disproportionate prevalence of kidney disease in certain racial groups and that they are simultaneously exposed to higher levels of air pollutants as well.

The authors found that about 24% of the subjects in the pooled cohort experienced a 40% decline in estimated glomerular filtration rate or progressed to end-stage kidney disease. For each doubling of baseline PM2.5 and BC, there was a clinically significantly higher risk of disease progression with a hazards ratio of 1.55 (95% confidence interval: 1.00–2.38, $P = 0.0489$) for PM2.5 and hazards ratio of 1.43 (95% confidence interval: 0.98–2.07, $P = 0.06$) for BC. These results were adjusted for age, baseline estimated glomerular filtration rate, race, and maternal education (which was used as a proxy for socioeconomic status). The association persisted when levels above 1 SD of PM 2.5 and BC were evaluated.

Although there was no association of disease progression with sulfates, circulating levels of tumor necrosis factor (TNF) had a positive correlation with exposure to sulfates ($r = 0.71$, $P = 0.003$). Sulfate exposure also positively correlated with activation of gene expression of TNF and the Janus kinase/signal transducer and activator of transcription signaling (JAK-STAT) pathways in both glomerular and tubular tissue compartments. The mechanism of kidney injury by air pollutants has been hypothesized. Numerous reasons, including oxidative stress, development of autoantibodies against phospholipase A2 receptors, formation of immune complexes, direct vascular injury, and systemic and focal renal inflammation have been identified.[8] This study underscores the role of systemic inflammatory cascade set off by air pollutants, particularly sulfates. Of note, a small study from Toronto, Canada, also reported a positive correction between serum interleukin-6 levels and ambient air sulfate levels, which corroborates this study's finding.[9]

This well-done study highlights the direct health consequences of air pollution on kidney function. Furthermore, the authors observed that racial and ethnic minority neighborhoods had higher air pollution levels. The disproportionate impact of air pollution on vulnerable populations emphasizes the need for targeted public health interventions.

Despite the use of well-defined datasets with covariate adjustment, residual confounding from unmeasured confounders is an issue. Although the point estimates were large, the statistical significance was marginal, perhaps related to sample size.

In conclusion, although the levels of PM2.5 in the United States have been on the decline since 2000, they remain above the recommended guidelines set by global health organizations, posing a continued threat to public health. The long-term impact of PM2.5 exposure on kidney function necessitates keen study and prospective follow-up to better understand and mitigate this risk. The recent ruling by the Supreme Court of the United States to stay the "Good Neighbor Plan" has significantly hampered the U.S. Environmental Protection Agency ability to enforce crucial air quality standards, underscoring the urgent need for legislative and regulatory actions to protect vulnerable populations. Addressing air pollution is not just an environmental issue but a critical public health imperative that requires immediate and sustained efforts from all sectors of society.

DISCLOSURE

All the authors declared no competing interests.

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