and exhibited greater asthma risk and more severe disease than the overall population, limiting the generalizability of the findings. Samples were taken from the hypopharynx and, although clearly informative and correlated to the clinical response, may not precisely reflect microbial community structure in the lower airways. The samples were obtained after 3 days of symptom development, so it is not known whether these patterns of microbiome structure would have been detectable even earlier in the course or whether they reflect the potential effects of an intercurrent viral infection on the microbiome. Unfortunately, there are no data presented on the direct effect of azithromycin on the microbiome structure after treatment, which would help to determine if the antimicrobial effects paralleled clinical response. Although the initial study report demonstrated no effect modification by viral infection (5), there are no data presented with quantification of the effect of azithromycin treatment on viral load or immune markers after treatment.

Our understanding of the infectious components of these lower respiratory tract illnesses in young children continues to evolve. Viral infections remain important triggers of episodes, but there is a clear interaction with nonviral airway microbes that influence episode development and likely impact treatment responses. Additional research is needed to further disentangle these factors and ultimately allow for more effective and targeted therapies that reduce the substantial morbidity associated with these episodes. ■

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Are Adults with Chronic Obstructive Pulmonary Disease Vulnerable to Air Pollution and Cardiovascular Risk?

Substantial research has provided evidence that long-term exposure to air pollution, especially fine particulate matter (particles ⩽2.5 μm in aerodynamic diameter [$PM_{2.5}$]), contributes to cardiovascular disease (CVD) (1, 2). Key to this evidence is the growing number of cohort studies that have found long-term exposures to $PM_{2.5}$ air pollution to be associated with increased risk of mortality, including CVD, nonmalignant respiratory disease, and lung cancer mortality (3, 4).

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$PM_{2.5}$–mortality relationships have been observed mostly in broad, population-based cohorts. A few specific, susceptible subpopulations that may be especially vulnerable to air pollution exposures have been identified. For example, relatively large $PM_{2.5}$–mortality associations have been observed in cohorts of patients who received a cardiac transplant (5) and survivors of myocardial infarction (MI) (6). Also, relatively large associations between $PM_{2.5}$ air pollution and CVD mortality risk have recently been observed in a cohort of U.S. patients with cancer and cancer survivors (7).

Another identifiable subpopulation that may be especially vulnerable to CVD risk from exposure to air pollution consists of adults with chronic obstructive pulmonary disease (COPD). There is substantial CVD comorbidity in adults with COPD, and those with COPD are at greater risk of CVD and death (8, 9). A recent cohort study

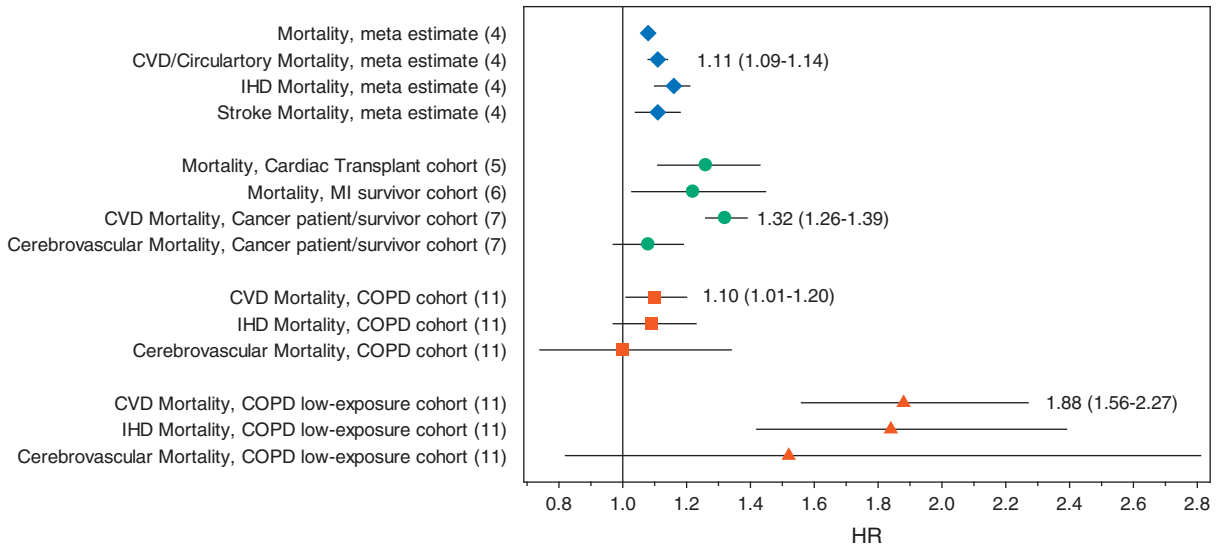

Figure 1. Mortality hazard ratios (95% confidence intervals) associated with a 10 μg/m^3 increase in $PM_{2.5}$ for all/natural-cause mortality, CVD/circulatory mortality, ischemic heart disease mortality, and stroke/cerebrovascular mortality. Blue diamonds are meta estimates from a recent systematic review (4). Green circles are estimates from selected other potentially vulnerable cohorts, including the cardiac transplant cohort (5), the MI survivor cohort (6), and the patients with cancer/cancer survivor cohort (7). Orange squares and triangles are estimates from the analysis by Alexeeff and colleagues (11) of the full chronic obstructive pulmonary disease cohort and the low-exposure subcohort, respectively. COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; $PM_{2.5}$ = particulate matter ≤2.5 m in aerodynamic diameter.

of patients with COPD and CVD or risk factors for CVD found that even acute exacerbations of COPD resulted in considerable elevated risk of subsequent CVD events (10).

In this issue of the *Journal*, Alexeeff and colleagues (pp. 159–167) present novel and important estimates of associations between long-term exposures to $PM_{2.5}$ air pollution and risk of CVD events in a potentially vulnerable cohort—adults with COPD (11). The study area consisted of a 35-county region of northern California. Time-varying 1-year average $PM_{2.5}$ air pollution exposure estimates were based on high-quality and well-documented ensemble modeling using ground, satellite, and other data with spatial resolution of 1 km × 1 km across the study area. The cohort was constructed from members of the Kaiser Permanente Northern California health plan for the years 2007–2016, allowing for excellent validation of COPD status and CVD event outcomes. In addition, the researchers had access to key covariates that allowed for model adjustments for age, sex, race/ethnicity, smoking, body mass index, baseline comorbidities, and medications as well as neighborhood education and Medicaid insurance status. After adjustment for these covariates, $PM_{2.5}$ exposures were observed to be significantly associated with elevated risk of CVD mortality but not MI or stroke.

Somewhat surprisingly, the associations between $PM_{2.5}$ exposures and risk of CVD mortality were not exceptionally large in the full cohort of adults with COPD compared with associations observed in broader, population-based cohorts or compared with cohorts of other potentially vulnerable populations. Figure 1 illustrates and compares $PM_{2.5}$–mortality estimated hazard ratios (HRs) and 95% confidence intervals per 10 μg/m^3 increase in long-term $PM_{2.5}$. Estimates for all/natural-cause mortality, CVD/circulatory mortality, ischemic heart disease mortality, and stroke/cerebrovascular mortality are presented. To allow for easy direct comparisons, the actual numeric values of the HRs for CVD mortality are also presented in Figure 1. The blue diamonds are estimates from a systematic review and meta-analysis (4) and are meta estimates representative of broad-based cohorts from the general population—although there is substantial heterogeneity in estimates across cohorts. The green circles are estimates from other selected potentially vulnerable cohorts, including the cardiac transplant cohort (5), the MI survivor cohort (6), and the patients with cancer/cancer survivor cohort (7). The orange squares are estimates from the analysis by Alexeeff and colleagues of the full cohort of adults with COPD (11). The orange triangles are estimates from the analysis by Alexeeff and colleagues of the low-exposure subcohort of adults with COPD who had $PM_{2.5}$ exposure below 12 μg/m^3 for their entire follow up (11).

In Figure 1, it is observed that the $PM_{2.5}$–mortality HRs for the full cohort of adults with COPD are not larger than the HRs for broad-based cohorts or for the other potentially vulnerable cohorts. However, given that these adults with COPD likely have a substantially larger baseline risk for CVD, comparisons of relative risk estimates clearly do not account for potential differences in attributable risk of $PM_{2.5}$ exposure among those with COPD.

Maybe the most stunning finding from this study of adults with COPD is evidence of much larger adverse $PM_{2.5}$–mortality HRs per 10 μg/m^3 of $PM_{2.5}$ among the low-exposure (<12 μg/m^3 over the full follow up) subcohort of subjects with COPD (see Figure 1). These results are somewhat troubling and perplexing. How is it plausible for these relative hazards to be so much larger in this low-exposure subcohort? Are relatively large $PM_{2.5}$–mortality associations at low exposures somehow unique to persons with COPD? Or are these results because of substantive differences in the makeup and underlying baseline hazard of the low-exposure subcohort? Supplemental analysis presented with the paper (11) indicates that

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 $PM_{2.5}$ and cardiovascular mortality in the low-exposure subcohort indicated that the greatest increase in the HR occurred between 7 and 12 $\mu g/m^3$ of $PM_{2.5}$.

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 $PM_{2.5}$–CVD mortality associations are observed in broad, population-based cohorts as in the full cohort of adults with COPD (Figure 1). Furthermore, adverse $PM_{2.5}$–mortality associations are often observed even when long-term average concentrations are below the current annual U.S. $PM_{2.5}$ national ambient air quality standard for $PM_{2.5}$ of 12 $\mu g/m^3$ (3, 12). As Alexeeff and colleagues clearly note (11), their study contributes to the evidence that long-term exposure to $PM_{2.5}$ air pollution is a risk factor for CVD and that the current long-term $PM_{2.5}$ 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 $\leqslant$2.5 μm in aerodynamic diameter [$PM_{2.5}$]), based on a model of ROS in human epithelial lining fluid and a land use regression model of iron and copper in $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$-associated ROS could be

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