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Ecological factors and posttransplant outcomes: Causation or correlation?

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Social determinants of health (SDOH), defined by the World Health Organization as "the conditions in which people are born, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life," are widely acknowledged to contribute to variation in health outcomes.[1] The Healthy People 2030 framework identifies an individual's neighborhood as one of the five key areas of SDOH.[2] The neighborhoods where people live can influence health outcomes through a variety of pathways, including access to transportation, availability of healthy foods and physical activity spaces, rates of crime and violence, and prevalence of poor air and water quality. These forces continue to disproportionately impact racial and ethnic minority populations and low income persons who live and work in at-risk neighborhoods.[3] In the transplant literature, place of residence has been previously correlated with patient outcomes including waitlist mortality[4] and post-transplant outcomes.[5]

In this issue of AJT, Feng et al. describe the association between fine particular matter ($PM_{2.5}$) concentration in a patient's zip code and outcomes after kidney transplantation.[6] Using data from the Scientific Registry of Transplant Recipients (SRTR), the authors found that a 10-μg increase in $PM_{2.5}$ concentration was associated with a 59% increased odds of delayed graft function (DGF), 31% increased odds of acute rejection, and 15% increased odds of all-cause mortality. These associations were robust after adjustment for a variety of individual and zip code-level confounders, including population composition and area-level socioeconomic status. Limitations of this study include the use of area-level measures of air pollution, which are only proxy measures for an individual's exposure to $PM_{2.5}$, and the

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potential for residual confounding resulting from macro-level factors that comprise social-structural influences on health, such as local and state governmental policies and housing market dynamics. In addition, there may be organ transplant system differences, including organ quality and aggressive kidney acceptance practices, which are more common in urban areas with greater waiting times and potentially higher $PM_{2.5}$ levels, and are known to impact the incidence of study outcomes including DGF. Despite potential limitations, the results of this study suggest that measures to mitigate exposure to environments which have high levels of $PM_{2.5}$ may be beneficial for kidney transplant recipients.

While this manuscript was not intended to directly investigate the role of air pollution in transplant health disparities, the reported results demonstrate the two major mechanisms by which air pollution is thought to contribute to health inequity.[7] The first is through *differential exposure*, where disadvantaged population groups bear a disproportionate burden of harmful environmental exposures. Kidney transplant recipients who lived in zip codes with higher $PM_{2.5}$ concentrations were less likely to be non-Hispanic white and less likely to have a college education; these recipients also lived in zip codes with a higher proportion of Hispanic residents, a lower median household income, and a higher proportion of residents living in poverty. All of these factors have been shown to contribute to adverse health outcomes, are correlated with $PM_{2.5}$ concentrations, and, collectively, impact patient survival. The second mechanism is through *differential susceptibility*, where disadvantaged populations are at greater risk for deleterious health effects from environmental exposures. Feng et al. identified stronger associations between $PM_{2.5}$ and delayed graft function for Hispanic patients, and a significant association between $PM_{2.5}$ and death-censored graft failure only among Black patients. These two pathways can work together synergistically to contribute to inequity in health outcomes resulting from environmental factors.

It is crucial to note that this observational study does not establish causation. The reported association with air pollution and death rates has a potential biologic basis with a clear evidence base. The mechanism of the association between air pollution and DGF is less clear and may reflect unmeasured confounding. High pollution regions may be geographically co-located with OPOs that have varying organ procurement and offer acceptance practices, including increased utilization of high risk organs, which increases the likelihood that a kidney transplant will have DGF. Further work is needed to elucidate the mechanism behind this association, identify an appropriate mitigation strategy, and reduce unnecessary mortality.

Differential exposure to environmental and social risk factors such as air pollution may potentially influence the measurement of health care quality at centers that care for a high proportion of disadvantaged patients. Previous work has called for the inclusion of ecological factors in risk adjustment for transplant center quality ratings so as not to inappropriately penalize centers that care for vulnerable communities.[8,9] Importantly, this would also reduce potential disincentives for centers to list patients that they perceive to be at higher risk of poor outcomes resulting from environmental and social mechanisms that are largely beyond the control of the patient or center. While more research on the mechanisms by which SDOH influence transplant outcomes, such as differential exposure to air pollution, is needed, it is critical that fear of “poor outcomes” does not exacerbate pre-existing disparities in access to transplant. Additionally, while careful investigation is needed to determine whether the association between $PM_{2.5}$ and transplant outcomes is causal, there is already clear evidence that “upstream” SDOH are causally associated with poor outcomes and continue to impact our most at-risk patients. Transplant programs and policymakers can take action by identifying patients who live in neighborhoods at higher risk for SDOH exposures and providing support to help patients both access and maintain healthy transplants; regulators can incorporate area-level SDOH into transplant center quality measures to ensure programs are not penalized for providing care for patients with higher social risk; and the transplant community can collectively advocate for policies that impact significant SDOH at a societal level, such as expanding Medicaid, addressing structural racism, and promoting environmental justice in policy development.

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