

those in the low-exposure subcohort were relatively more likely to be white, live in more educated neighborhoods, and have fewer comorbidities. Supplemental analysis of estimated nonlinear associations with PM<sub>2.5</sub> and cardiovascular mortality in the low-exposure subcohort indicated that the greatest increase in the HR occurred between 7 and 12 µg/m<sup>3</sup> of PM<sub>2.5</sub>.

In a general sense, the results of this cohort study of adults with COPD are somewhat consistent with other cohort studies of air pollution. Similar PM<sub>2.5</sub>–CVD mortality associations are observed in broad, population-based cohorts as in the full cohort of adults with COPD (Figure 1). Furthermore, adverse PM<sub>2.5</sub>–mortality associations are often observed even when long-term average concentrations are below the current annual U.S. PM<sub>2.5</sub> national ambient air quality standard for PM<sub>2.5</sub> of 12 µg/m<sup>3</sup> (3, 12). As Alexeeff and colleagues clearly note (11), their study contributes to the evidence that long-term exposure to PM<sub>2.5</sub> air pollution is a risk factor for CVD and that the current long-term PM<sub>2.5</sub> standard is not adequately protective—especially for adults with COPD. ■

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## Stress Is in the Air: Ambient Reactive Oxygen Species and COVID-19

The paper by Stieb and colleagues (pp. 168–177) in this issue of the *Journal* is of interest in several domains (1). First, although still an ecological study of the potential impact of exposure to air pollution on the risk of coronavirus disease (COVID-19), it addresses some of the critiques of previously published studies (2). Instead of a comparison across regions with differing exposures that inherently includes regional differences regarding potentially confounding variables, it is a study of neighborhood differences across a single city, Toronto. Second, the

authors used a novel air pollution exposure metric, estimated reactive oxygen species (ROS) in fine particulate matter (particulate matter ≤2.5 µm in aerodynamic diameter [PM<sub>2.5</sub>]), based on a model of ROS in human epithelial lining fluid and a land use regression model of iron and copper in PM<sub>2.5</sub> from multiple monitoring sites across Toronto in 2016–2017 (3). Yet another important aspect of the use of ROS as the exposure metric is the support the analysis gives to the putative oxidative stress mechanism for the PM<sub>2.5</sub> association with COVID-19 outcomes observed in other studies (4–6).

Although the estimated ROS exposure is an innovative method for an air pollution epidemiological study, this method would be strengthened if it were to be used effectively by other investigators in different settings to study a variety of health outcomes. Actual measurement of ROS concentrations or oxidative potential in ambient air has been advocated for air pollution health studies (7). The method used by Stieb and colleagues to estimate PM<sub>2.5</sub>-associated ROS could be

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validated with comparison to ambient concentrations. Of course, this method does not account for ROS generated in human epithelial lining fluid from exposure to gaseous pollutants like ozone and NO<sub>2</sub>. The current internationally accepted approach to regulating the outdoor air pollution mixture of particles and gases involves setting standards for ambient concentrations for single pollutants (e.g., U.S. Environmental Protection Agency National Ambient Air Quality Standards or World Health Organization Air Quality Guidelines) (8, 9). If it could be shown that ambient ROS concentrations or the oxidative potential of the pollution mixture were robustly associated with health outcomes, then air quality regulation could be targeted to an appropriately representative exposure metric.

The authors' statistical analysis was careful to adjust for multiple likely confounders of any association of air pollution exposure and COVID-19, including socioeconomic status (SES), racialized group status, linguistic difference, use of public transportation, housing crowding, days elapsed since the first case, days since peak daily incidence of cases, case outcomes, and weekly rates of COVID-19 testing. In addition, other exposures tested were PM<sub>2.5</sub>, NO<sub>2</sub>, and greenness. Analyses were stratified by age, sex, and sporadic versus outbreak case status. An appropriate statistical model for count data (negative binomial) and sensitivity analyses were conducted.

A significant positive association was observed between neighborhood-level estimated ROS and COVID-19 incidence. The expected effect modification by neighborhood-level measures of racialized group membership and SES (percent unemployed, with less than high school education or with income below poverty level) was also observed (10, 11). The association with ROS was greater for men and for those under 50, perhaps because these subgroups spend more time outside of their homes during the pandemic and thus have greater opportunity for exposure to air pollution. A nonsignificant positive association with COVID-19 incidence was observed in neighborhoods where the proportion of Black residents was greater, and independent of this proportion, measures of lower SES were also positively associated with COVID-19 incidence. Individuals with lower income are more likely to be essential workers who cannot work at home and are more likely to live in crowded housing (12).

Although a measure of traffic-related air pollution, NO<sub>2</sub>, was associated with COVID-19 incidence in a bivariate analysis, this association was attenuated when ROS was included in a joint model. Another exposure of interest, greenness as measured by the normalized difference vegetation index, was negatively associated with COVID-19 incidence in a bivariate analysis, but this association was also attenuated when ROS was included in the model. In contrast to other reports involving multiregional comparisons (4–6), Stieb and colleagues did not observe a significant positive association of COVID-19 incidence with PM<sub>2.5</sub> mass, likely because of a relative lack of spatial variability across Toronto.

Although this study addressed many of the limitations of other studies attempting to study the impact of exposure to air pollution on COVID-19, it remains an ecological study from which causality cannot be inferred. Studies with individual-level data for both exposures and outcomes are needed. To date, it has been difficult for investigators to obtain data from public health agencies that include both residential addresses and individual-level covariate data. Although this is understandable in terms of privacy concerns, it remains imperative to determine if exposure to air pollution is truly a risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and/or COVID-19 morbidity, especially if this exposure is a mediator of the

increased risks for people of color who are at lower incomes. The COVID-19 pandemic has dramatically demonstrated the chronic health inequity that low-income communities of color experience in the United States and apparently Canada as well (13, 14). The results of the Toronto study are just another reminder of the disproportionate burden of exposure to air pollution borne by such communities (15). Environmental justice is a necessary component of dismantling the systemic racism upon which U.S. society has been built and that also may blight Canadian society. ■

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## ⦿ Mortality Prediction Models: Another Barrier to Racial Equity in a Pandemic

Surges in patient volume during the course of the coronavirus disease (COVID-19) pandemic have raised the very real concern that hospitals may run out of critical resources such as mechanical ventilators and ICU beds. In response to these concerns, crisis standards of care (CSCs) were developed to provide a framework for the allocation of scarce resources. CSCs are designed to be objective, efficient, and ethical, frequently abiding to the principle of maximizing the number of lives or life-years saved. CSCs prioritize the allocation of resources to patients who are more likely to survive to hospital discharge, and they do this by incorporating a tool to predict in-hospital mortality (1). The most commonly used prognostic tool in CSCs is the Sequential Organ Failure Assessment (SOFA) score, although the Laboratory-based Acute Physiology Score version 2 (LAPS2) has been suggested as well (2). In addition, many CSCs include a system to account for a person's likelihood of postdischarge survival based on their comorbidities. It is important to note that neither the full scoring systems used by CSCs nor individual components of CSCs such as the SOFA score had previously been validated for use in allocating scarce resources but were suggested at the onset of the pandemic to fulfill an urgent need where no validated tool existed.

There is now abundant evidence that Black persons are significantly more likely to contract, be hospitalized with, and die of COVID-19 than white persons (3). These differences are not due to biological features but are rather due to socioeconomic disparities associated with race and racism in the United States, such as decreased access to high-quality health care, exposures related to employment, and higher prevalence of chronic diseases such as obesity and diabetes (4). With recognition of these disparities, concerns have grown that CSCs may place nonwhite patients at an additional disadvantage because of disparities in the performance of mortality prediction models or increased prevalence of medical comorbidities in these communities (5). A recent study found that one CSC priority scoring system, which employed the SOFA score to estimate short-term mortality and comorbidities to estimate longer-term mortality, was not associated

with race or ethnicity in a cohort of 1,127 adults admitted with COVID-19 at two urban U.S. hospitals (6). Although this is somewhat reassuring, the small study size and limited patient population raise the importance of further research on the performance of not only CSC systems as a whole but also the individual component scores among larger numbers of patients and in different populations.

In this issue of the *Journal*, Dr. Ashana and colleagues (pp. 178–186) report the results of their assessment of the prognostic accuracy of the SOFA and LAPS2 scores among 113,158 Black and white patients with sepsis or acute respiratory failure at 27 U.S. hospitals (7). The authors frame their analyses within the context of the inclusion of these two scores as components of CSCs developed for use during the COVID-19 pandemic, but, importantly, none of the patients included in this study had COVID-19, as data were collected before 2019. To assess the scores, the authors evaluated two main features of prognostic models, discrimination and calibration. Discrimination is the ability of a model to separate people within categories; a model with good discrimination should give a higher risk estimate, or score, for patients who experience the outcome (in this case, hospital mortality) than for those who do not. Calibration is the agreement between observed and predicted risk. The authors found that both the SOFA and, to a lesser extent, the LAPS2 score, as well as several modified versions of the scores, had poor to acceptable discrimination overall, and both underestimated hospital mortality for white patients and overestimated hospital mortality for Black patients. This has very important implications; when used in a CSC system that prioritizes allocation of resources to patients with the lowest risk of hospital mortality, Black patients would thus systematically be underallocated to receive scarce resources relative to white patients.

The population included in this study was mostly white, and compared with white patients, the Black patients were significantly younger (mean age 62 vs. 68 yr), were more likely to be female (52% vs. 46%), and had lower hospital mortality (7.5% vs. 8.6%). This is important, as both older age and male sex are associated with increased risk for hospital mortality among patients with sepsis or acute respiratory failure. However, even after adjusting models for age and sex, the authors still identified significant miscalibration. One potential reason for miscalibration in the SOFA score is the higher renal subscore among Black patients, possibly because of higher creatinine levels given the same glomerular filtrate rate found in some previous studies. To address this, the authors created and tested several modifications of the SOFA score, including versions that lessened, or eliminated entirely, the

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