

Long-Term Exposure to Air Pollution and COVID-19 Outcomes in Denmark

BACKGROUND

Research from toxicology, human clinical studies, and epidemiology have linked air pollution exposure with risk of respiratory infections, influenza, and respiratory syncytial virus. Some early studies on air pollution and COVID-19 reported potential associations, suggesting that the number of COVID-19 deaths might have been higher in areas with higher levels of air pollution. The data and methodologies used in these early studies were so fraught with errors, however, that the potential for biased results was very high. In May 2020, only two months after the WHO declared the COVID-19 outbreak a global pandemic, HEI issued RFA 20-1B, soliciting studies to investigate potential links between air pollution, COVID-19, and human health, and selected five studies in various countries. This Statement highlights a study by Dr. Zorana Andersen and colleagues at the University of Copenhagen.

APPROACH

Andersen and colleagues aimed to investigate whether long-term exposure to air pollution is associated with increased risk of COVID-19–related incidence, hospitalization, and mortality in Danish adults. They focused on fine particulate matter <math><2.5 \mu\text{g}/\text{m}^3</math> in diameter, coarse particulate matter <math><10 \mu\text{g}/\text{m}^3</math> in diameter, black carbon, nitrogen dioxide, and ozone. Second, they aimed to identify the most susceptible subgroups of the population according to age, sex, socioeconomic status, ethnicity, and whether pre-existing cardiovascular and respiratory disease, dementia, or diabetes increased susceptibility. Third, they were interested in determining whether the prognosis of COVID-19 hospitalization and mortality

What This Study Adds

- This study evaluated whether there is an association between exposure to outdoor air pollution and the risk of COVID-19 incidence, hospitalization, and mortality in a cohort of 3.7 million Danish adults.
- Andersen and colleagues found elevated risks of all three COVID-19 outcomes associated with exposures to fine and coarse particulate matter, black carbon, and nitrogen dioxide.
- Individuals aged 65 years and older who were exposed to nitrogen dioxide and people with lower socioeconomic status who were exposed to nitrogen dioxide or fine particulate matter were at greater risk of contracting COVID-19 compared to younger or higher socioeconomic status individuals, respectively.
- Major strengths of the study were the inclusion of all Danish adults and the rigorous adjustments for many individual- and contextual-level characteristics.
- This study showed that long-term exposures to outdoor air pollution appear to be associated with adverse COVID-19 morbidity and mortality among Danish adults.

was poorer in a subgroup of people who had tested positive for the disease.

Briefly, they used national registers to create a cohort of all adults residing in Denmark on March 1, 2020, and at least 1 year prior to that. The cohort of 3.7 million people included detailed personal and community-level demographic and socioeconomic information. They assigned annual estimates of pollution exposures for the year 2019 based on data from chemical transport models to each participant's residential address. They used Cox proportional hazard models to estimate associations between each pollutant and COVID-19 incidence, hospitalization, mortality, and death from any cause until April 26, 2021, adjusting for many individual and community-level characteristics.

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The investigators conducted many additional analyses, including testing for effect modification of any associations according to age, sex, socioeconomic status, and comorbidities. They examined the shapes of exposure–response functions, results from two-pollutant models, and whether associations between the pollutants and these outcomes differed during two separate waves of the pandemic. The investigators also examined associations between pollutants and COVID-19 hospitalization and death in a subgroup of individuals who had tested positive for COVID-19.

KEY RESULTS

In the full cohort of 3.7 million Danish adults, about 139,000 individuals tested positive for COVID-19, about 11,000 were hospitalized, and about 2,500 died from COVID-19 during the 14 months of follow-up. Annual average exposures were estimated at 7.4 $\mu\text{g}/\text{m}^3$ for fine particulate matter, 12.7 $\mu\text{g}/\text{m}^3$ for coarse particulate matter, 0.3 $\mu\text{g}/\text{m}^3$ for black carbon, 10.7 $\mu\text{g}/\text{m}^3$ for nitrogen dioxide, and 54.5 $\mu\text{g}/\text{m}^3$ ozone.

Andersen and colleagues found elevated risks of all three COVID-19 outcomes associated with exposures to all the pollutants examined, with the exception of ozone, which was inversely associated with these outcomes (see **Statement Figure** for results for deaths from COVID-19). Overall, patterns for the three outcomes were fairly similar to each other. Risks of increased COVID-19 incidence and hospitalizations were strongest with exposure to nitrogen dioxide (i.e., hazard ratios and 95% confidence intervals: 1.18 [1.14–1.23] and 1.19 [1.12–1.27] per 3.49 $\mu\text{g}/\text{m}^3$, respectively), whereas risk of COVID-19 mortality was strongest with exposure to fine particulate matter (i.e., 1.23 [1.04–1.44] per 0.55 $\mu\text{g}/\text{m}^3$). Risks for death from COVID-19 associated with fine or coarse particulate matter or nitrogen dioxide were much higher than those from all causes.

Interestingly, the investigators found no associations between pollutant exposures and COVID-19 outcomes during the first wave of the pandemic (March 1 to July 31, 2020), when the number of cases, hospitalizations, and deaths were much lower than during the second wave (August 1, 2020 to April 26, 2021).

They found that older adults experienced greater risks associated with nitrogen dioxide exposure (compared to younger people) and people with lower socioeconomic status (according to several indicators) had greater risks associated with both nitrogen dioxide and fine particulate matter exposures (compared to those of higher socioeconomic status). The investigators also reported greater risks for COVID-19 incidence with

nitrogen dioxide and fine particulate matter exposures among those who had pre-existing cardiovascular and respiratory disease and among individuals who had dementia and diabetes, although not all of these results were statistically significant.

In analyses restricted to individuals who tested positive for COVID-19, the investigators found that only exposures to nitrogen dioxide and fine particulate matter were associated with increased risks of hospitalizations; but the risks were notably smaller than those reported for the full cohort.

Last, results from analyses using two pollutants showed generally weaker associations.

INTERPRETATION AND CONCLUSIONS

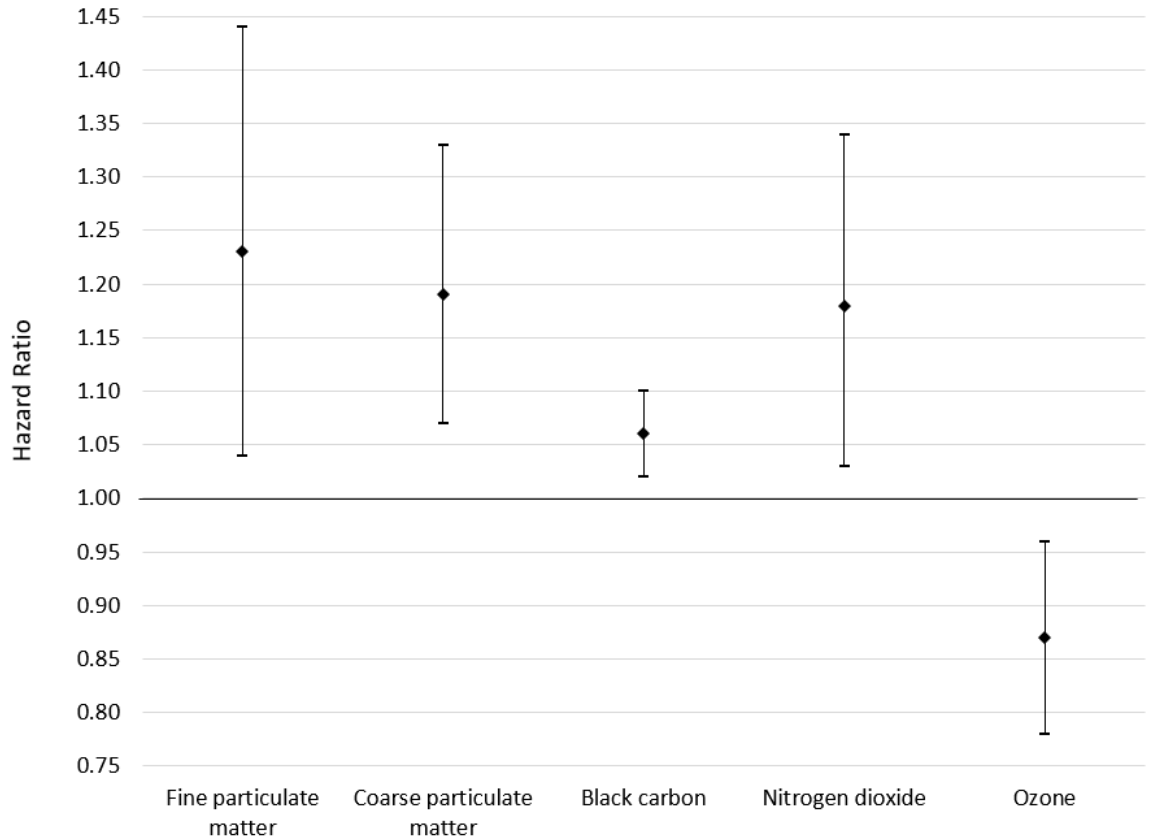
In its independent evaluation of the Investigators' Report, the HEI Review Committee concluded that this study represents an important contribution to our knowledge about potential associations between long-term exposure to air pollution and COVID-19-related health outcomes. Elevated risks for hospitalizations were seen both in the general population and among those who tested positive for COVID-19. The investigators also identified groups potentially most susceptible to air pollution-related COVID-19 outcomes. Major strengths of the study design were the inclusion of the entire adult Danish population and the rigorous adjustments for individual- and contextual-level characteristics.

Some of the findings, however, remained difficult to interpret, including much higher estimates of risk than those reported in many previous studies of air pollution. For example, the reported risks for all-cause mortality are much greater than those observed elsewhere. Other results that are difficult to explain included the weaker associations among those who had tested positive for COVID-19 (as compared to among the full cohort) and the inverse associations between exposure to ozone and several outcomes.

The Committee agrees with the investigators that there are many challenges to measuring cases of COVID-19 incidence, hospitalization, and death accurately. The accuracy of the data depends on voluntary participation in testing, testing capacity, accessibility, cost, and accuracy, which are likely to vary across Denmark and throughout the pandemic.

Ultimately, the study design used here is a great improvement over others used in the currently available literature on this topic. The results document that long-term exposures to outdoor air pollution do appear to be associated with adverse COVID-19 morbidity and mortality among Danish adults.

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Statement Figure. Associations between estimated annual average pollutant concentrations and deaths from COVID-19. Hazard ratios and 95% confidence intervals estimated per interquartile range increases in 1-year mean exposure, namely: 0.55 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 1.14 $\mu\text{g}/\text{m}^3$ for PM_{10} , 0.09 $\mu\text{g}/\text{m}^3$ for BC, 3.49 $\mu\text{g}/\text{m}^3$ for NO_2 , and 2.79 $\mu\text{g}/\text{m}^3$ for O_3 . (Source: Investigators' Report Table 3).