baseline biochemical findings? Is the renal function deterioration in pregnancy in these rats a result of hemodynamic injury or related to the systemic effects of placental dysfunction and antigenic imbalance resulting in glomerular endotheliosis? These are critical next steps to understanding the maternal and placental contributions to the observed phenotype.

In summary, we applaud the authors who pursued an animal model that mirrors the human observations. As such, this rat model of pregnancy after AKI holds promise as an important tool to further investigate the relationship between kidney function and fetal-placental development. Already, it supports our hypothesis that baseline eGFR alone, even if completely "normal" in the clinician's eye, is insufficient to identify women with previous kidney injury who are risk for pregnancy complications. This model can hopefully be exploited further to investigate biochemical signaling pathways critical for maternal adaptation in pregnancy and placental development, to test novel therapeutics, and to inform future human clinical trials aimed at reducing the burden of maternal and fetal morbidity in women with kidney disease.

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See related article, "Adverse Maternal and Fetal Outcomes in a Novel Experimental Model of Pregnancy after Recovery from Renal Ischemia-Reperfusion Injury," on pages 375–384.

The Road Ahead for Research on Air Pollution and Kidney Disease

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Over the past several years, substantial progress has been made in understanding the relationship between exposure to ambient

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fine particulate matter ($PM_{2.5}$) air pollution and risk of kidney disease.[1,2] We and others have reported that increased levels of $PM_{2.5}$—even at concentrations below the US National Ambient Air Quality Standards of an annual average of 12.0 $\mu g/m^3$—were associated with increased risk of incident CKD, CKD progression, and ESKD.[1,2] A systematic evaluation of all causes of death associated with $PM_{2.5}$ exposure revealed a significant relationship between $PM_{2.5}$ and risk of death due to kidney disease.[3] Effort to estimate the burden of kidney disease attributable to $PM_{2.5}$ air pollution suggested that the global burden of CKD attributable to $PM_{2.5}$ may be substantial and disproportionally borne by low-income and lower middle–income countries.[4,5]

However, nearly all of the evidence on the association of $PM_{2.5}$ and kidney disease has so far been derived from studies in North America, which has relatively lower $PM_{2.5}$ concentrations than other geographies that house much of the world's population. For example, in 2019 the average annual population-weighted $PM_{2.5}$ was 7.66 $\mu g/m^3$ in the United States versus 83.2 and 47.7 $\mu g/m^3$ in India and China, respectively; together, India and China account for about 36% of the total world population.[6] Studies characterizing exposure-response functions for several noncommunicable diseases suggest that the relationship between $PM_{2.5}$ and health outcomes may not be linear. Therefore, evidence on the health effects of air pollution (including effect[s] on kidney function and disease) from countries with higher levels of $PM_{2.5}$ than North America is needed to gain a better understanding of the magnitude of risk associated with $PM_{2.5}$ across the spectrum of concentrations experienced by humans worldwide.

The study by Li *et al.*[7] in this issue of *JASN* is notable in that it offers insight into the relationship between $PM_{2.5}$ and kidney disease in China. The authors developed a cross-sectional assessment using data from the China National Survey of CKD, which included a representative sample of 47,204 Chinese adults. Exposure was assigned on the basis of estimates of $PM_{2.5}$ spatially resolved at approximately 10 $\times$10 km and geocoded to each participant's residential address. The 2-year mean $PM_{2.5}$ concentration (primary exposure) ranged from 31.3 to 87.5 $\mu g/m^3$ with a mean of 57.4 $\mu g/m^3$—much higher than $PM_{2.5}$ concentrations in most prior studies that examined the association of $PM_{2.5}$ and kidney disease.[4,5] The authors reported that increased 2-year mean ambient $PM_{2.5}$ was associated with increased risk of prevalent CKD and prevalent albuminuria.

This study is meritorious and adds to our understanding of the relationship between high levels of $PM_{2.5}$ and kidney disease. However, the cross-sectional design precludes it from being included in most metaregression estimates (*e.g.*, Global Burden of Disease [GBD], World Health Organization, *etc.*), and it will likely be deweighted or may not considered by evidence synthesis panels of regulatory agencies (*e.g.*, the Integrated Science Assessment performed periodically by the US Environmental Protection Agency). The coarse spatial resolution of exposure also substantially limits the interpretation of the findings. Nevertheless, the study provides a good launching pad to develop more optimally designed future investigations in China, other countries in East and South Asia, and beyond. In addition to broadening geographic diversity by including areas with high levels of $PM_{2.5}$, longitudinal cohorts leveraging exposure data with finer spatial resolution and improved methodologies will yield additional insights to deepen our understanding of the relationship between air pollutants and kidney disease.

Despite the progress made in the past several years, significant knowledge gaps remain. In addition to more robustly designed epidemiologic studies from geographies with high levels of $PM_{2.5}$ pollution, carefully designed studies are also needed from areas with very low air pollution levels. These studies will help determine which concentrations of $PM_{2.5}$ are safe and will inform more accurate estimation of the burden of disease attributable to $PM_{2.5}$ exposure.

Significant advances in remote sensing technologies and exposure modeling have been made over the last decade. These have yielded better estimates not only for $PM_{2.5}$ mass concentrations but also for individual components of $PM_{2.5}$ with high spatial resolution. Substantial progress has also been made in causal inference methodologies, estimation of exposure-response functions (*e.g.*, Global Exposure Mortality Model), joint estimation of the health effects of $PM_{2.5}$ and its components, and methods for source attribution.[8,9] Leveraging these advances in exposure science and environmental epidemiology will inform more accurate health effect assessments and precision guide air pollution target setting.

Climate change—the most consequential threat facing humanity in the twenty-first century, which will likely dwarf the health and economic tolls of the coronavirus disease 2019 global pandemic—is intimately related to air pollution. Polluting energy systems are the primary drivers of both PM pollution and climate change, and PM contributes substantially to climate change through its effects on the Earth's radiative energy balance both by absorption (*e.g.*, black carbon) and by dispersion and reflection of radiation. It is unclear yet to what extent climate change and its ramifications (extreme heat, wildfires, floods, droughts, rising sea level and coastal erosion, displacement and migration, emergence of climate-sensitive novel infectious diseases, threats to terrestrial and marine food security and undernutrition, *etc.*) will shape the epidemiology of kidney disease and its upstream risk factors.[10] Studies investigating the health effects of PM pollution and climate change (and potential synergetic effects on health outcomes) will also be needed.

It is also increasingly clear that racial minorities and socioeconomically disadvantaged communities are exposed to higher levels of air pollution and are at greater risk of adverse outcomes given a level of pollution exposure—compounding the risk of health loss due to $PM_{2.5}$ exposure.[11] The health burdens of air pollution are unevenly distributed and disproportionately borne by populations who have contributed the least to the problem—raising a deeper question of justice.

Greater attention should be paid to enhance our understanding of these disparities and to identify actionable solutions to address them.

The inclusion of $PM_{2.5}$-CKD as an environmental health risk-outcome pair in future iterations of the GBD study will be an important future milestone. Realizing this goal hinges on the availability of more high-quality longitudinal studies representing different geographic areas. GBD will then produce global and national estimates of the burden of kidney disease attributable to air pollution on an ongoing basis. GBD estimates are widely used by governments to set policy priorities and allocate budget. These estimates will not only provide a more comprehensive accounting of the health effects of air pollution but will also further elevate the stature of kidney disease as an important global health problem. We must all synergize our effort to realize this important goal and to ensure that evidence generated by our scientific inquiries is serving the greater public good.

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Missing Self and DSA—Synergy of Two NK Cell Activation Pathways in Kidney Transplantation

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Antibody-mediated rejection (ABMR) remains one of the leading causes of allograft dysfunction and kidney transplant failure. The diagnosis of ABMR relies on donor-specific antibodies (DSAs) detected in the recipient's blood, along with histopathologic features of active or chronic antibody-mediated damage evident in the graft microvasculature.[1] The prototypical lesions of ABMR are those of microvascular inflammation (MVI). Gene expression characteristics of endothelial activation and capillary deposition of complement breakdown product C4d are also regularly observed and are evident of immune attack on graft endothelial cells. Overall, the morphologic phenotype of ABMR indicates that DSA binds onto targets

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